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Review

Biobehavior of the human love of salt

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ABSTRACT

We are beginning to understand why humans ingest so much salt. Here we address three issues: The first is whether our salt appetite is similar to that in animals, which we understand well. Our analysis suggests that this is doubtful, because of important differences between human and animal love of salt. The second issue then becomes how our predilection for salt is determined, for which we have a partial description, resting on development, conditioning, habit, and dietary culture. The last issue is the source of individual variation in salt avidity. We have partial answers to that too in the effects of perinatal sodium loss, sodium loss teaching us to seek salt, and gender. Other possibilities are suggested. From animal sodium appetite we humans may retain the lifelong enhancement of salt intake due to perinatal sodium loss, and a predisposition to learn the benefits of salt when in dire need. Nevertheless, human salt intake does not fit the biological model of a regulated sodium appetite. Indeed this archetypal 'wisdom of the body' fails us in all that has to do with behavioral regulation of this most basic need.

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1. Introduction

Why do humans seek salt so? The notion that the 'wisdom of the body' directs us to acquire specific nutritional needs is vacuous except for sodium. Sodium appetite is the only proven innate behavioral mechanism for acquiring a specific nutrient molecule – other than thirst, its physiological Siamese twin (Fitzsimons, 1998; Rozin and Schulkin, 1990). However, all we know about sodium appetite is gleaned from animal research, and whether the human predilection for salt stems from the same biological source has not garnered serious consideration.

That question is relevant to how to control sodium intake in the face of its toxicity on the one hand, and the dangers of its deficiency on the other. With recent findings it has become relevant to how

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our lifelong craving may be initiated very early on, and whether it predicts cardiovascular vulnerability and predicates individual prescription for regulation of sodium intake. It is relevant to understand how individual differences in salt appetite arise, how palatability and pleasure may rest upon a biological rationale, and it is relevant in considering how a taste preference, largely habitual and fairly inconsequential in the individual, has had such a comprehensive influence on commerce since prehistory, and today is such a threat to public health.

Few animals pick and choose their diet. Most fulfill their nutritional needs with a single or restricted range of foods: certain eucalyptus leaves for koala, grasses for herbivores, meat for carnivores. However, very many terrestrial animals, possibly excepting the carnivores, share a predilection for sodium (Schulkin, 1982, 1984, 1991; Smedley and Eisner, 1995, 1996).

Our love of sodium additionally classes us humans with the vast majority of mammals, the vegetarians, which, although they have a restricted diet, possess an innate ability to regulate their sodium requirements by means of physiological husbandry and behavioral avidity. More specifically yet, humans are classed with a tiny group of omnivores that select, study, and vary their diet in a continual effort to compose their nutritional palette, *inter alia*, with sodium (Rozin and Schulkin, 1990).

Sodium is an irreplaceable ion of the solute base of living organisms and of the functioning and communication of cells. Life cannot be sustained if bodily sodium levels are not maintained, and animals dwelling in domains where sodium needs to be foraged are endowed with a robust sodium appetite, first recognized, studied and described by Curt Richter, founder of our science over 70 years ago (Denton, 1982; Epstein, 1990; Richter, 1956; Schulkin, 1991, 2005).

The essentials of such a sodium appetite are its innate origins, investment in seeking salt, consumption in excess of bodily need, and dramatic physiological, behavioral and ingestive responses to sodium deficit that conserve and redistribute bodily sodium reserves, impel the animal to rummage its memory and ecology for locations of sodium, to prioritize its forage by increasing its palatability, and to rapidly ingest it when found, at any high concentration, and as sodium partnered to virtually any radical (Coldwell and Tordoff, 1996; Denton, 1982; Epstein, 1990; Richter, 1956; Schulkin, 1991; Smedley and Eisner, 1995, 1996; Schulkin, 1991; Wolf, 1969).

Sodium appetite is described by a number of characteristics: The response to sodium deficit is recognized as a crucial component of the appetite, and is often termed a sodium 'hunger' because it is a response to a bodily deficit, and in order to distinguish it from 'need-free', or spontaneous, sodium intake. Sodium hunger is for life-saving crisis intervention. In the rat the brain substrates of sodium appetite are in place within 24 h of birth (Denton, 1982; Epstein, 1990; Leshem and Epstein, 1989; Leshem, 1999; Schulkin, 1991).

In contrast, it has been suggested that spontaneous intake, which is in excess of immediate bodily needs, is anticipatory, serving to ensconce sodium sources in memory, and to ward off hyponatremic challenge. Furthermore, should this fail and the animal nevertheless experiences a sodium deficiency, the spontaneous appetite will be enduringly enhanced, as redoubled protection against a now proven hazard (Dietz et al., 2006; Epstein, 1990; Falk, 1966; Fessler, 2003; Leshem et al., 2004; Rowland and Fregly, 1988; Sakai et al., 1987, 1989; Schulkin, 1991), albeit not invariably (Leshem et al., 2004; McCaughey et al., 1996).

The spontaneous avidity that natriuphilic animals display may similarly bear the traces of sodium deficit occurring perinatally as a long-term enhancement of its palatability (Arguelles et al., 1999; Galaverna et al., 1995; Leshem, 1999; Leshem et al., 1996, 1998; Nicolaidis et al., 1990; Vijande et al., 1996),

In many animals, including primates, the palatability of salt varies inversely with its availability to the body (Blair-West et al., 1998; Denton, 1982, 1991; Schulkin et al., 1984; Denton et al., 1993), and palatability is believed to be the device linking bodily deficit to appetitive behavior (Denton, 1982, 1991; Dietz et al., 2006; Berridge et al., 1984; Berridge and Schulkin, 1989; Epstein, 1991; Johnson and Thunhorst, 1997; McCaughey and Scott, 1998; Rozin and Schulkin, 1990; Schulkin, 1982, 1991; Tindell et al., 2006; Yeomans et al., 2000, 2004).

A coherent physiological model of the determinants of salt intake in laboratory rodents has emerged, including the notion that acute activation of the brain renin–angiotensin system conjointly with peripheral aldosterone, as by sodium deficit, can induce immediate, and possibly enduring, increases in sodium ingestion (Epstein, 1986, 1991; Fitzsimons, 1998; Fluharty and Epstein, 1983; Krause and Sakai, 2007; Sakai et al., 1987, 1989; Schulkin, 1991; Sakai et al., 2007; Shade et al., 2002; Weisinger et al., 1996), likely involving changes in dendritic morphology, neurochemistry, and neural activity (Contreras, 1977; Contreras et al., 1984; De Gobbi et al., 2007; De Oliveira et al., 2008; Geerling and Loewy, 2008; Jacobs et al., 1988; McCaughey and Scott, 1998; Na et al., 2007; Nachman and Pfaffmann, 1963; Roitman et al., 2002; Tamura and Norgren, 1997). Brain tachykinins and oxytocin down-regulate the appetite (Flynn, 2006; Massi et al., 1992; Stricker and Verbalis, 1990). Its anatomical infrastructure includes the circumventricular organs and tissue in their vicinity, a contribution from the amygdala and its mineralocorticoid receptors, and from executive functions by frontal regions (Geerling and Loewy, 2008; Krause and Sakai, 2007; Ma et al., 1993; Sakai et al., 1996, 2007; Schulkin, 1991; Schulkin et al., 1989). Much of this scheme is also known from the sheep, as are some differences (Denton et al., 1984a; May et al., 2000; Weisinger et al., 1980), and from the pigeon (Massi and Epstein, 1987, 1990).

Once ingested, the digestive fate of sodium is equally unique. Unlike most other ingesta, which are converted to generic matter, stored, accessed and reprocessed at need, sodium, rapidly and unaltered, takes up its various life-sustaining roles, and when required, its restorative powers are swift (Siegel, 2007; Valentine, 2007; Verbalis, 1990; Verbalis et al., 2007).

Sodium is an element of the universe, it cannot be synthesized; ingestion or injection are the sole means of replenishment. Nor are there passive stores of sodium in the body, but by a miracle of contradiction, sodium levels are regulated in blood to within some 2% of ~137 mmol, while simultaneously large quantities of the ion can be lost. This is orchestrated by the kidney and its adrenal cap, their respective enzyme and mineralocorticoid secretions cascading throughout the body to juggle blood vessel diameter, heart rate, sodium flux across cell membranes, and molecular filters in kidney to jettison water appropriately, all to maintain the sodium concentration immutable in our blood.

Sodium leaks routinely from our bodies in urine, feces, and perspiration, but its loss can be catastrophic, overwhelming its controls, in dehydration, diarrhea, hemorrhage, or adrenal pathology, leading to mental and physiological derangement, and death by hyponatremia.

Hence, the beauty of sodium appetite as a matter of study stems from its patent adaptive significance, the unequivocal definition, to the ion, of the object of these adjustments, the mystery of how a naive animal recognizes the remedy to its specific hyponatremic affliction by taste, the biological prescience to rapidly complete the connection between the malaise of sodium deficit, the enhanced palatability it primes, the previously learned location of salt, and

relief or cure, and finally, to consolidate this sequence enduringly in readiness for a recurring challenge.

The uniqueness of sodium appetite as a matter of laboratory study stems from it being measurable, in all its complexity, by a burette.

2. Do humans have a sodium appetite?

However, in humans, behavioral evolution has far outstripped the physiological, making it pertinent to enquire how much our predilection for salt derives from sodium appetite in animals.

Like many animals, humans love salt and have a special taste organ to detect it: like the rat, we have about three taste transducers for the multitude of our tastes, and one dedicated just to sodium (McCaughey and Scott, 1998). This may not be surprising when we consider that in our bodies the ion is as essential as it is for animals, and its disposition is regulated by similar hormonal and physiological checks and balances. Indeed, human renin and angiotensinogen expressed in mutant mice brains increases their preference for salt (Morimoto et al., 2002). Finally, like rats, sodium deficit around the time of our birth programs us to increase our avidity for salt when we are old enough to seek it (below).

There the similarities end. Unlike sodium-loving animals, humans will rarely ingest pure NaCl, and find aqueous solution of pure salt at the least distasteful or at worst, emetic (Cowart and Beauchamp, 1986; Moder and Hurley, 1990). Humans eat their salt in food, rats prefer it in fluid – possibly because, in food, regulation of sodium intake is hampered by linkage to other nutrients, whereas rats exquisitely juggle their fluid intakes by sodium concentration to control its intake precisely (Beauchamp and Bertino, 1985; Bertino and Tordoff, 1988; Richter, 1936; Stricker and Verbalis, 1990).

As mentioned, rats will take their sodium with any radical, humans only as the chloride (Schulkin, 1991; Coldwell and Tordoff, 1996).

Most tellingly, sodium deficient humans do not show a robust increase in salt intake. That is, we lack a sodium hunger, unlike animals, including our primate relatives (Blair-West et al., 1998; Schulkin et al., 1984). Human instances of sodium privation are consequent upon neonatal hyponatremia, adrenal or hormonal pathology, hemorrhage, diarrhea, dehydration, vomiting, and exertion-induced sodium losses in perspiration. The most cited reports of sodium hunger in humans are practically anecdotal, and no study has been adequately controlled to exclude a learned response (Beauchamp et al., 1990; Bertino et al., 1981): a posthumous case report (Wilkins and Richter, 1940), statements in studies of Addison's disease (Henkin et al., 1963; Thorn et al., 1942), and a report that three of four drastically sodium deficient volunteers did not crave salt (McCance, 1936) (Table 1). A more recent and methodological study confirms the tenuousness of human salt hunger, so that severely sodium deficient volunteers, treated almost daily for almost a fortnight with diuretics spewing the sodium from their bodies, and additionally maintained on a sodium deficient diet to curtail its replenishment, listed more salty foods, but showed negligible indications of a specific sodium appetite (Beauchamp et al., 1990). In fact, spontaneous ingestion of salt in response to acute sodium depletion has never been recorded in humans, even with severe hyponatremia.

This is no trivial observation. Hyponatremia kills humans with salt about them, arguably more than dehydration kills humans when water is available, arguably because we are protected by a keen sensation of thirst (Boscoe et al., 2006; Kratz et al., 2005; Lien and Shapiro, 2007; Noakes, 2007; Siegel, 2007; Siegel et al., 2007).

Thus, we will seek salt to please our palate, but not to save our life. There is a diminished biological rationale for a sodium appetite devoid of sodium hunger.

Finally, despite a rich vocabulary of words and idioms derived from salt (Kurlansky, 2003), in English and related languages, there is no colloquialism for 'salt appetite'. Hebrew, a uniquely ancient language recording an ancient culture with salt rituals, has no term for salt appetite. Similarly, the rich vocabulary of ingestive behavior expresses our desires and appreciation in hunger, appetite, satiety, thirst, slate, palate, sweet tooth, craving, etc., multiplied by manifold adjectives, highly refined in culinary art. Yet while salt is used, liked, avoided, and passed, it abides but two adjectives: too little or too much. We have no specific terminology for reflection upon salt. 'Salt appetite' cannot exist in daily experience if it has no name. In all likelihood, the term was coined for animal experiments, not human experience.

Hence, without physiological regulation, and without encultured recognition, on balance, the human predilection for the taste of salt cannot constitute an 'appetite' or 'hunger' as we know it either from animal motives or from the other human ingestive desires of hunger and thirst.

3. If not a 'sodium appetite' – do humans have a 'salt appetite'?

The practical relevance of the question of whether humans have a salt appetite stems from the consensus that dietary sodium is toxic and the contention that it is not (Alderman, 2004; Cohen et al., 2006; He and MacGregor, 2002; Lozada et al., 2007; McCarron, 2000; Phillips et al., 1985; Taubes, 1998; Scientific Advisory Committee on Nutrition, 2003). Studying salt appetite may reveal its source and determinants, and assist in addressing human behavioral regulation, largely sodium over-consumption leading to cardiovascular disease, but increasingly the problems of hyponatremia and fluid regulation neonatally, in exertion, in disease, in senescence, and possibly in mental anguish (Boscoe et al., 2006; De Lorenzo et al., 1997; Grippo et al., 2006; Johnson and Grippo, 2006; Lien and Shapiro, 2007; Siegel et al., 2007; Valentine, 2007).

Sodium appetite is defined by the desire for sodium. Since this does not seem to be the case for humans, perhaps it is the taste of sodium chloride, generically referred to as 'salt' in many languages, that we seek, rather than any sodium salt.

Table 1
Differences and similarities in sodium regulation between humans and animals

Obvious similarities	Obvious differences
• Love salt.	• Humans reject pure salt, e.g., rock salt – animals seek it.
• Have special sense organ to detect it.	• Humans only eat salt with food and reject it in water (Cowart and Beauchamp, 1986). Rats prefer sodium in solution to salt in food (Beauchamp and Bertino, 1985; Bertino and Tordoff, 1988).
• Physiologically the ion is essential.	• Humans will only ingest sodium chloride. Animals have a sodium appetite – they will ingest almost any sodium salt.
• Bodily sodium regulated by similar hormonal and physiological systems.	• Humans do not respond spontaneously to acute sodium deficit by seeking salt - it is impossible to acutely arouse salt hunger in humans. Animals respond with robust sodium hunger to sodium deficit.
• Early sodium deficit programs increased avidity for salt throughout life.	

Perhaps, our predominantly carnivorous heritage of 2 million years, followed by 8000 years of mining salt, trading and taxing it, using it primarily to preserve our food, and its consequent over-consumption, have obscured the bodily need and dispensed with the evolutionary imperative (Cordain et al., 2002; Denton, 1982; Kurlansky, 2003; Mann, 2000. cf. Mattes, 1997 for a different view). The greatest reduction in salt use coincided with the invention of the refrigerator, yet well over a century later we still relish the cured hams, salted beef, sauerkraut, soused herring, anchovies, salted hard cheeses and biscuits, olives and brine-pickled vegetables of that bygone era, so that we now desire the taste of salt as we have learned to enjoy capsaicin, caffeine, ferments, sweet, fat, and familiar – bereft of physiological need, even if of some physiological utility (Kurlansky, 2003; van den Brandt et al., 2003; Yeomans et al., 2004).

Yet, while regulatory physiology may not apply to the human avidity for salt, it can certainly be physiologically influenced in the short- and long-term, in health and in disease, and now we even have some understanding of the physiological roots of individual differences in the proclivity for salt.

Moreover, even if such influences are incidental rather than part of the integrated regulatory system for sodium homeostasis, it remains possible that physiological determinants of animal sodium appetite may have residual effects in humans. A prime example of this is the discovery that prenatal sodium loss engenders a life-long avidity for salt in rats (Galaverna et al., 1995; Nicolaidis et al., 1990) followed by confirmation of a similar effect in humans (Crystal and Bernstein, 1995, 1998), and extended from rats to people for postnatal sodium loss too (Leshem, 1998; Leshem et al., 1998; Shirazki et al., 2007; Stein et al., 1996).

Additionally, there is modest evidence for physiologically bound sodium palatability in humans, just possibly linked to bodily sodium levels. Although two studies found that haemodialysis, during which sodium levels are reduced from high-normal to low-normal, did not increase sodium palatability (Shepherd et al., 1986; Farleigh et al., 1987), another found suggestive effects of haemodialysis (Leshem and Rudoy, 1997) or natriuretic treatment (Beauchamp et al., 1990). Intense exercise, wherein a substantial amount of sodium is lost in perspiration, does seem to increase sodium palatability more replicatively (Kanarek et al., 1995; Leshem et al., 1999; Takamata et al., 1994; Wald and Leshem, 2003, Fig. 1), and conditioning of a sodium preference after exercise may be related to the amount of perspiration, suggesting a relationship between sodium losses and increased palatability (Wald and Leshem, 2003). Indeed, salt preference may not change with swimming, where perspiration is negligible (Yativ et al., 2003). More recently, we have found increased sodium palatability in those congenital adrenal hyperplasia (CAH) patients who are salt-wasting and not stabilized by medication (Kochli et al., 2005). Together with a report that insensible sodium reduction partially increases salt intake (Beauchamp et al., 1987), and insensible salt preload may reduce it (Huggins et al., 1992), if inconsistently (Bertino et al., 1986), these studies constitute fair, but not overwhelming, evidence that salt palatability is modulated by bodily sodium availability in humans.

Again, this correlational link of sodium levels and palatability in humans need not imply a regulatory mechanism. The correlations with exertion may be mediated by sympathetic activation rather than missing sodium, as well as by the hyperphagia or anorexia following exertion (Blundell et al., 2003; King et al., 1997). Learning can account for some of them. Such preferences may be conditioned via the postingestive restorative role of sodium on hydration and electrolyte balance (Wald and Leshem, 2003). Similar conditioning is known with caffeine or thiamine (Rozin and Schulkin, 1990; Yeomans et al., 2000). Moreover, it has been noted that a taste sensation "activates a wide array of physiologic processes. These rapid, neurally mediated, cephalic-phase responses include stimulation of salivation, secretion of gastric acid and increased gastric motility, release of pancreatic digestive enzymes and hormones, enhanced thermogenesis, and alterations of cardiovascular and renal function. Sodium chloride may elicit these responses through its specific taste or via an influence on a food's palatability" (Mattes, 1997).

Finally, in many of these studies, alterations to other tastes were not controlled although it is well known that the avidity for sweet may also increase after exertion (Leshem et al., 1999 (Fig. 1), Horio and Kawamura, 1998; King et al., 1997; Passe et al., 2000).

The avidity for salt may also vary with genes, gender, its hormones, and their cycle. There is no evidence for genetic differences in the human avidity for salt, although these are known in rodents (Bachmanov et al., 2002; Greene et al., 1975; Rowland and Fregly, 1988). Gender differences in sodium intake are evident in rats, especially the greater intake in females during reproduction, particularly during lactation, which may enduringly enhance spontaneous intake even between reproductive episodes (Chow et al., 1992; Frankman et al., 1991; Leshem et al., 2002; Stricker et al., 1991; Thiels et al., 1990). But for humans the evidence for variation with the reproductive cycle is inconsistent and has yet to be related to physiological sodium need (Bartoshuk et al., 1998; Bartoshuk, 2000; Bowen, 1992; Bowen and Bernstein, 1999; Brown

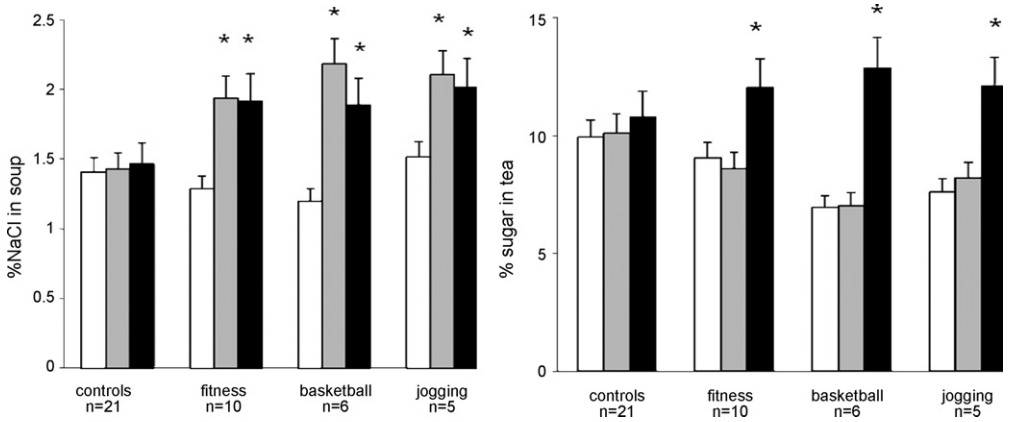

Fig. 1. Salt added to tomato soup (left panel) and sugar to tea (right panel) in the morning 7 h before 40 min exercise (white), immediately after it (grey), and next morning (black), in three types of sports. Controls did not exercise. Males only participated. *$p < 0.05$–0.01 different from the morning before exercise (adapted from Leshem et al., 1999).

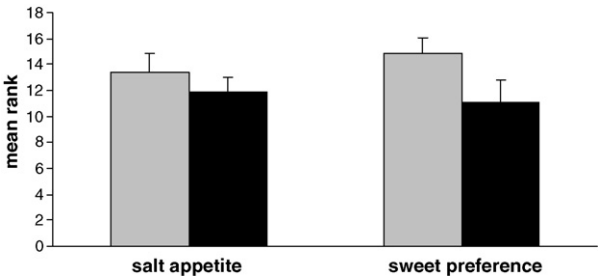

Fig. 2. Salt appetite and sweet preference compared in mothers who are nursing ($n = 15$, black) and those that are not ($n = 9$, grey), matched for age and number of births. There were no significant differences in salt appetite, sweet preference, other measures of salt and sweet preference, or intake of dietary electrolytes and macronutrients (Leshem, unpublished data). Salt appetite and sweet preference were assessed as in Kochli et al. (2005).

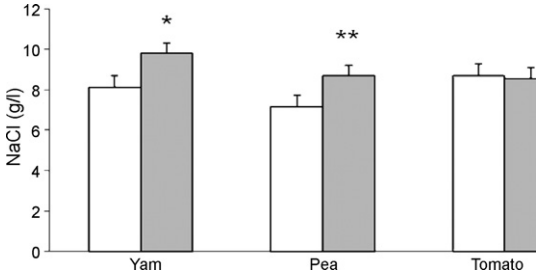

Fig. 3. Gender difference in preferred salt concentration in soups. Students were offered free cups of soup at a stall in the university corridor. The soup given each student was salted at a concentration they chose from six samples of the soup differing in concentration of salt. Yam, pea and tomato soups were tested on different days. Women, white columns, men, grey columns, $n = 41–110$/column, $n = 509$, $^{*}p > 0.02$, $^{**}p < 0.005$.

and Toma, 1986; Duffy et al., 1998; Frye and Demolar, 1994; Kanarek et al., 1995; Mattes, 1997; Ochsenbein-Kölble et al., 2005; Verma et al., 2005).

We find no increase in sodium preference or intake of nursing mothers with singletons, and no increase with number of births, which might be expected to enhance intake in the long-term, as suggested by the animal studies (Fig. 2).

For gender differences, it is well established that salt intake is *lower* in women as a function of their lower absolute caloric intake (Lozada et al., 2007; Dietary Reference Intakes for Water, 2004; MABAT, 2004; Wright et al., 2003). Women and men do not differ on overall salt appetite or sweet preference in our test battery (e.g., Kochli et al., 2005, Table 2) or for aversive concentrations of NaCl in water (Desor et al., 1975a; Greene et al., 1975), but women add less salt to soups than men (Fig. 3), and in our other experiments women ($n = 68–152$) scored significantly lower on their reported salting, and on hedonics of oral salt, spray than men ($n = 55–111$). However, women also scored lower on reported sweetening of food, sweet snacks eaten, hedonics of oral sucrose spray, and dietary sweet carbohydrate (CHO) intake (p's $< 0.05–0.001$), indicating that men might also season their food more (Greene et al., 1975).

Most striking, calculated from data sets for 1999–2000, adults over 20 years (albeit different samples for dietary sodium (Ervin et al., 2004) and body weight (McDowell et al., 2005), n's = 1979–4314), US men ingest 45.4 mg/d/kg body weight Na^+ and women 39.0 mg/d/kg, vastly less. This is confirmed by calculation from data from the Israeli Ministry of Health for 1999–2001, adults over 25 years, 1391 men and 1423 women giving values of 41.25 and 33.91 mg/kg, respectively, an even greater difference of ~20% (MABAT, 2004). For a 75 kg individual (~mean weight for the sample), this is about 1.4 g/d more salt for a man than a woman. More seasoning by men does not account for this difference because the data do not include salting at the table. Presumably it derives from gender specific dietary choices, intriguingly, in both cultures. Clearly, the greater intake of sodium by men, its causes, mechanism and implications, require investigation.

Table 2
Components of salt and sweet preference $n = 262$

components	1	2	3
Tests & questions	32[a]	21 [53]	15 [68]
sugar in tea[b]	0.77		
salt in soup[b]	0.72		
salting food	0.69		
sweetening food	0.64		-0.46
salty snacks[b]		0.78	
sweet snacks[b]		0.73	
dietary sodium			0.80

Rotated component matrix of tests and questions with Varimax rotation, Kaiser normalization, and $r > 0.40$. Measures of salt preference are shaded. [a]% Variance explained (cumulative). [b]Tests of preference, others are questionnaire scores.

Thus, manifold physiological changes, whether modifying salt appetite or modified by it, may have little to do with maintaining sodium homeostasis. On the other hand, they may well provide a fecund bed of stimuli to condition subsequent sodium intake, if when sodium is lost salt is offered. This may underlie the increased acceptability of isotonic drinks in athletes and exercisers, and sodium wasting patients discovering salt as prophylactic, and for relief of hyponatremic strain. (Booth et al., 1982; Kochli et al., 2005; Sawka and Montain, 2000; Wald and Leshem, 2003; Yeomans et al., 2004).

There is a troublesome flaw in this literature showing the palatability of salt to vary with physiological flux in humans: there is no evidence at all that it leads to voluntary salt intake. In all these studies, salt is proffered for evaluation of preference, palatability and taste, but in none of them have participants been able to actually, spontaneously, request salt, nor have such requests been documented. It is unimaginable that people analogously deprived of calories or drink would be so serene. Hence, it is not clear how increased salt palatability that does not increase sodium ingestion or craving can be regulatory. Indeed, McCance (1936) describes intense salt craving in one of four sodium-drained individuals, but the others reported unfamiliar sensations, some of which they mistook for (unquenchable) thirst. The sodium-starved McCance found an oral rinse with saline "very refreshing" but his detailed description does not mention an irresistible urge to swallow it; thus, the palatability of salt was increased, but failed to arouse a sodium hunger even when it was in his mouth!

Can this dissociated palatability be the evolutionary vestige of the lost sodium hunger? Can it be the means by which the next episode of sodium deficit will be prevented, as when in animals an episode of sodium deficit can enhance the appetite enduringly (Falk, 1966; Leshem et al., 2004; Na et al., 2007; Sakai et al., 1987, 1989).

The enhanced palatability of sodium evinced by rats that have been previously sodium depleted may be an allostatic response, an evolutionary strategy, whereby past crises engender a proactive,

preventive, strategy of increased sodium intake (Epstein, 1990, 1991; Fessler, 2003; Schulkin, 2003: below). However, we have no good evidence for that occurring in humans following sodium loss in adulthood. In a series of unpublished experiments we have failed to reliably demonstrate enhanced salt appetite after repeated sodium loss due to hemorrhage (blood donors with up to 12 donations, Erez et al., 2000), army veterans that had been dehydrated up to eight times in training, mothers who had up to six births, and hyperhydrosis sufferers, losing 88 ± 17 mg sweat from their palms in 120 s compared to 12 ± 17 for controls ($p < 0.005$, $n = 12$ and 12, respectively).

The contrast to the facility with which the enduring enhancement of salt appetite by perinatal sodium loss can be demonstrated in humans (Crystal and Bernstein, 1995, 1998; Kochli et al., 2005; Leshem et al., 1998; Stein et al., 1996; Shirazki et al., 2007) suggests an early developmental window for enhancement of the spontaneous appetite in humans.

4. Is the human avidity for salt an 'appetite'?

Not only is there doubt about the regulatory nature of our appetite for salt, but there is also uncertainty about whether we have such an appetite altogether. Alternative formulations might emphasize the utility of salt as a taste enhancer, taste modulator, and taste protector, especially against bitter (Breslin and Beauchamp, 1997; Mattes, 1997). Salt preference might also fit a broader hedonic model of palatability that does not simply reflect internal need states but may arise through past associations between flavours and consequences, that increase the palatability of salt when it is long dissociated from the need state (Booth et al., 1982; Capaldi and Privitera, 2007; Sclafani, 1999; Wald and Leshem, 2003; Yeomans et al., 2004).

Presumably, the rationale for a human salt appetite rests on the widespread use of salt in food, but mere reflection reveals the inadequacy of this argument that could equally be applied to sugar, fat, pepper, or in some societies, umami or ketchup. These are probably not appetites, ubiquitous, physiologically regulated, biologically adaptive and evolved. Does our fondness for the salty permeate our nutrition, independent of ingestive context, as expected from a salt appetite, or does it constitute a partiality for many and particular foods which we like salty, as we may like other foods sweet or spicy? As noted, humans are averse to aqueous salt solution, whereas the same concentration of salt in a slightly adulterated solution, such as soup, is relished, suggesting context-dependence rather than sodium seeking (Beauchamp and Cowart, 1985; Beauchamp et al., 1994; Cowart and Beauchamp, 1986). Indeed, many foods would be abhorred salted, such as sweet foods in Western cuisine. Hence, whether a particular individual loves salted macadamia nuts, but takes little salt on his vegetables, and none on her pudding, are pertinent queries taxing the notion of an ubiquitous salt appetite.

A commonality of salt intake over many foods, as required by the appetite hypothesis, is testable. We employ a number of tests of salt preference to evaluate avidity for salt, and combine them to provide a measure of the overall 'appetite', thus defined (Kochli et al., 2005; Leshem, 1998; Shirazki et al., 2007). A test of salting of soup provides a measure of conscious salt use. The technique we employ, of mixing solutions, ensures that the result is driven by palatability rather than habit (Pangborn and Pecore, 1982; Greenfield et al., 1983; Beauchamp et al., 1987; Shepherd et al., 1989). Conscious salt use is also evaluated by asking participants how much salt they add to each of ~65 food items or categories. To obtain an indication of insensible sodium intake, we use dietary recall. To obtain a measure of preference for salt in other contexts, we monitor intake of salty snacks (Crystal and Bernstein, 1995). To measure the hedonic response to pure NaCl, and its intensity, while avoiding drinking the solutions (aversive to humans, Beauchamp and Moran, 1984), we spray six concentrations into the mouth and plot responses on visual analogue scales. We ask how much a participant likes salt to probe her awareness of how her salt use compares with others, and we ask whether he licks salt. As a control, we obtain scores of sweet palatability in analogous tests. Wherever possible (requiring blood and urine samples), we derive the fractional excretion of sodium (Fe_{Na}^{+}), an indication of recent sodium intake (Leshem et al., 1998; Malaga et al., 2005).

Clumping our experiments together to an n of 262, we find a correlation between the summary salt appetite and sweet preference measures ($r = 0.40$, $p < 0.001$, similar for both men and women), again, suggesting that many humans who like salty will like sweet too, and further undermining the notion of a unique salt appetite (Table 2). Moreover, the coherence of salt preference is also in doubt, because different measures of salt preference may be independent (Pangborn and Pecore, 1982).

Nevertheless, a salt appetite by the intercorrelational definition may well well up through the data. This happens in patients with CAH. CAH is a form of adrenal insufficiency due to genetic mutations shunting metabolism to increase testosterone at the expense of cortisol and aldosterone, the sodium-preserving hormone. Hence, there is virilization and, in the severe form, salt-wasting – a persistent urinary loss of sodium. Untreated children are prone to life-threatening hyponatremic crisis and many of them score high on tests of salt appetite (Kochli et al., 2005, Fig. 4).

In comparison to their healthy siblings, these patients show an intercorrelation of all the measures of salt appetite and it is distinct from their preference for sweet (Table 3).

To enquire whether this might indeed be a "sodium appetite", we interviewed the CAH children about the origins of their predilection for salt.

Asked when they discovered they liked salt, of 14 salt-wasters, one reported eating salt at 2 years (according to his parents, already drinking pickle-brine at that age), and 12 children discovered it after 6 years of age. Asked how they discovered their love of salt, seven reported discovering it by themselves; one salt-wasting patient remembered her revelation well, that of her first taste of pure salt, in a kindergarten taste experiment. Six children reported having been shown the habit by siblings, relatives or friends.

Consider these cases, cross-referenced from separate interviews:

MM was 12.3 years old. Virilised, he was raised as a boy, although chromosomally 46XX (he subsequently received dis-

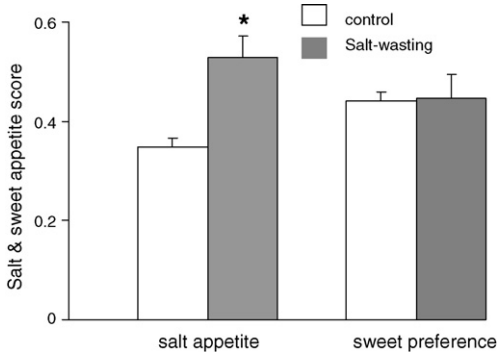

Fig. 4. Salt appetite and sweet preference in salt-wasting CAH (gray columns) and sibling controls (blank columns). Scores are compendium of tests and questionnaires. *Salt appetite different from controls, $p < 0.001$ (after Kochli et al., 2005).

Table 3
Salt and sweet preference in congenital adrenal hyperplasia (CAH)

(CAH).**Control siblings** n=41					**CAH** n=41			
component	1	2	3	4	component	1	2	3
% variance	19	16	14	12	% variance	24	19	13
explained [cum]		[34]	[48]	[60]	explained [cum]		[43]	[57]
salt hedonic[b]	0.7	0.5			salt licking	0.7		
salt licking	0.6				love salty	0.7		
salting soup[b]	0.5	0.6			salting soup[b]	0.6		
salting	0.4		0.5		salt hedonic[b]	0.6		
love salty	0.5		0.5		salting	0.6		
sweeten	-0.5				dietary sodium	0.6		-0.7
love sweet	-0.5		0.5		salty snacks[b]	0.4		0.5
dietary sodium		0.8			Fe_{Na}[b]	0.5		
dietary sweet - CHO		0.5			sweeten		0.8	
sweeten tea[b]		0.4			love sweet		0.8	
Fe_{Na}[b]			0.6		sweet snacks[b]		0.6	
sweet snacks[b]			-0.5	0.7	sweeten tea[b]		0.6	
salty snacks[b]				0.8	Dietary sweet · CHO			-0.8

Rotated component matrix of tests and questions with Varimax rotation, Kaiser normalization, and $r > 0.40$. Measures of salt preference are shaded. [a]% Variance explained [cumulative]. [b]Tests of preference, others are questionnaire scores.

pensation from his religious court for gender-change surgery). He likes salt very much, but scores low on sweet preference. He licks salt frequently, from his hand and from the salt-cellar, and puts a lot of salt on his food. He eats a lot of brine-pickled olives and cucumbers, and salty cheeses. He eats lemons, figs, and instant-coffee powder, all with salt (another child ate salt mixed with sugar). He discovered his liking for salt by himself. UM, 9.8 years, his younger brother, is also salt-wasting, with similar habits, which he learned from MM. In the tomato soup test, he liked best the undiluted high concentration of 3.3% NaCl – more concentrated than sea-water. Their cousin NM, 6.4 years, salt-wasting too, told us he learned to eat salt from them. Three of their siblings were controls, all healthy heterozygote carriers with normal salt appetite measures, so the behavior is specific to CAH within the families (Kochli et al., 2005. cf. Stein et al., 1996 for another example of salt preferences differing between siblings).

These observations suggest that eating salt among salt-wasting youngsters is not spontaneous, but an acquired strategy. Its first application might be prompted by advice from others, such as relatives with CAH or physicians. However, it seems that having once discovered the taste of salt, it is clearly delectable for these salt-wasting children.

Their descriptions do not suggest that they first used salt to ameliorate or prevent hyponatremic crisis spontaneously ('instinctively'), although it is likely that they were in chronic deficit, and may have quickly discovered that the salt improved their well-being, as it does for dehydrated exercisers within four exposures (Wald and Leshem, 2003).

The tenacity of this behavior in the salt-wasting children, the early age at which it is acquired, its persistence in the face of some parents' chagrin, and that nine of 14 salt-wasters were therapeutically unbalanced, i.e., they staked their health on salt rather than their medication, all suggest that although the appetite itself is not innate, there is a powerful predisposition to learn rapidly about the benefits of salt. It is as if the instant sodium accesses the receptors in blood vessels and brain of a body in need, the connection is made between sodium taste and relief, and the connection is permanent. Epstein termed this an organizational effect of the hormones and indeed, surging the hormones of sodium conservation angiotensin II and aldosterone, even in rats that have no access to salt, enhances their sodium appetite when salt is first offered months later (Epstein, 1991; Sakai et al., 1989). Indubitably these CAH children had experienced sodium deficit, although it is not known if their aldosterone levels can sustain the attendant surge. It is therefore possible that they were primed to love salt before they first experienced it as a distinct taste, precisely as the little girl related her kindergarten revelation. This acquisition of salt preference is reminiscent of the rapid learning of a conditioned taste preference

or aversion which is regarded as a biological predisposition (Rozin and Schulkin, 1990).

Now review the tragic case of DW, the boy who craved salt and water, often cited as indicative of salt appetite in humans. Denied his salt in hospital, the 3 1/2-year-old child was reduced to very defective behavior, vomiting, anorexia, and died within a week. In a poignant letter the dead boy's parents meticulously describe how he discovered salt on crackers at 12 months of age, the word and the salt-cellar at 18 months. Their narrative emphasizes the child's discovery and learning process. Wilkins and Richter (1940) who published the letter surmised that the child had survived until hospitalized by eating salt to compensate for his salt-wasting hyperplasic adrenal glands.

Thus, learning to self-medicate with salt might be an inbred predisposition in humans.

The conclusions drawn from these analyses are that most people ingest their salt for a variety of reasons that may, or may not, coalesce into high salt intake. A unitary 'sodium appetite' as defined above, innate, regulatory and homeostatically relevant, does not appear necessary even in CAH. Rather, such unusual avidity for salt may be conditioned and learned, possibly on a fundament of biological predisposition activated by deficit, to provide the extraordinary quantities of sodium CAH requires.

5. The origins of individual difference in salt appetite in humans

5.1. Ontogeny of salt appetite

Early development is considered to be a crucial period for establishing individuality in behavior and we have evidence that it may similarly determine individual differences in salt preference.

The newborn rat barely tastes salt, enormous concentrations (1–2 M (1 M is approximately twice the concentration of sea water, or six times the generally preferred level of salt in soup)) are required to elicit responses (Bernstein and Courtney, 1987; Hill and Mistretta, 1990; Leshem and Epstein, 1989; Leshem et al., 1994; Moe, 1986), yet, amazingly, its brain contains the circuits for sodium appetite. Kick-starting these with an injection of renin into the brain triggers the cascade of neurochemicals that stir sodium appetite, with increasing vigor with days postnatal. However, the pup's peripheral mediators of sodium appetite, those that sense the deficit, that taste sodium (at reasonable concentrations) and distinguish it from contiguous cations, that activate the hormones of sodium conservation, and that inform the brain of the life-threatening deficit, are not operative until a dozen days after birth, when the pup's eyelids first unfurl and its kidneys begin to secrete renin to sympathetic stimulation (Hill and Mistretta, 1990; Leshem, 1999; Kirby and Johnson, 1990).

We humans also do not start life with an obvious love of the salty, unlike the sweet. There has been adequate research to suggest that all neonates may not easily detect salt (Beauchamp et al., 1986; Harris and Booth, 1987; Harris et al., 1990; Birch, 1999), and earlier studies concluded that babies are indifferent or reject it (Crook, 1978; Desor et al., 1975b; Nowlis, 1973). However, as with sweet preference, there are individual differences already evident at 2–4 days of age, when about half the babies are indifferent to it at 0.3 M, about double the adult preferred concentration of salt in soup. The other babies divide into those that prefer it more, or less, than water (Zinner et al., 2002). At 2 months about half the babies already prefer salt at the lower concentration of 0.17 M, and fewer at the high concentration of 0.34 M (Stein et al., 2006) suggesting a developing sensitivity to its taste.

Both studies find that salt preference is related to birth weight although by 2 months the relationship is reversed and may dissipate gradually thereafter through 4 years (Stein et al., 2006) and is absent at 10–15 years (Shirazki et al., 2007). One might speculate that the postnatal obligate dehydration and hyponatremia of preterm babies (Haycock and Aperia, 1991; Al-Dahhan et al., 2002) might underlie this preference, consistent with the increase in salt preference at 16 weeks postnatal, imprinted by *in utero* electrolyte loss due to maternal vomiting during the pregnancy (Crystal and Bernstein, 1998). These researchers make the illuminating suggestion that the average indifference to salt reported in babies may, in fact, comprise babies averse and avid for salt, depending upon their mother's gestational history of sodium loss.

We note here the very early appearance of individual differences in salt palatability, their possible modulation by sodium flux pre- or neonatal, and the linkage to cardinal metabolic indicators such as birth weight and BP.

Other reports confirm the spontaneous liking of salt emerging at 4 months, and suggest that it develops as a maturational process and may already be buttressed by learning of salted foods, because by 2–3 years the preference for salt in food, e.g., soup, increases, while in parallel, the uniquely human aversion to salt in aqueous solution emerges (Beauchamp et al., 1986; Harris and Booth, 1987; Harris et al., 1990). Subsequently, at 3–11 years a preference for salt greater than that of adults emerges (Beauchamp et al., 1986, 1994; Beauchamp and Cowart, 1985, 1990; De Courcy et al., 1986; Desor et al., 1975b; Scientific Advisory Committee on Nutrition, 2003; Verma et al., 2007), possibly peaking in the teens (Nelson et al., 2007, Fig. 5).

A similar course of emerging, peaking, and lowered sodium appetite is described for suckling rat pups, except that in stark contrast to humans, it is entirely based on aqueous solutions (Leshem and Del Canho, 2005; Midkiff and Bernstein, 1983; Moe, 1986).

During childhood, studies on salt preference most consistently show that children learn to like specific foods, some of which may be salty or require salting such as the salt "sweets" so beloved of the Dutch and Swedes but horrendously unpalatable to others. However, all caution that there is no evidence for the generation of a general salt liking (Beauchamp and Moran, 1982; Beauchamp et al., 1991; Birch, 1999; Harris et al., 1990; Kanarek et al., 1995; Sullivan and Birch, 1990).

There is a pervasive and persistent notion that "mere exposure" to dietary sodium, particularly early exposure, increases its adult attraction, and primarily accounts for human salt intake. This is difficult to determine in humans, but a plethora of studies exposing rats, from *in utero* to adolescence, to high dietary salt have failed to

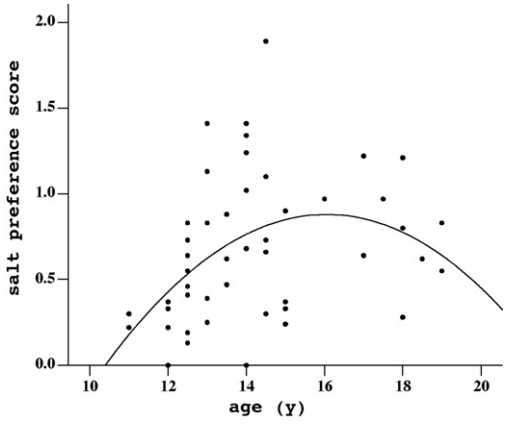

Fig. 5. Salt preference in teens. ($r = 0.64$, $p < 0.02$: further analysis of data from Leshem (1998)).

Table 4
Perinatal "mere exposure" to high salt diet in rats

Reference	Dietary sodium level and duration	Sodium appetite	Specificity[a]	Critical variable
Contreras and Kosten, 1983.	Low, medium high gestation to weaning	↑	Non-specific	
Bird and Contreras, 1987.	Low, medium high gestation to lactation	↑	No control	
Contreras and Ryan, 1990	High salt diet gestation to lactation	↑	No control	
Curtis et al., 2004.	Low, medium, high gestation to lactation	No change	Water	↑ Only after dietary Na^+ deprivation
Vijande et al., 1996.	(1) partial aortal ligature, (2) high salt diet gestation to lactation	↑	No control	Dietary or hormonal exposure?
Myers et al., 1985.	High salt diet during gestation	↓	No control	Depends on strain
Midkiff and Bernstein, 1983.	Low, medium high sodium weaning to adulthood	No change	No control	
Przekop et al., 1990.	Sodium restriction	↓ No change	No control	One exposure to sodium reverses the effects
Mouw et al., 1978.	Sodium restriction from preconception to lactation	↓ No change	Fluids	Depends on gender
Smriga et al., 2002	One application of salt milk to neonate tongue	↑	Non-specific: salt and sweet	
Erkadius et al., 1996	Embryo-cross-transferred SHR and WKY	↑↓	Hypertensive strain	Depends on strain of womb
McBride and Flynn, 2007	High sodium conception to weaning	↑	WKY not SHR	Depends on strain

[a] Whether another comparison tastant or fluid was used to establish specificity of the effect to sodium. Arrows indicate increased or decreased sodium appetite.

reveal a systematic, sodium-specific, relationship to long-term salt preference, severely undermining this notion (Table 4).

Similarly, in humans, studies on the determinants of individual variability in salt preference and intake concentrating on early, even fetal, exposure or acculturation, particularly in infancy, have failed to reveal a contribution to individual variability in later salt preference (Beauchamp and Moran, 1982, 1984; Cowart and Beauchamp, 1986; Harris et al., 1990, Mattes, 1997). No relationship was found between maternal dietary salt intake and offspring salt intake (Beauchamp and Moran, 1984) or between a mother's preferences during pregnancy for sweet and salty foods and her adolescent offspring's preferences (Leshem, 1998), unlike for other flavors (Mennella et al., 2001). The relationship between parental and offspring food preferences seems generally tenuous (Rozin, 1991), but may firm with age (Birch, 1999).

Studies in the 80's showed consistently that manipulations to increase or decrease salt intake for weeks, respectively, increase or decrease preference for salted items (Beauchamp et al., 1983; Bertino et al., 1982, 1986; DiNicolantonio et al., 1984; Teow et al., 1985–1986). But whether the acute preference for a single salted test item translates to a generalized voluntary increased intake of sodium is quite uncertain (Drewnowski et al., 1996; Pangborn and Pecore, 1982).

In sum, from birth, babies taste salt at high concentrations, some prefer it to water, others are averse. There is some evidence that even this early preference can be increased by the physiology of reduced sodium *in utero* or neonatally, but no evidence that an aversion to sodium can be increased. The preference matures, climaxing in a high intake in childhood and in adolescence. The contribution of learning, while evident at 4 months, seems limited to specific salty foods, and there is no good evidence that 'mere exposure' promotes salt intake.

This ontogenetic course is not trivial: by 5 years of age children ingest more than double the recommended amounts (De Courcy et al., 1986; Kallio et al., 1998).

5.2. Perinatal determinants of salt liking

The doyen researcher of human salt appetite has stated "we know of no reason for intake of salt in humans" (Beauchamp, 1987; Beauchamp et al., 1982), supported more recently by a similar statement that "the basis for the high, apparently need-free, sodium chloride ingestion ... has not been established" (Mattes, 1997).

However, the source of individual variation in salt appetite is now partially understood. We owe the most significant breakthrough to Stelios Nicolaidis and Olivier Galaverna who modeled maternal vomiting specifically as sodium loss in pregnant rats and demonstrated that the offspring had enhanced sodium appetites, an effect dependent upon AII activation (Galaverna et al., 1995; Nicolaidis et al., 1990). Crystal and Bernstein (1995, 1998) made the translational leap and showed the effect in humans, the first discovery of a determinant of salt preference in humans. Surprisingly, this enduring enhancement of sodium palatability following on putative perinatal sodium privation is the most replicated determinant of the human love of salt. It is consequent upon sodium loss *in utero* by maternal vomiting during pregnancy (Crystal and Bernstein, 1995, 1998; Leshem, 1998; Kochli et al., 2005) or upon infantile vomiting and diarrhoea (Kochli et al., 2005; Leshem, 1998), or to electrolyte-deficient infant formula (Stein et al., 1996), or to neonatal hyponatremia (Shirazki et al., 2007) and possibly neonatal furosemide (Leshem et al., 1998).

In analyzing data from 200 participants in our various studies (Kochli et al., 2005; Shirazki et al., 2007; Bracha et al., 2003; Dally Farah et al., 2003) we find that prenatal and childhood putative sodium loss (recorded neonatal hyponatremia and recall of pre- and postnatal vomiting and diarrhea) account for some 16% of the variance in dietary sodium intake (Fig. 6). It also correlates

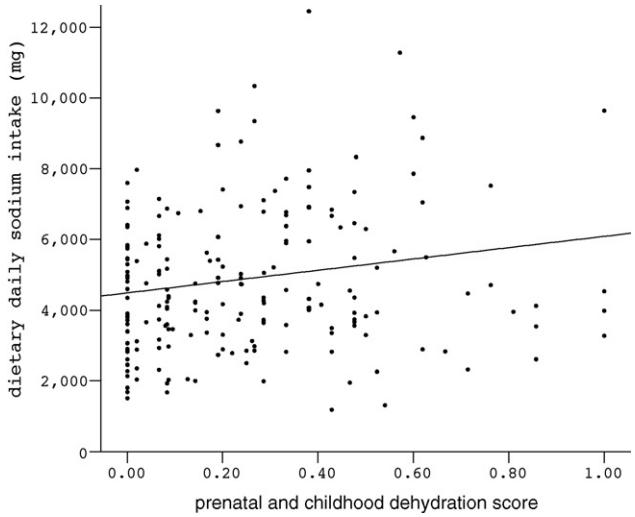

Fig. 6. The relationship of daily dietary sodium intake and prenatal and childhood putative sodium loss (expressed as a proportion of greatest score). $r = 0.40$, $p < 0.05$, $n = 200$.

inversely with dietary sweet carbohydrates, $r = -0.23$, $p < 0.05$, $n = 122$.

Much of the human data are based on recall from years or decades earlier; however, pediatricians monitor blood sodium levels in preterm infants of less than 32–35 weeks gestation or less than 1500 g at birth, because they have obligate high renal and intestinal sodium losses during the first fortnight of life, leading to cumulative negative sodium balance in most, and hyponatremia in many (Al-Dahhan et al., 2002; Haycock and Aperia, 1991). Using data from medical records we showed that a single measurement, the lowest neonatal serum sodium, was robustly related to dietary sodium intake assessed in children 10–15 years old (controlled for gestational age, birth weight, frequency of diuretic therapy, and did not predict intake of any other dietary electrolyte or macronutrient). This was true for boys or girls, Arab or Jewish. Arab and Jewish diets differ, but tellingly, in each diet different foods supplied the sodium that correlated with the lowest neonatal sodium. The effects were evident in a relatively small sample ($n = 41$), and were portentous - the children who 8–15 years earlier were most hyponatremic, ingested ~1700 mg *more* sodium per day (Shirazki et al., 2007).

Infant sodium deficiency has long-term adverse effects on the child's development and health, and in preterm neonates has been linked to long-term and wide-ranging impairments, motor, audioneurological, growth, cognitive, and affective. It has been suggested that sodium plays an important role in early growth by stimulating protein synthesis and cell proliferation and mass, so that deprivation of NaCl in these early developmental stages leads to reduced body and brain weight (Al-Dahhan et al., 2002; Chevalier, 2001; Ertl et al., 2001; Haycock, 1993; Haycock and Aperia, 1991; Law et al., 2002; Martin et al., 2005). Conversely, the restorative capacity of sodium is well known and in preterm neonates sodium supplementation is routinely practiced, and has been found to improve performance in tests of IQ, motor function, memory and language skill (Al-Dahhan et al., 2002), and prevent the accelerated weight gain that typifies preterm and low birthweight children (Barker and Bagby, 2005; Bateson et al., 2004; Haimov-Kochman, 2005; Haycock, 1993).

In rats too, perinatal sodium loss enduringly increases sodium appetite after varied instances of perinatal mineralofluid loss: offspring of dams that during pregnancy were dehydrated, lost sodium, had the hormones or receptors of sodium conservation activated, or rats that were acutely sodium deprived postnatally, all show increased sodium intake in adulthood (Arguelles et al., 1999; Butler et al., 2002; Galaverna et al., 1995; Leshem, 1999; Leshem et al., 1996; Nicolaidis et al., 1990; Vijande et al., 1996). We have failed to enhance long-term sodium appetite in only one experiment, after intracerebroventricular injection of renin in rat pups (Leshem and Maroun, unpublished).

The likely common substrate for these effects is perturbation of the developing renin–angiotensin–aldosterone system leading to greater neonatal salt loss and long-term increases in sodium appetite (Arguelles et al., 1999; Epstein, 1991; Galaverna et al., 1995; Vijande et al., 1996). It has long been recognized that sodium depletion enlists the renin–angiotensin–aldosterone system, primarily central but also peripheral, to increase sodium intake, and the same system may program the long-term increase in sodium appetite (Epstein, 1991; Na et al., 2007; Sakai et al., 1989; Schulkin, 1991) even if activated *in utero* (Arguelles et al., 1999; Galaverna et al., 1995; Vijande et al., 1996).

It has been proposed that such perinatal alterations, occasionally referred to as 'programming' or 'imprinting', may be adaptive, specifically in increasing sodium appetite to anticipate recurring challenge (Epstein, 1990; Fessler, 2003; Leshem, 1999; Ross and Desai, 2005; Ross et al., 2005) or more generally to meet future cardiovascular or hydrational challenges (Alexander, 2006; Barker and Bagby, 2005; Bateson et al., 2004).

Note that we have suggested above that sodium deficit in *adult* humans is not followed by an enduringly enhanced penchant for salt. Human babies are on an evolutionary continuum of hedonic facial responses to tastes including salt (Crystal and Bernstein, 1998; Steiner et al., 2001). It is thus possible that the perinatal potential for enhancement is an evolutionary relic of sodium appetite that is lost with age, as are some early responses and reflexes.

In sum, it is now clear that perinatal sodium loss, from a variety of causes, is a consistent and significant contributor to long-term sodium intake. Neonatal serum sodium may be one marker of future sodium intake, and clinicians might wish to appraise families of neonates with low serum sodium of the risks for early increased sodium intake, its recognition, management, and implications (De Courcy et al., 1986; Kallio et al., 1998).

5.3. Adult determinants of salt liking

Other causes of individual variation in salt preference have been considered. Stress is related to the neuro-endocrine systems subserving sodium homeostasis, personality traits are the archetypal expression of behavioral variability, and habit is a biobehavioral expression of constancy. The relationship of culture to biological determinants of behavior is moot and hence beyond the scope of this discussion, but some perspective on its relative contribution to sodium intake might be useful.

5.3.1. Stress

The possibility that stress enhances salt intake is an attractive hypothesis, primarily because of the association of adrenal corticoids with both salt appetite and stress response, but also because of the association of stress, salt intake and hypertension. Indeed in laboratory rats and sheep, but not pigs, ACTH administration increases sodium intake (Denton et al., 1984b; Jankevicius and Widowski, 2003; Weisinger et al., 1980), but for humans the results are quite clear – no increase in salt intake obtained after experimental stress in medical students, or when cortisol was administered for 5 days raising blood pressure and body weight (Miller et al., 1998; Wong et al., 1993) or after an exam, when stress scores were significantly higher (Fig. 7). What has not been adequately addressed empirically is the possibility that chronic stress increases salt intake (Denton et al., 1984a; Henry, 1988).

5.3.2. Personality

The notion that salt intemperance reflects personality has received some attention. Using a variety of personality tests to

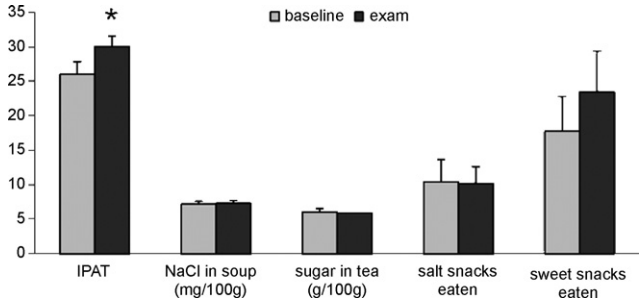

Fig. 7. Spontaneous salt appetite assessed some weeks before or after exams (baseline, grey) compared with immediately after an exam in 17 students (exam, black). Immediately after exams, stress (IPAT questionnaire) is increased (*$p < 0.0001$), but preference for salt (or sweet) is not altered (Leshem, unpublished).

correlate with a variety of measures of taste preference, high hostility students and those who felt that chance or others controlled their health, put more salt in a test soup. Lower neuroticism, extraversion, tough poise (compulsivity) and anxiety correlated with some measures of salt preference but not with others, or with total intake, and correlations with sweet preference were similarly vague, although a recent report indicates that participants high in novelty seeking show strong preference for salty tastes (Day et al., 2008; Miller et al., 1998; Shepherd and Farleigh, 1986; Stone and Pangborn, 1990). Considering the multitude of questions in a personality questionnaire, the sparse and inconsistent correlations with salt preference are probably spurious, and do not support salt preference as a trait integrated with our personality. However, beliefs about salt, and specifically its health implications, do affect sodium intake and bridge personality and culture (Phillips et al., 1985; Shepherd and Farleigh, 1986; Smith et al., 2006).

5.3.3. Culture

The cultural contribution to sodium intake patently separates humans from rats and other animals and therefore cannot be treated in depth in our quest for the biological underpinnings of our love of salt (Jones, 1923; Kurlansky, 2003; Mattes, 1997; Rozin and Schulkin, 1990). Availability of salt can be a compounding variable – salt intake can be boosted where commercially prepared food with high sodium content contributes significantly to intake even though it may be insensible (De Courcy et al., 1986; He and MacGregor, 2002; Mattes et al., 1990; Nelson et al., 2007; Shepherd et al., 1989), or it can be negligible where environmentally scarce (Cordain et al., 2002; Lozada et al., 2007; Mattes, 1997; Oliver et al., 1975). Our own studies have shown that in a unique society in unique environs, the Negev Desert Bedouin, salt preference and intake is high. It is possible that the parched environment has promoted sodium intake to reinforce hydration. Yet this high salt appetite is maintained in urban Bedouin for at least a generation after the environs change from a nomad tent to an urban house, from a weekly journey to the grocer's to one across the street, and from salted to refrigerated preservation of food (Leshem et al., 2008, Table 5). In contrast to the constancy of this dietary culture, we have found disparate levels of dietary sodium in three different Galilean communities within a 20 km radius where foodstuffs, their price and availability, are identical (Table 6). Similar differences between African and Caucasian American communities are well known in the USA (Smith et al., 2006).

Table 5
Diet of Bedouin encampment women, urban Bedouin women, and urban Jewish women (n)

daily intake	encampment Bedouin (30)	Urban Bedouin (15)	Urban Jewish (15)
energy (kcal)	3470 ± 285**	3304 ± 198*	2307 ± 211
fat (g)	117.3 ± 9.6*	131.5 ± 10.0 **	84.2 ± 8.8
protein (g)	158.7 ± 10.5***	151.2 ± 10.1*	108.9 ± 7.7
CHO[1] (g)	484.1 ± 43.1***	408.2 ± 23.2*	275.8 ± 26.0
Na^+ (mg)	6717 ± 491*	6886 ± 618*	4574 ± 811
K^+ (mg)	4125 ± 245***	3851 ± 200**	2697 ± 219
Ca^{++} (mg)	1741 ± 124***†	1327 ± 117	1016 ± 86
Fluid (ml)	2444 ± 164*	2437 ± 169*	2001 ± 178

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, Bedouin differ from Jewish women. †$p < 0.05$, different from urban Bedouin. [1]Carbohydrates (derived from Leshem et al., 2008).

Table 6
Mineral and macronutrient composition of three ethnic diets in the Galilee in 2006

Daily Intake	Christian	Moslem	Druze
energy (KC)	1969 ± 177^{dmm}	3197 ± 207^{ddcc}	2533 ± 118^{mmc}
protein (g)	92 ± 7^{dmm}	121 ± 7^{cc}	117 ± 6^{c}
fat (g)	84±7	100±5	86±5
CHO (g)	228 ± 21^{ddmm}	465 ± 33^{ddcc}	340 ± 19^{mmcc}
Na^+ (mg)	3550 ± 420^{mm}	5030 ± 371^{cc}	4275±365
K^+ (mg)	2290 ± 212^{mmdd}	3198 ± 193^{cc}	3330 ± 233^{cc}
Ca^{++} (mg)	651 ± 55^{m}	878 ± 43^{dc}	670 ± 97^{m}
Age (y)	32.0±1.3	29.5±1.2	32.2±1.8
BMI (kg/m^2)	23.2±0.5	23.1±0.7	25.2±1.0

$n = 25$ Women in each group. c,m,d, different from Christian (Nazareth), Moslem (Abu Alhija) and Druze (Abu Snan), respectively, $p < 0.05$, double letters: $p < 0.01$ (Leshem, unpublished).

Thus, salt intake is robustly and doubly dissociated from environment by culture: resistant to extreme alterations in environment and availability, yet differing where environment and availability are identical. How culture exerts its powerful influence on salt intake is not entirely clear, but it is does seem that sodium is but one component of an individual's diet, bound to its culturally determined composition.

Possibly too, 'mere exposure' may have a different dynamic in the cultural domain of humans from its indeterminate effects in the laboratory rat (above, and Table 4).

5.3.4. The salt habit

Although we may not fully know how our love of salt arises, one of the mechanisms proposed for its perpetuation is habit (Greenfield et al., 1983; Mittelmark and Sternberg, 1985). "When habits are formed, subsequent behavior may be associated with, and automatically triggered by, the specific situational cues that normally precede it" (Aarts et al., 1997; Kremers et al., 2007; Robinson and Berridge, 2003). Certainly, mealtime is a stew of situational cues and well-practiced habits determining preferences and amount ingested, of which salt is probably an integral ingredient (e.g., Booth, 1994; De Castro, 1996; Smith, 1996).

Such descriptions fit the observed habitual use of the salt shaker. Habit is generally accepted as determining voluntary salt intake, and there is experimental support for that. Changing salt-cellar hole size does not alter the motor pattern of salting (Greenfield et al., 1983), and the motor habit is also anchored in eating ritual since most people consistently salt either before tasting their food or after it, a minority before and after, and only a much smaller minority do so inconsistently (Mittelmark and Sternberg, 1985).

Habit might also extend beyond motor patterns to an habitual favored level of tasted saltiness, because when levels of tasted salt, high or low, are imposed, respectively, increased and decreased salt preference often persists beyond the period of imposition (Beauchamp et al., 1983, 1986, 1987; Bertino et al., 1982, 1986; Blais et al., 1986; DiNicolantonio et al., 1984; Mattes, 1997; Teow et al., 1985–1986), but this does not occur if changes in dietary salt are not tasted (Bertino et al., 1986; Huggins et al., 1992).

The relevant question for our discussion is whether the salt habit can be related to a regulatory function. Salt-cellar use is often indiscriminate, applied to the whole plate, rather than specific foods thereon. This observation could suggest that the habit is an indiscriminate means to obtain salt. However, it could also be a sprinkling of a general taste enhancer, unrelated to a sodium-

regulatory function. A regulatory function is also less likely because salt-cellar use compensates inadequately for reduced dietary intake of sodium (Beauchamp et al., 1987; Shepherd et al., 1989; Bertino et al., 1982, 1986; Pangborn and Pecore, 1982; Greenfield et al., 1983; Cowart and Beauchamp, 1986, 1991; Harris et al., 1990; Ayya and Beauchamp, 1992; Beauchamp, 1987; Kanarek et al., 1995).

Nevertheless, some caution is required here because all these tests are acute. It is quite likely that in time people adjust their motor or taste habits in response to alterations in sodium availability as they may do so even to untasted sodium supplementation or reduction (Huggins et al., 1992; Mattes and Donnelly, 1991).

A salt habit can also be established because sodium can be an important reinforcer – this typifies athletes who take salted drinks that are often initially aversive. The consequences of sodium intake after exertion are well documented: faster rehydration, recovery and well being (Valentine, 2007; Nose et al., 1988; Wald and Leshem, 2003).

Even more than a habit, the excess and persistent intake of salt is occasionally viewed as addictive (Tekol, 2006), more often in colloquial discourse. However, there is no experimental study of a putative sodium addiction, and there are good arguments for dissociating a habit such as salt intake from addiction (Robinson and Berridge, 2003).

6. Summary and conclusions

Table 7 summarizes much of the information on the putative determinants of salt intake in humans.

To understand the pervading preference we humans have for salt in our food, we queried whether it is the biological imperative familiar from animal sodium appetite, which is well understood. The biological foundations of sodium requirement and the physiological systems managing it are so robust and shared by humans and animals to such a degree that makes it difficult to envisage how the behavior, love of salt, so intimately involved in these systems in animals, could be unrelated to them in humans. Yet the differences between the human and animal drive for salt suggests that, in the main, salt intake in humans is not related to sodium appetite.

In considering the human avidity for salt, we explain that while physiological flux can increase the palatability of salt in the long-term as in perinatal sodium deficit, and in the short-term, as by conditioning to a state of sodium need, it is not broadly consistent with what we know of the physiological basis of sodium appetite in animals, namely the fine tuning of drinking, salt intake, and physiological need, the immediate response to sodium deficit, the selectivity for the sodium ion, etc.

We trace the development of salt preference from the neonate into a peak adolescent preference, but can provide only a partial explanation in the developing sensitivity to the taste of sodium. We also recognize the obvious contribution of culinary culture to our intake of sodium, partly by teaching love of specific salty dishes, partly by involuntary intake of salt in prepared foods, and partly as a component of our dietary preferences, yoked, *inter alia*, to caloric intake and sweet preference.

For the determination of individual differences in salt preference, they are already evident spontaneously in the baby, although we do not know whether they persist into childhood and beyond. However, early homeostatic challenges tapping an innate predisposition to learn the protective potential of salt prime its palatability for the long-term, possibly by reinforcing subsequent learning. We suggest that an enhanced love of salt in people who are dependent upon it for survival in congenital adrenal

Table 7
Putative lifelong determinants of human salt appetite

Epoch	Event	Contribution	References
Prenatal	Maternal vomiting	Increases long-term sodium appetite Ages 4 months, and 9–22 years Reduces sodium taste threshold 9–21 years	Crystal and Bernstein (1995, 1998); Leshem et al. (1998) Leshem et al. (1998, 2005). Malaga et al. (2005).
Neonatal	Birth-weight	Increases salt preference 48h Reduces salt preference 2–48 mo	Zinner et al. (2002). Stein et al. (2006).
	Individual variation	Preference, indifference, aversion	Crystal and Bernstein (1998); Stein et al. (2006); Zinner et al. (2002).
	Diuretic treatment, low serum sodium	Increases dietary sodium 6–15y	Leshem et al., 1998; Shirazki et al., 2007.
Infancy	Vomiting, diarrhea, dehydration, Salt-wasting (CAH)	Increases sodium appetite 9–22 y	Leshem, 1998; Kochli et al., 2005.
	Chloride deficient infant formula	Increases sodium appetite in adolescence	Stein et al., 1996.
Childhood	Learning	Specific foods and contexts	Beauchamp (1987), Beauchamp et al. (1990,1991), Harris and Booth (1987), Harris et al. (1990), Kochli et al. (2005); Sullivan and Birch (1990).
Adulthood	High salt diet	Increased mineral preference Reduced voluntary salt intake (acute)	Teow et al. (1985). Huggins et al. (1992).
	Low salt diet	Reduced sodium preference	Beauchamp (1987); Mattes (1997).
	Exercise and sweat loss	Increased preference (acute?)	Takamata et al. (1994), Leshem et al. (1999), Wald and Leshem (2003).
	Hemodialysis	Increased preference (acute)	Leshem and Rudoy (1997).
	10 Days diuresis	Increased preference, not intake (acute)	Beauchamp et al., 1990.
	Births, hyperhydrosis, repeated dehydration, hemorrhage.	No effects	Leshem, unpublished
Lifetime	Personality	No effects	
	Habit	Salt shaker – small contribution Habitual saltiness of food?	Greenfield et al. (1983), Mittelmark and Sternberg (1985). Beauchamp et al. (1983, 1986, 1987), Bertino et al. (1982, 1986), Blais et al. (1986); DiNicolantonio et al. (1984); Mattes (1997); Teow et al., 1985-1986
	Culture	Influences intake and preference	Leshem et al. (2008); Smith et al. (2006).

hyperplasia is thus best understood as learned, catalysed by a biological predisposition for such learning.

In adults, depletion may no longer imprint an enhanced salt appetite, pointing to a perinatal developmental window for increasing lifelong salt intake. In adulthood, specific situational challenges of sodium loss (such as in exercise-induced perspiration) reinforce learning of contingent, specific, salt resources (e.g., isotonic drinks), but we have no evidence that it generalizes to a salt appetite.

We note that men ingest substantially more salt than women, show that this is true relative to body weight too, and that this has not been researched.

Once salting preferences are established, habit may perpetuate them, for example, hampering recommendations to reduce sodium intake.

From the realm of animal research, Alan Epstein has elaborated the fundamental theoretical framework for understanding salt appetite and its various aspects as an adaptive behavior, proposing that the need-free spontaneous avidity for salt is regulatory, motivating the sodium-dependent animal to maintain adequate intake, but simultaneously to seek and learn about sources of sodium in its surroundings. He further suggested that the enhanced appetite, that ensuing from instances of sodium deprivation, is an expression of biological preparedness, hormonally organized, working as a hedge against a recurring salt deficit in an environment of proven scarcity, by further prioritizing the seeking and memorizing of sodium resources (Epstein, 1990, 1991). These ideas have been developed, and Schulkin (2003) has recently argued elegantly for the enhanced spontaneous sodium appetite, as a prime example of allostasis: homeostasis broadened to encompass preparedness and anticipatory responses. The specific mechanism may be enhanced palatability, so that sodium need, long past, nevertheless determines contemporary sodium palatability (Yeomans et al., 2004). Fessler (2003) carries these ideas to the realm of human salt avidity suggesting that "high salt intake may provide protection against sudden dehydration" and "that an adaptive mechanism calibrates salt preference as a function of the risk of dehydration as indexed by past dehydration events and maternal salt intake" (although we have seen that maternal salt intake does not determine offspring salt intake, it is maternal sodium loss that does so) and puts forth the novel idea that salt appetite may also have evolved as protection against the many pathogens that can cause catastrophic fluid loss.

I suggest that environmental scarcity might be extended to include an individual's vulnerability to sodium privation, for example, a tendency to dehydration, hyperthermia, perspiration, diarrhea, or vomiting, whether of constitutional or behavioural origins (Yeomans et al., 2004). Thus, it is possible that individual differences in retention of minerals and fluids under challenge of heat or dehydration comprise an internal milieu that triggers adaptive salt preference, as does a sodium-scarce ecology in animals.

Evolutionary notions have also been applied to suggest how high sodium intake may have been selected among African-Americans as survivors of the horrendous privations of the slave ships (Grim and Robinson, 2003), though this suggestion is highly controversial (Kaufman and Hall, 2003).

Currently, it would seem that the contribution of evolution to the human avidity for salt is that expressed enduringly after early hyponatremic challenge, and the specialized, learned response to the restorative powers of salt after sodium loss.

The predominant contributors must be cultural and culinary and comprise the many salty dishes of our learned diet, those due to sodium's' unique taste modulating properties acting on the multitude of items where our diet is varied, those due to salt being a universal seasoner, along with sugar, fats and oils, pepper, and other seasonings typifying specific cultures. By these means the majority of our sodium intake is yoked to our dietary intake (including untasted sodium, the main source).

The human love of salt is thus multifactorial in origin, but most salt intake of most people contradicts the adaptive rationale, perhaps in analogy to the rampant hyperphagia of today.

Salt appetite in humans differs in important ways from hunger and thirst. Hunger and thirst are mainly expressed through conscious effort. In contrast, sodium ingestion is mostly unconscious and habitual. There is no spontaneous situation in which a human will exclaim "I could eat a spoonful of salt right now!" It is so profoundly unconscious that we have no extant name for it, other than the cumbersome and technical "sodium appetite".

Hence, I argue that humans do not have a sodium appetite as we know it in animals, leaving us with a rather limited understanding of why humans ingest so much salt.

One heretical possibility – emanating from the intense drive for salt we have, our resistance to reducing its intake, and the argument of the 'wisdom of the body' as we know it from animals – is that human excess salt intake is not such at all. While it certainly exceeds the requirements of a static model of physiological sodium balance as we know it (some 500 mg/d, Dietary Reference Intakes for Water, 2004), it may be that our bodies require a higher sodium turnover. The fact that some populations survive on extremely low levels of sodium is no argument against this hypothesis: it is a safe assumption that their health (other than possibly hypertension), growth, size, longevity, and that of their offspring are lesser than people in most of the high sodium societies, and the environment they contend with is very different. A number of studies have shown that surreptitious reduction of dietary sodium over days or weeks induces a partial compensatory response – whether the reduction is severe or mild, some of the deficit is made up by voluntary means (e.g., salt-cellar), but note that even this partial compensatory behavior maintains sodium intake well above the conventionally accepted sodium requirement (Beauchamp et al., 1987; Shepherd et al., 1989). Using the adaptive rationale, might we assume that there is some utility to this obdurate defense of excess? Could it somehow be related to the processing or absorption of the enormous and varied amounts of food we ingest, to the stress, well-being, or mental functioning in lifestyles attendant on high sodium societies (Denton et al., 1984b; Johnson and Grippo, 2006; Henry, 1988; Wald and Leshem, 2003)?

Innovative research is called for to understand and control the human penchant for salt.

References

Aarts, H., Paulussen, T., Schaalma, H., 1997. Physical exercise habit: on the conceptualization and formation of habitual health behaviours. Health Educ. Res. 12, 363–374.

Al-Dahhan, J., Jannoun, L., Haycock, G.B., 2002. Effects of salt supplementation of newborn premature infants on neurodevelopmental outcome at 10–13 years of age. Arch. Dis. Child. Fetal Neonatal Edn. 86, 120–123.

Alderman, M.H., 2004. Dietary sodium and cardiovascular health in hypertensive patients: the case against universal sodium restriction. J. Am. Soc. Nephrol. 15, S47–S50.

Alexander, B.T., 2006. Fetal programming of hypertension. Am. J. Physiol. Regul. Integr. Comp. Physiol. 290, R1–R10.

Arguelles, J., Brime, J.I., Lopez-Sela, P., Perillan, C., Vijande, M., 1999. Adult offspring long-term effects of high salt and water intake during pregnancy. Horm. Behav. 37, 156–162.

Ayya, N., Beauchamp, G.K., 1992. Short-term effects of diet on salt taste preference. Appetite 18, 77–82.

Bachmanov, A.A., Beauchamp, G.K., Tordoff, M.G., 2002. Voluntary consumption of NaCl, KCl, CaCl2, and NH_4Cl solutions by 28 mouse strains. Behav. Genet. 32, 445–457.

Barker, D.J., Bagby, S.P., 2005. Developmental antecedents of cardiovascular disease, a historical perspective. J. Am. Soc. Nephrol. 16, 2537–2544.

Bartoshuk, L.M., 2000. Comparing sensory experiences across individuals, recent psychophysical advances illuminate genetic variation in taste perception. Chem. Senses 25, 447–460.
Bartoshuk, L.M., Duffy, V.B., Lucchisodium, L.A., Prutkin, J., Fast, K., 1998. PROP (6-*n*-propylthiouracil) supertasters and the saltiness of NaCl. Ann. N.Y. Acad. Sci. 855, 793–796.
Bateson, P., Barker, D., Clutton-Brock, T., Deb, D., D'Udine, B., Foley, R.A., Gluckman, P., Godfrey, K., Kirkwood, T., Lahr, M.M., McNamara, J., Metcalfe, N.B., Monaghan, P., Spencer, H.G., Sultan, S.E., 2004. Developmental plasticity and human health. Nature 22, 419–421.
Beauchamp, G.K., 1987. The human preference for excess salt. Am. Sci. 75, 27–33.
Beauchamp, G.K., Bertino, M., 1985. Rats (*Rattus norvegicus*) do not prefer salted solid food. J. Comp. Psychol. 99, 240–247.
Beauchamp, G.K., Cowart, B.J., 1990. Preference for high salt concentrations among children. Dev. Psychol. 26, 539–545.
Beauchamp, G.K., Bertino, M., Moran, M., 1982. Sodium regulation: Sensory aspects. J. Am. Diet. Assoc. 80, 40–45.
Beauchamp, G.K., Moran, M., 1982. Dietary experience and sweet taste preference in human infants. Appetite 3, 139–152.
Beauchamp, G.K., Moran, M., 1984. Acceptance of sweet and salty taste in 2-year-old children. Appetite 5, 291–305.
Beauchamp, G.K., Bertino, M., Engelman, K., 1983. Modification of salt taste. Ann. Intern. Med. 98, 763–769.
Beauchamp, G.K., Cowart, B.J., 1985. Congenital and experiential factors in the development of human flavor preferences. Appetite 6, 357–372.
Beauchamp, G.K., Cowart, B.J., Moran, M., 1986. Developmental changes in salt acceptability in human infants. Dev. Psychobiol. 19, 17–25.
Beauchamp, G.K., Bertino, M., Engelman, K., 1987. Failure to compensate decreased dietary-sodium with increased table salt usage. J. Am. Med. Assoc. 258, 3275–3278.
Beauchamp, G.K., Bertino, M., Burke, D., Engelman, K., 1990. Experimental sodium depletion and salt taste in normal human volunteers. Am. J. Clin. Nutr. 51, 881–889.
Beauchamp, G.K., Bertino, M., Engelman, K., 1991. Human salt appetite. In: Friedman, M.I., Tordoff, M.G., Kare, M.R. (Eds.), Appetite and Nutrition. Dekker, New York, pp. 85–107.
Beauchamp, G.K., Cowart, B.J., Mennella, J.A., Marsh, R.R., 1994. Infant salt taste, developmental, methodological, and contextual factors. Dev. Psychol. 27, 353–365.
Bernstein, I.L., Courtney, L., 1987. Salt preference in the preweanling rat. Dev. Psychobiol. 20, 443–453.
Berridge, K.C., Schulkin, J., 1989. Palatability shift of a salt associated incentive during sodium depletion. Q. J. Exp. Psychol. 41B, 121–138.
Berridge, K.C., Flynn, F.W., Schulkin, J., Grill, H.J., 1984. Sodium depletion enhances salt palatability in rats. Behav. Neurosci. 98, 652–660.
Bertino, M., Beauchamp, G.K., Riskey, D.R., Engelman, K., 1981. Taste perception in three individuals on a low sodium diet. Appetite 2, 67–73.
Bertino, M., Beauchamp, G.K., Engelman, K., 1982. Long-term reduction in dietary sodium alters the taste of salt. Am. J. Clin. Nutr. 36, 1134–1144.
Bertino, M., Beauchamp, G.K., Engelman, K., 1986. Increasing dietary salt alters salt taste preference. Physiol. Behav. 38, 203–213.
Bertino, M., Tordoff, M.G., 1988. Sodium depletion increases rats' preferences for salted food. Behav. Neurosci. 102, 565–573.
Birch, L.L., 1999. Development of food preferences. Annu. Rev. Nutr. 19, 41–62.
Bird, E., Contreras, R.J., 1987. Maternal dietary NaCl intake influences weanling rats' salt preference without affecting taste nerve responsiveness. Dev. Psychobiol. 20, 11–130.
Blair-West, J.R., Carey, K.D., Denton, D.A., Weisinger, R.S., Shade, R.E., 1998. Evidence that brain angiotensin II is involved in both thirst and sodium appetite in baboons. Am. J. Physiol. 275, R1639–R1646.
Blais, C.A., Pangborn, R.M., Borhani, N.O., Ferrell, M.F., Prineas, R.J., Laing, B., 1986. Effect of dietary sodium restriction on taste responses to sodium chloride: a longitudinal study. Am. J. Clin. Nutr. 44, 232–243.
Blundell, J.E., Stubbs, R.J., Hughes, D.A., Whybrow, S., King, N.A., 2003. Cross talk between physical activity and appetite control: does physical activity stimulate appetite? Proc. Nutr. Soc. 62, 651–661.
Booth, D.A., 1994. Integration of sensory, somatic and social determinants of appetite for food and drink. Appetite 23, 197.
Booth, D.A., Mather, P., Fuller, J., 1982. Starch content of ordinary foods associatively conditions human appetite and satiation, indexed by intake and eating pleasantness of starch-paired flavours. Appetite 3, 163–184.
Boscoe, A., Paramore, C., Verbalis, J.G., 2006. Cost of illness of hyponatremia in the United States. Cost Eff. Resour. Allocation 4, 10.
Bowen, D.J., 1992. Taste and food preference changes across the course of pregnancy. Appetite 19, 233–242.
Bowen, D.J., Bernstein, I.L., 1999. Morning sickness and salt intake, food cravings, and food aversions. Physiol. Behav. 67, 181–187.
Bracha, A., Portnoy, F., Zach, G., Leshem, M., 2003. Salt appetite is not dependent upon taste-related sensory variables. Neural Plast. 10 (Suppl. 3), 188.
Breslin, P.A., Beauchamp, G.K., 1997. Salt enhances flavour by suppressing bitterness. Nature 387, 563.
Brown, J.E., Toma, R.B., 1986. Taste changes during pregnancy. Am. J. Clin. Nutr. 43, 414–418.
Butler, D.G., Pak, S.H., Midgely, A., Nemati, B., 2002. AT1 receptor blockade with losartan during gestation in Wistar rats leads to an increase in thirst and sodium appetite in their adult female offspring. Regul. Pep. 105, 47–57.
Capaldi, E.D., Privitera, G.J., 2007. Flavor-nutrient learning independent of flavor-taste learning with college students. Appetite 49, 712–715.
Chevalier, R.L., 2001. The moth and the aspen tree Sodium in early postnatal development. Kidney Int. 59, 1617–1625.
Chow, S.Y., Sakai, R.R., Witcher, J.A., Adler, N.T., Epstein, A.N., 1992. Sex and sodium intake in the rat. Behav. Neurosci. 106, 172–180.
Cohen, H.W., Hailpern, S.M., Fang, J., Alderman, M.H., 2006. Sodium intake and mortality in the NHANES II follow-up study. Am. J. Med. 119 (275), e7–e14.
Coldwell, S.E., Tordoff, M.G., 1996. Acceptance of minerals and other compounds by calcium-deprived rats 24-h tests. Am. J. Physiol. 271, R1–R10.
Contreras, R.J., 1977. Changes in gustatory nerve discharges with sodium deficiency, a single unit analysis. Brain Res. 121, 373–378.
Contreras, R.J., Kosten, T., 1983. Prenatal and postnatal sodium chloride intake modifies the solution preference of adult rats. J. Nutr. 113, 1051–1062.
Contreras, R.J., Ryan, K.W., 1990. Perinatal exposure to a high NaCl diet increases the NaCl intake of adult rats. Physiol. Behav. 47, 507–512.
Contreras, R.J., Kosten, T., Frank, M.E., 1984. Activity in salt taste fibers, peripheral mechanism for mediating changes in salt intake. Chem. Senses 8, 275–288.
Cordain, L., Eaton, S.B., Miller, J.B., Mann, N., Hill, K., 2002. The paradoxical nature of hunter-gatherer diets, meat-based, yet non-atherogenic. Eur. J. Clin. Nutr. 56 (Suppl. 1), S42–S52.
Cowart, B.J., Beauchamp, G.K., 1986. The importance of sensory context in young children's acceptance of salty tastes. Child Dev. 57, 1034–1039.
Crook, C.K., 1978. Taste perception in the newborn infant. Infant Behav. Dev. 1, 52–69.
Crystal, S., Bernstein, I.L., 1995. Morning sickness, impact on offspring salt preference. Appetite 25, 231–240.
Crystal, S.R., Bernstein, I.L., 1998. Infant salt preference and mother's morning sickness. Appetite 30, 297–307.
Curtis, K.S., Krause, E.G., Wong, D.L., Contreras, R.J., 2004. Gestational and early postnatal dietary NaCl levels affect NaCl intake, but not stimulated water intake, by adult rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 286, R1043–R1050.
Dally Farah, R., Khair, A., Shalev, E., Yonas, A., Leshem, M., 2003. Salt preference, dietary intake, taste papillae, PROP response, and taste responses in Ethiopian immigrants. Neural Plast. 10, 191 Suppl.
Day, C.J., Francis, J., Mchale, S., 2008. Associations between temperamental personality and taste preferences in a non-clinical population. Appetite 50, 557.
De Castro, J.M., 1996. How can eating behavior be regulated in the complex environments of free-living humans? Neurosci. Biobehav. Rev. 20, 119–1131.
De Courcy, S., Mitchell, H., Simmons, D., MacGregor, G.A., 1986. Urinary sodium excretion in 4–6 year old children: a cause for concern? BMJ (Clin. Res. Ed.) 292, 1428–1429.
De Gobbi, J.I., Martinez, G., Barbosa, S.P., Beltz, T.G., De Luca Jr., L.A., Thunhorst, R.L., Johnson, A.K., Menani, J.V., 2007. 5-HT2 and 5-HT3 receptors in the lateral parabrachial nucleus mediate opposite effects on sodium intake. Neuroscience 146 (4), 1453–1461.
De Oliveira, L.B., De Luca, L.A. Jr., Menani, J.V., 2008. Opioid activation in the lateral parabrachial nucleus induces hypertonic sodium intake. Neuroscience Jun 11 [epub ahead of print].
De Lorenzo, F., Hargreaves, J., Kakkar, V.V., 1997. Pathogenesis and management of delayed orthostatic hypotension in patients with chronic fatigue syndrome. Clin. Auton. Res. 7, 185–190.
Denton, D., 1982. The Hunger for Salt. Springer-Verlag, Berlin, Heidelberg, New York.
Denton, D.A., Coghlan, J.P., Fei, D.T., Mckinley, M., Nelson, J., Scoggins, B., Tarjan, E., Tregear, G.W., Tresham, J.J., Weisinger, R., 1984a. Stress, ACTH, salt intake and high blood pressure. Clin. Exp. Hypertens. A 6, 403–415.
Denton, D.A., McKinley, M.J., Nelson, J.F., Osborne, P., Simpson, J., Tarjan, E., Weisinger, R.S., 1984b. Species differences in the effect of decreased CSF sodium concentration on salt appetite. J. Physiol. (Paris) 79, 499–504.
Denton, D., 1991. Mineral appetite, an overview. In: Ramsay, D.J., Booth, D.A. (Eds.), Thirst—Physiological and Psychological Aspects. Springer-Verlag, Berlin, pp. 131–146.
Denton, D.A., Eichberg, J.W., Shade, R., Weisinger, R.S., 1993. Sodium appetite in response to sodium deficiency in baboons. Am. J. Physiol. 264, R539–R543.
Desor, J.A., Greene, L.S., Maller, O., 1975a. Preferences for sweet and salty in 9- to 15-year-old and adult humans. Science 190, 686–687.
Desor, J.A., Maller, O., Andrews, K., 1975b. Ingestive responses of human newborns to salty, sour, and bitter stimuli. J. Comp. Physiol. Psychol. 89, 966–970.
Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate, Institute of Medicine of the National Academies, 2004.
Dietz, D.M., Curtis, K.S., Contreras, R.J., 2006. Taste, salience, and increased NaCl ingestion after repeated sodium depletions. Chem. Senses 31, 33–41.
DiNicolantonio, R., Teow, B.H., Morgan, T.O., 1984. Sodium detection threshold and preference for sodium chloride in humans on high and low sodium diets. Clin. Exp. Pharmacol. Physiol. 11, 335–338.
Drewnowski, A., Henderson, S.A., Driscoll, A., Rolls, B.J., 1996. Salt taste perceptions and preferences are unrelated to sodium consumption in healthy older adults. J. Am. Diet. Assoc. 96, 471–474.
Duffy, V.B., Bartoshuk, L.M., Striegel-Moore, R., Rodin, J., 1998. Taste changes across pregnancy. Ann. N.Y. Acad. Sci. 855, 805–809.
Epstein, A.N., 1986. Hormonal synergy as the cause of salt hunger. In: Epstein, A.N., Massi, M., de Caro, G. (Eds.), The Physiology of Thirst and Sodium Hunger. Plenum, New York, pp. 395–404.

Epstein, A.N., 1990. Thirst and salt intake, a personal review and some suggestions. In: Ramsay, D.J., Booth, D.A. (Eds.), Thirst—Physiological and Psychological Aspects. Springer-Verlag, Berlin, pp. 481–501.
Epstein, A.N., 1991. Neurohormonal control of salt intake in the rat. Brain Res. Bull. 27, 315–320.
Erez, H., Wald, N., Leshem, M., 2000. Physiological determinants of human salt appetite, i) Blood donors have a greater salt appetite. Neurosci. Lett. 55 (Suppl.), S16.
Erkadius, E., Morgan, T.O., Di Nicolantonio, R., 1996. Full expression of the exaggerated salt appetite of the spontaneously hypertensive rat requires a prenatal factor. Clin. Exp. Pharmacol. Physiol. 23, 619–620.
Ertl, T., Hadzsiev, K., Vincze, O., Pytel, J., Szabo, I., Sulyok, E., 2001. Hyponatremia and sensorineural hearing loss in preterm infants. Biol. Neon. 79, 109–112.
Ervin, R.B., Wang, C.Y., Wright, J.D., Kennedy-Stephenson, J., 2004. Dietary intake of selected minerals for the United States population: 1999–2000. Advance data from vital and health statistics, no. 341, National Center for Health Statistics, Hyattsville, Maryland.
Falk, J.L., 1966. Serial sodium depletions and NaCl solution intake. Physiol. Behav. 1, 75–77.
Farleigh, C.A., Shepherd, R., Jevons, S., Pryor, J.S., 1987. Effects of haemodialysis on taste for salt in relation to changes in blood constituents. Hum. Nutr. Clin. Nutr. 41, 441–451.
Fessler, D.M., 2003. An evolutionary explanation of the plasticity of salt preferences, prophylaxis against sudden dehydration. Med. Hypoth. 613, 412–415.
Fitzsimons, J.T., 1998. Angiotensin, thirst, and sodium appetite. Physiol. Rev. 78, 583–686.
Fluharty, S.J., Epstein, A.N., 1983. Sodium appetite elicited by intracerebro-ventricular infusion of angiotensin II in the rat. II. Synergistic interaction with systemic mineralocorticoids. Behav. Neurosci. 97, 746–758.
Flynn, F.W., 2006. Intraventricular injections of tachykinin NK3 receptor agonists suppress the intake of "salty" tastes by sodium deficient rats. Behav. Brain. Res. 6 (166), 1–8.
Frankman, S.P., Ulrich, P., Epstein, A.N., 1991. Transient and lasting effects of reproductive episodes on NaCl intake of female rats. Appetite 16, 193–204.
Frye, C.A., Demolar, G.L., 1994. Menstrual cycle and sex differences influence salt preference. Physiol. Behav. 55, 193–197.
Galaverna, O., Nicolaidis, S., Yao, S.Z., Sakai, R.R., Epstein, A.N., 1995. Endocrine consequences of prenatal sodium depletion prepare rats for high need-free NaCl intake in adulthood. Am. J. Physiol. 269, R578–R583 (Regul. Integr. Comp. Physiol., 38).
Geerling, J.C., Loewy, A.D., 2008. Central regulation of sodium appetite. Exp. Physiol. 93, 178–209.
Greene, L.S., Desor, J.A., Maller, O., 1975. Heredity and experience: their relative importance in the development of taste preference in man. J. Comp. Physiol. Psychol. 89, 279–284.
Greenfield, H., Maples, J., Wills, R.B.H., 1983. Salting of food – a function of hole size and location of shakers. Nature 301, 331–332.
Grim, C.E., Robinson, M., 2003. Salt, slavery and survival- hypertension in the African diaspora. Epidemiology 14, 120–122.
Grippo, A.J., Moffitt, J.A., Beltz, T.G., Johnson, A.K., 2006. Reduced hedonic behavior and altered cardiovascular function induced by mild sodium depletion in rats. Behav. Neurosci. 120, 1133–1143.
Haimov-Kochman, R., 2005. Fetal programming – the intrauterine origin of adult morbidity. Harefuah 144, 97–101 (Hebrew).
Harris, G., Booth, D.A., 1987. Infants' preference for salt in food,its dependence upon recent dietary experience. J. Reprod. Infant. Psychol. 5, 97–104.
Harris, G., Thomas, A., Booth, D.A., 1990. Development of salt taste in infancy. Dev. Psychol. 26, 534–538.
Haycock, G.B., 1993. The influence of sodium on growth in infancy. Pediatr. Nephrol. 7, 871–875.
Haycock, G.B., Aperia, A., 1991. Salt and the newborn kidney. Pediatr. Nephrol. 5, 65–70.
He, F.J., MacGregor, G.A., 2002. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials Implications for public health. J. Hum. Hypertens. 16, 761–770.
Hemingway, E., 1935. Green hills of Africa. Scribner's.
Henkin, R.I., Gill, J.R., Bartter, F.C., 1963. Studies on taste thresholds in normal man and in patients with adrenal cortisol insufficiency, the role of adrenal cortical steroids and of serum concentration. J. Clin. Invest. 42, 727–735.
Henry, J.P., 1988. Stress, salt and hypertension. Soc. Sci. Med. 26, 293–302.
Hill, D.L., Mistretta, C.M., 1990. Developmental neurobiology of salt taste sensation. Trends Neurosci. 13, 188–195.
Horio, T., Kawamura, Y., 1998. Influence of physical exercise on human preferences for various taste solutions. Chem. Senses 23, 417–421.
Huggins, R.L., Nicolantonio, R.D., Morgan, T.O., 1992. Preferred salt levels and salt taste acuity in human subjects after ingestion of untasted salt. Appetite 18, 111–119.
Jacobs, K.M., Mark, G.P., Scott, T.R., 1988. Taste responses in the nucleus tractus solitarius of sodium deprived rats. J. Physiol. 406, 393–410.
Jankevicius, M.L., Widowski, T.M., 2003. Exogenous adrenocorticotrophic hormone does not elicit a salt appetite in growing pigs. Physiol. Behav. 78, 277–284.
Johnson, A.K., Grippo, A.J., 2006. Sadness and broken hearts: neurohumoral mechanisms and co-morbidity of ischemic heart disease and psychological depression. J. Physiol. Pharmacol. 57 (Suppl. 11), 5–29.
Johnson, A.K., Thunhorst, R.L., 1997. The neuroendocrinology of thirst and salt appetite, visceral sensory signals and mechanisms of central integration. Front. Neuroendocrin. 18, 292–353.
Jones, E., 1923. The symbolic significance of salt in folk-lore and superstition. In: Essays in Applied Psycho-Analysis., The International Psycho-Analytical Press, London and Vienna, pp. 454.
Kallio, K., Jokinen, E., Puotsaari, T., Lagstrom, H., Kotilainen, S., Seppanen, R., Viikari, J., Ronnemaa, T., Valimaki, I., Simell, O., 1998. Salt intake in young children. Nord. Med. 113, 222–225.
Kanarek, R.B., Ryu, M., Przypek, J., 1995. Preferences for foods with varying levels of salt and fat differ as a function of dietary restraint and exercise but not the menstrual cycle. Physiol. Behav. 57, 821–826.
Kaufman, J.S., Hall, S.A., 2003. The slavery hypertension hypothesis, dissemination and appeal of a modern race theory. Epidemiology 14, 111–118.
King, N.A., Tremblay, A., Blundell, J.E., 1997. Effects of exercise on appetite control: implications for energy balance. Med. Sci. Sports Exerc. 29, 1076–1089.
Kirby, R.F., Johnson, A.K., 1990. Effects of sympathetic activation on plasma renin activity in the developing rat. J. Pharm. Exp. Ther. 253, 152–157.
Kochli, A., Tenenbaum-Rakover, Y., Leshem, M., 2005. Increased salt appetite in patients with congenital adrenal hyperplasia 21-hydroxylase deficiency. Am. J. Physiol. Regul. Integr. Comp. Physiol. 288, R1673–R1681.
Kratz, A., Siegel, A.J., Verbalis, J.G., Adner, M.M., Shirey, T., Lee-Lewandrowski, E., Lewandrowski, K.B., 2005. Sodium status of collapsed marathon runners. Arch. Pathol. Lab. Med. 129, 227–230.
Krause, E.G., Sakai, R.R., 2007. Richter and sodium appetite, from adrenalectomy to molecular biology. Appetite 49, 353–367.
Kremers, S.P., van der Horst, K., Brug, J., 2007. Adolescent screen-viewing behaviour is associated with consumption of sugar-sweetened beverages: the role of habit strength and perceived parental norms. Appetite 48, 345–350.
Kurlansky, M., 2003. Salt—a world history. Penguin 2003.
Law, C.M., Shiell, A.W., Newsome, C.A., Syddall, H.E., Shinebourne, E.A., Fayers, P.M., Martyn, C.N., de Swiet, M., 2002. Fetal, infant, and childhood growth and adult blood pressure, a longitudinal study from birth to 22 years of age. Circulation 1059, 1088–1092.
Leshem, M., 1998. Salt preference in adolescence is predicted by common prenatal and infantile mineralofluid loss. Physiol. Behav. 63, 699–704.
Leshem, M., 1999. The ontogeny of salt hunger in the rat. Neurosci. Biobehav. Rev. 23, 649–659.
Leshem, M., Neufeld, M., Del Canho, S., 1994. Ontogeny of the ionic specificity of sodium appetite in the rat pup. Dev. Psychobiol. 27, 381–394.
Leshem, M., Maroun, M., Del Canho, S., 1996. Sodium depletion and maternal separation in the suckling rat increase its salt intake when adult. Physiol. Behav. 59, 199–204.
Leshem, M., Maroun, M., Weintraub, Z., 1998. Neonatal diuretic therapy may not alter children's preference for salt taste. Appetite 30, 53–64.
Leshem, M., Abutbul, A., Eilon, R., 1999. Exercise increases the preference for salt in humans. Appetite 32, 251–260.
Leshem, M., Levin, T., Schulkin, J., 2002. Intake and hedonics of calcium and sodium during pregnancy and lactation in the rat. Physiol. Behav. 75, 313–322.
Leshem, M., Kavushansky, A., Devys, J.-M., Thornton, S., 2004. Enhancement revisited,the effects of multiple depletions on sodium intake in rats vary with strain, substrain, and gender. Physiol. Behav. 82, 571–580.
Leshem, M., Del Canho, S., 2005. Ontogeny of urine preference and its relationship to NH_4Cl preference and sodium hunger in suckling rat pups. Dev. Psychobiol. 46, 111–117.
Leshem, M., Epstein, A.N., 1989. Ontogeny of renin-induced salt appetite in the rat pup. Dev. Psychobiol. 22, 437–445.
Leshem, M., Rudoy, J., 1997. Hemodialysis increases the preference for salt in soup. Physiol. Behav. 61, 65–69.
Leshem, M., Saadi, A., Alem, N., Hendi, K., 2008. Enhanced salt appetite, diet and drinking in traditional Bedouin women in the Negev. Appetite 50, 71–82.
Lien, Y.H., Shapiro, J.I., 2007. Hyponatremia, clinical diagnosis and management. Am. J. Med. 120, 653–658.
Lozada, M., Sánchez-Castillo, C.P., Cabrera, G.A., Mata, I.I., Pichardo-Ontiveros, E., James, W.P.T., 2007. Salt, its goodness and perversities. Rev. Invest. Clin. 59, 382–393.
Ma, L.Y., McEwen, B.S., Sakai, R.R., Schulkin, J., 1993. Gluco-corticoids facilitate mineralocorticoid-induced sodium appetite in the rat. Horm. Behav. 27, 240–250.
MABAT – First Israeli National Food and Nutrition Survey 1999–2001, 2004. Israel Ministry of Health.
Malaga, I., Arguelles, J., Diaz, J.J., Perillan, C., Vijande, M., Malaga, S., 2005. Maternal pregnancy vomiting and offspring salt taste sensitivity and blood pressure. Pediatr. Nephrol. 20, 956–960.
Mann, N., 2000. Dietary lean red meat and human evolution. Eur. J. Nutr. 39, 71–79.
Martin, R.J., Fanaroff, A.A., Walsh, M.C., 2005. Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant, 8th ed. Mosby Inc..
Massi, M., Epstein, A.N., 1987. Salt appetite in the pigeon in response to pharmacological treatments. J. Physiol. 393, 555–568.
Massi, M., Epstein, A.N., 1990. Angiotensin/aldosterone synergy governs the salt appetite of the pigeon. Appetite 14, 181–192.
Massi, M., Gentili, L., Pompei, P., de Caro, G., Epstein, A.N., 1992. Central tachykinin injection potently suppresses the need-free salt intake of the female rat. Brain. Res. 584, 77–82.
Mattes, R.D., 1997. The taste for salt in humans. Am. J. Clin. Nutr. 65 (Suppl.), 692S–697S.

Mattes, R.D., Donnelly, D., 1991. Relative contributions of dietary sodium sources. J. Am. Coll. Nutr. 10, 383–393.
Mattes, R.D., Christensen, C.M., Engelman, K., 1990. Effects of hydrochlorothiazide and amiloride on salt taste and excretion (intake). Am. J. Hypertens. 3, 436–443.
May, C.N., McAllen, R.M., McKinley, M.J., 2000. Renal nerve inhibition by central NaCl and ANG II is abolished by lesions of the lamina terminalis. Am. J. Physiol. (Regul. Integr. Comp. Physiol.) 279, R1827–R1833.
McBride, S.M., Flynn, F.W., 2007. Centrally administered vasopressin cross-sensitizes rats to amphetamine and drinking hypertonic NaCl. Am. J. Physiol. (Regul. Integr. Comp. Physiol.) 293, R1452–R1458.
McCance, R.A., 1936. Experimental sodium chloride deficiency in man. Proc. R. Soc. B. 119, 245–268.
McCarron, D.A., 2000. The dietary guideline for sodium, should we shake it up? Yes! Am. J. Clin. Nutr. 71, 1013–1019.
McCaughey, S.A., Scott, T.R., 1998. The taste of sodium. Neurosci. Biobehav. Rev. 22, 663–676.
McCaughey, S.A., Giza, B.K., Scott, T.R., 1996. Activity in rat nucleus tractus solitarius after recovery from sodium deprivation. Physiol. Behav. 60, 501–506.
McDowell, M.A., Fryar, C.D., Hirsch, R., Ogden, C.L., 2005. Anthropometric reference data for children and adults, U.S. population, 1999–2002. Advance data from vital and health statistics, no 361, National Center for Health Statistics, Hyattsville, MD
Mennella, J.A., Jagnow, C.P., Beauchamp, G.K., 2001. Prenatal and postnatal flavor learning by human infants. Pediatrics 107, E88.
Midkiff, E.E., Bernstein, I.L., 1983. The influence of age and experience on salt preference of the rat. Dev. Psychobiol. 165, 385–394.
Miller, S.B., Friese, M., Dolgoy, L., Sita, A., Lavoie, K., Campbell, T., 1998. Hostility, sodium consumption, and cardiovascular response to interpersonal stress. Psychosom. Med. 60, 71–77.
Mittelmark, M.B., Sternberg, B., 1985. Assessment of salt use at the table: comparison of observed and reported behavior. Am. J. Public Health 75, 1215–1216.
Moder, K.G., Hurley, D.L., 1990. Fatal hypernatremia from exogenous salt intake, report of a case and review of the literature. Mayo Clin. Proc. 65, 1587–1594.
Moe, K.E., 1986. The ontogeny of salt preference in rats. Dev. Psychobiol. 19, 185–196.
Morimoto, S., Cassell, M.D., Sigmund, C.D., 2002. Neuron-specific expression of human angiotensinogen in brain causes increased salt appetite. Physiol. Genomics 9, 113–120.
Mouw, D.R., Vander, A.J., Wagner, J., 1978. Effects of prenatal and early postnatal sodium deprivation on subsequent adult thirst and salt preference in rats. Am. J. Physiol. 234, F59–F63.
Myers, J.B., Smidt, V.J., Doig, S., Di Nicolantonio, R., Morgan, T.O., 1985. Blood pressure, salt taste and sodium excretion in rats exposed prenatally to high salt diet. Clin. Exp. Pharmac. Physiol. 12, 217–220.
Na, E.S., Morris, M.J., Johnson, R.F., Beltz, T.G., Johnson, A.K., 2007. The neural substrates of enhanced salt appetite after repeated sodium depletions. Brain Res. 1171, 104–110.
Nachman, M., Pfaffmann, C., 1963. Gustatory nerve discharge in normal and sodium-deficient rats. J. Comp. Physiol. Psychol. 56, 1007–1011.
Nelson, M., Erens, R., Bates, B., Church, S., Boshier, T., 2007. Low income diet and nutrition survey. Food Consumption Nutrient intake, vol. 2, Her Majesty's Stationery Office, Crown Copyright.
Nicolaidis, S., Galaverna, O., Metzler, C.H., 1990. Extracellular dehydration during pregnancy increases salt appetite of offspring. Am. J. Physiol. 258 (Reg. Integr. Comp. Physiol.) 27, R281–R283.
Noakes, T.D., 2007. Hydration in the marathon, using thirst to gauge safe fluid replacement. Sports Med. 37, 463–466.
Nose, H., Mack, G.W., Shi, X.R., Nadel, E.R., 1988. Involvement of sodium retention hormones during rehydration in humans. J. Appl. Physiol. 65, 332–336.
Nowlis, G.H., 1973. Taste elicited tongue movements in human newborn infants, an approach to palatability. In: Bosma, J. (Ed.), The Fourth Symposium on Oral Sensation and Perception, Development in the Fetus and Infant. Government Printing Office, Washington, DC, pp. 292–303.
Ochsenbein-Kölble, N., von Mering, R., Zimmermann, R., Hummel, T., 2005. Changes in gustatory function during the course of pregnancy and postpartum. BJOG, Int. J. Obstet. Gynaecol. 112, 1636–1640.
Oliver, W.J., Cohen, E.L., Neel, J.V., 1975. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a 'no-salt' culture. Circulation 52, 146–151.
Pangborn, R.M., Pecore, S.D., 1982. Taste perception of sodium chloride in relation to dietary intake of salt. Am. J. Clin. Nutr. 35, 510–520.
Passe, D.H., Horn, M., Murray, R., 2000. Impact of beverage acceptability on fluid intake during exercise. Appetite 2000 (35), 219–229.
Phillips, K., Holm, K., Wu, A.C., 1985. Contemporary table salt practices and blood pressure. Am. J. Public Health 75, 405–406.
Przekop Jr., P., Mook, D.G., Hill, D.L., 1990. Functional recovery of the gustatory system after sodium deprivation during development, how much sodium and where. Am. J. Physiol. 259 (Pt 2), R786–R791.
Richter, C.P., 1936. Increased salt appetite in adrenalectomized rats. Am. J. Physiol. 115, 155–161.
Richter, C.P., 1956. Salt appetite of mammals, its dependence on instinct and metabolism. L'instinct dans le comportement des animaux et de l'homme, Paris, France. pp. 577–632.
Robinson, T.E., Berridge, K.C., 2003. Addiction. Ann. Rev. Psychol. 54, 25–53.
Roitman, M.F., Na, E., Anderson, G., Jones, T.A., Bernstein, I.L., 2002. Induction of a salt appetite alters dendritic morphology in nucleus accumbens and sensitizes rats to amphetamine. J. Neurosci. 22, RC225.
Ross, M.G., Desai, M., 2005. Gestational programming,population survival effects of drought and famine during pregnancy. Am. J. Physiol. (Regul. Integr. Comp. Physiol.) 2881, R25–R33.
Ross, M.G., Desai, M., Guerra, C., Wang, S., 2005. Prenatal programming of hypernatremia and hypertension in neonatal lambs. Am. J. Physiol. (Regul. Integr. Comp. Physiol.) 2881, R97–R103.
Rowland, N.E., Fregly, M.J., 1988. Sodium appetite, species and strain differences and role of renin–angiotensin–aldosterone system. Appetite 11, 143–178.
Rozin, P., 1991. Family resemblance in food and other domains, the family paradox and the role of parental congruence. Appetite 16, 93–102.
Rozin, P., Schulkin, J., 1990. Food selection. In: Adler, N.T. (Ed.), Handbook of Behavioral Neurobiology, vol. 10. In: Stricker, E.M. (Ed.), Neurobiology of Food and Fluid Intake. Plenum Press, New York and London, pp. 297–328.
Sakai, R.R., Fine, W.B., Epstein, A.N., 1987. Salt appetite is enhanced by one prior episode of sodium depletion in the rat. Behav. Neurosci. 101, 724–731.
Sakai, R.R., Frankman, S.P., Fine, W.B., Epstein, A.N., 1989. Prior episodes of sodium depletion increase the need-free sodium intake of the rat. Behav. Neurosci. 103, 186–192.
Sakai, R.R., Ma, L.Y., Zhang, D.M., McEwen, B.S., Fluharty, S.J., 1996. Intracerebral administration of mineralocorticoid receptor antisense oligonucleotides attenuate adrenal steroid-induced salt appetite in rats. Neuroendocrinology 64, 425–429.
Sakai, K., Agassandian, K., Morimoto, S., Sinnayah, P., Cassell, M.D., Davisson, R.L., Sigmund, C.D., 2007. Local production of angiotensin II in the subfornical organ causes elevated drinking. J. Clin. Invest. 117, 1088–1095.
Sawka, M.N., Montain, S.J., 2000. Fluid and electrolyte supplementation for exercise heat stress. Am. J. Clin. Nutr. 72, 564S–572S.
Schulkin, J., 1982. Behavior of sodium deficient rats, the search for a salty taste. J. Comp. Physiol. Psychol. 96, 628–634.
Schulkin, J., Leibman, D., Ehrman, R.N., Norton, N.W., Ternes, J.W., 1984. Salt hunger in the rhesus monkey. Behav. Neurosci. 98, 753–756.
Schulkin, J., Marini, J., Epstein, A.N., 1989. A role for the medial region of the amygdala in mineralocorticoid-induced salt hunger. Behav. Neurosci. 103, 178–185.
Schulkin, J., 1991. Sodium Hunger the Search for a Salty Taste. University Press, New York, Port Chester, Melbourne, Sidney, Cambridge.
Schulkin, J., 2003. Rethinking homeostasis. In: Allostatic Regulation in Physiology and Pathology, MIT Press, Cambridge, MA.
Schulkin, J., 2005. Curt Richter: A life in the laboratory. John Hopkins University Press, Baltimore and London.
Scientific Advisory Committee on Nutrition. The Stationery Office, Crown Copyright, 2003.
Sclafani, A., 1999. Macronutrient-conditioned flavor preferences. In: Berthoud, H.R., Seeley, R.J. (Eds.), Neural Control of Macronutrient Selection. CRC Press, Boca Raton, FL, pp. 93–106.
Shade, R.E., Blair-West, J.R., Carey, K.D., Madden, L.J., Weisinger, R.S., Denton, D.A., 2002. Synergy between angiotensin and aldosterone in evoking sodium appetite in baboons. Am. J. Physiol. (Regul. Integr. Comp. Physiol.) 283, R1070–R1078.
Shepherd, R., Farleigh, C.A., 1986. Attitudes and personality related to salt intake. Appetite 7, 343–354.
Shepherd, R., Farleigh, C.A., Pryor, J.S., 1986. Changes in salt taste in dialysis and their relationship to blood constituents. Percept. Motor Skills 62, 343–347.
Shepherd, R., Farleigh, C.A., Wharf, S.G., 1989. Limited compensation by table salt for reduced salt within a meal. Appetite 13, 193–200.
Shirazki, A., Weintraub, Z., Reich, D., Gershon, E., Leshem, M., 2007. Lowest neonatal serum sodium predicts sodium intake in low-birthweight children. Am. J. Physiol. (Reg, Integr. Comp. Physiol.) 292, R1683–R1689.
Siegel, A.J., 2007. Hypertonic (3%) sodium chloride for emergent treatment of exercise-associated hypotonic encephalopathy. Sports Med. 37, 459–462.
Siegel, A.J., Verbalis, J.G., Clement, S., Mendelson, J.H., Mello, N.K., Adner, M., Shirey, T., Glowacki, J., Lee-Lewandrowski, E., Lewandrowski, K.B., 2007. Hyponatremia in marathon runners due to inappropriate arginine vasopressin secretion. Am. J. Med. 120 461.e11–461.e17.
Smedley, S.R., Eisner, T., 1995. Sodium uptake by puddling in a moth. Science 15 (270), 1816–1818.
Smedley, S.R., Eisner, T., 1996. Sodium: a male moth's gift to its offspring. Proc. Natl. Acad. Sci. U.S.A. 93, 809–813.
Smith, G.P., 1996. The direct and indirect controls of meal size. Neurosci. Biobehav. Rev. 20, 41–46.
Smith, S.L., Quandt, S.A., Arcury, T.A., Wetmore, L.K., Bell, R.A., Vitolins, M.Z., 2006. Aging and eating in the rural, southern United States, beliefs about salt and its effect on health. Soc. Sci. Med. 62, 189–198.
Smriga, M., Kameishi, M., Torii, K., 2002. Brief exposure to NaCl during early postnatal development enhances adult intake of sweet and salty compounds. Neuroreport 13, 2565–2569.
Stein, L.J., Cowart, B.J., Epstein, A.N., Pilot, L.J., Laskin, C.R., Beauchamp, G.K., 1996. Increased liking for salty foods in adolescents exposed during infancy to a chloride-deficient feeding formula. Appetite 27, 65–77.
Stein, L.J., Cowart, B.J., Beauchamp, G.K., 2006. Salty taste acceptance by infants and young children is related to birth weight, longitudinal analysis of infants within the normal birth weight range. Eur. J. Clin. Nutr. 602, 272–279.

Steiner, J.E., Glaser, D., Hawilo, M.E., Berridge, K.C., 2001. Comparative expression of hedonic impact, affective reactions to taste by human infants and other primates. Neurosci. Biobehav. Rev. 25, 53–74.
Stone, L.J., Pangborn, R.M., 1990. Preferences and intake measures of salt and sugar, and their relation to personality traits. Appetite 15, 63–79.
Stricker, E.M., Verbalis, J.G. 1990. Sodium appetite. In: Adler, N.T. (Ed.), Handbook of Behavioral Neurobiology, vol. 10. In: Stricker, E.M. (Ed.), Neurobiology of Food and Fluid Intake. Plenum Press, New York and London, pp. 387–419.
Stricker, E.M., Thiels, E., Verbalis, J.G., 1991. Sodium appetite in rats after prolonged dietary sodium deprivation, a sexually dimorphic phenomenon. Am. J. Physiol. 260 (6 Pt. 2), R1082–R1088.
Sullivan, S.A., Birch, L.L., 1990. Pass the sugar pass the salt, experience dictates preference. Dev. Psychol. 26, 546–551.
Takamata, A., Mack, G.W., Gillen, C.M., Nadel, E.R., 1994. Sodium appetite, thirst, and body fluid regulation in humans during rehydration without sodium replacement. Am. J. Physiol. 266, R1493–R1502.
Tamura, R., Norgren, R., 1997. Repeated sodium depletion affects gustatory neural responses in the nucleus of the solitary tract of rats. Am. J. Physiol. 273, R1381–R1391.
Taubes, G., 1998. The (political) science of salt. Science 281, 898–907.
Tekol, Y., 2006. Salt addiction: A different kind of drug addiction. Med. Hypotheses 67, 1233–1234.
Teow, B.H., Di Nicolantonio, R., Morgan, T.O., 1985–1986. Sodium chloride preference and recognition threshold in normotensive subjects on high and low salt diet. Clin. Exp. Hypertens. A 7, 1681–1695.
Thiels, E., Verbalis, S., Stricker, M., 1990. Sodium appetite in lactating rats. Behav. Neurosci. 104, 742–750.
Thorn, G.W., Dorrance, S.S., Day, E., 1942. Addison's disease, evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients. Ann. Intern. Med. 16, 1053–1096.
Tindell, A.J., Smith, K.S., Pecina, S., Berridge, K.C., Aldridge, J.W., 2006. Ventral pallidum firing codes hedonic reward, when a bad taste turns good. J. Neurophysiol. 96, 2399–2409.
Valentine, V., 2007. The importance of salt in the athlete's diet. Curr. Sports Med. Rep. 6, 237–240.
van den Brandt, P.A., Botterweck, A.A., Goldbohm, R.A., 2003. Salt intake, cured meat consumption, refrigerator use and stomach cancer incidence, a prospective cohort study (Netherlands). Cancer Causes Control 14, 427–438.
Verbalis, J.G., 1990. Clinical aspects of body fluid homeostasis in humans. In: Stricker, E.M. (Ed.), Handbook of Behavioral Neurobiology. Plenum Press, New York, pp. 421–426.
Verbalis, J.G., Goldsmith, S.R., Greenberg, A., Schrier, R.W., Sterns, R.H., 2007. Hyponatremia treatment guidelines 2007, expert panel recommendations. Am. J. Med. 120 (11 Suppl. 1), S1–S21.
Verma, P., Mahajan, K.K., Mittal, S., Ghildiyal, A., 2005. Salt preference across different phases of menstrual cycle. Indian J. Physiol. Pharmacol. 49, 99–102.
Verma, P., Mittal, S., Ghildiyal, A., Chaudhary, L., Mahajan, K.K., 2007. Salt preference, age and sex related variability. Indian J. Physiol. Pharmacol. 51, 91–95.
Vijande, M., Brime, J.I., Lopez-Sela, P., Costales, M., Arguelles, J., 1996. Increased salt preference in adult offspring raised by mother rats consuming excessive amounts of salt and water. Regul. Pept. 66, 105–108.
Wald, N., Leshem, M., 2003. Salt conditions a flavor preference or aversion after exercise depending on NaCl dose and sweat loss. Appetite 40, 277–284.
Weisinger, R.S., Coghlan, J.P., Denton, D.A., Fan, J.S., Hatzikostas, S., McKinley, M.J., Nelson, J.F., Scoggins, B.A., 1980. ACTH-elicited sodium appetite in sheep. Am. J. Physiol. 239, E45–E50.
Weisinger, R.S., Blair-West, J.R., Burns, P., Denton, D.A., McKinley, M.J., Tarjan, E., 1996. The role of angiotensin II in ingestive behavior,a brief review of angiotensin II, thirst and sodium appetite. Regul. Pept. 66, 73–81.
Wilkins, L., Richter, C.P., 1940. A great craving for salt by a child with cortico-adrenal insufficiency. J. Am. Med. Assoc. 114, 866–868.
Wolf, G., 1969. In: Pfaffman, K. (Ed.), Innate mechanisms for regulation of sodium intake Olfaction and taste. Rockefeller Press, New York, pp. 548–553.
Wong, K.S., Williamson, P.M., Brown, M.A., Zammit, V.C., Denton, D.A., Whitworth, J.A., 1993. Effects of cortisol on blood pressure and salt preference in normal humans. Clin. Exp. Pharmacol. Physiol. 20, 121–126.
Wright, J.D., Wang, C.Y., Kennedy-Stephenson, J., Ervin, R.B., 2003. Dietary intake of ten key nutrients for public health, United States, 1999–2000. Advance data from vital and health statistics, no. 334. Hyattsville, Maryland, National Center for Health Statistics. (http//www.cdc.gov/nchs/data/ad/ad334.pdf).
Yativ, M., Stern, S., Leshem, M., 2003. Salt appetite is not increased in swimmers. Neural Plast. 10 (3), 238 Suppl.
Yeomans, M.R., Jackson, A., Lee, M.D., Nesic, J.S., Durlach, P.J., 2000. Expression of flavour preferences conditioned by caffeine is dependent on caffeine deprivation state. Psychopharmacology 150, 208–215.
Yeomans, M.R., Blundell, J.E., Leshem, M., 2004. Palatability, response to nutritional need or need-free stimulation of appetite? Br. J. Nutr. 92 (Suppl. 1), S3–S14.
Zinner, S.H., McGarvey, S.T., Lipsitt, L.P., Rosner, B., 2002. Neonatal blood pressure and salt taste responsiveness. Hypertension 40, 280–285.