Review

Caffeine use in children: What we know, what we have left to learn, and why we should worry

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ABSTRACT

Caffeine is a widely used psychoactive substance in both adults and children that is legal, easy to obtain, and socially acceptable to consume. Although once relatively restricted to use among adults, caffeine-containing drinks are now consumed regularly by children. In addition, some caffeine-containing beverages are specifically marketed to children as young as 4 years of age. Unfortunately, our knowledge of the effects of caffeine use on behavior and physiology of children remains understudied and poorly understood. The purpose of this article is to review what is known about caffeine use in children and adolescents, to discuss why children and adolescents may be particularly vulnerable to the negative effects of caffeine, and to propose how caffeine consumption within this population may potentiate the rewarding properties of other substances. The following topics are reviewed: (1) tolerance and addiction to caffeine, (2) sensitization and cross-sensitization to the effects of caffeine, (3) caffeine self-administration and reinforcing value, and (4) conditioning of preferences for caffeine-containing beverages in both adults and children.

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1. Introduction

Caffeine is the most commonly used psychoactive substance throughout the world (Nehlig, 1999). It is classified as a stimulant drug that is typically used for its ability to arouse the central nervous system. Although recognized as safe by the Food and Drug Administration, caffeine use in excess can result in serious health hazards and, in rare cases, death (Broderick and Benjamin, 2004; Kerrigan and Lindsey, 2005). The safety of caffeine use among children is understudied and poorly understood. Given that some caffeine-containing beverages are marketed directly to children (Bramstedt, 2007) and that caffeine use is on the rise among children (Frary et al., 2005), it is important to understand the potential effects of caffeine use within this population.

Children and adolescents are the fastest growing population of caffeine users with an increase of 70% in the past 30 years (Harnack et al., 1999). Coincident with this rise in caffeine use is the development of novel, caffeine-containing beverages called energy drinks. These drinks contain caffeine levels ranging from 50 mg (equivalent to a can of soda) to 500 mg (equivalent to five cups of coffee) and, often, very high levels of sugar (Energyfiend website, 2008). Energy drink sales have grown by more than 50% since 2005 and represent the fastest growing segment of the beverage industry (Chandrasekaran, 2006). Energy drinks are marketed specifically to young adults and children with advertisements featuring high risk activities and extreme sports, such as rock climbing, parasailing, and BASE jumping and with catchy slogans such as "Red Bull gives you wings" and "Excite your sense" (reviewed in Miller, 2008a). This, coupled with growing concerns from parents and physicians, strengthens the imperative to empirically determine the effects of caffeine use in children.

The purpose of this review is to provide an overview of the literature on caffeine use and to discuss why children may be particularly vulnerable to potentially negative effects of caffeine, with an emphasis on how caffeine use relates to both ingestive behavior and use of illicit drugs. First, caffeine sources and consumption rates will be reviewed followed by a brief discussion of the mechanisms of caffeine action. After this, the specific topics of tolerance, sensitization and cross-sensitization, conditioning, and reinforcement will be discussed. Finally, the review will focus on why caffeine consumption during childhood and adolescence may have particularly harmful consequences.

2. Caffeine sources and consumption

Caffeine is produced by a variety of beans, leaves, and fruit where its bitterness acts as a deterrent to pests. Caffeine is found in coffee, black tea, and chocolate, as it is produced naturally in the beans and leaves of the plants used to manufacture these products (Friedman, 2007; Kovacs and Mela, 2006). Caffeine is also used as an additive in other products, such as soda, energy drinks, and some pain relievers (Frary et al., 2005). The levels of caffeine can vary widely in these products depending on the strength of the preparation, as in the case of tea and coffee, or the amount that is added exogenously, as in the case with soda and energy drinks. Approximately 90% of adults report regular caffeine use, with an average daily intake of ~227 mg (Frary et al., 2005). The top three sources of caffeine in adults are coffee (70%), soda (16%), and tea (12%) (Frary et al., 2005).

While moderate caffeine use is "generally recognized as safe" by the US Food and Drug Administration and the American Medical Association, this classification is largely based on studies conducted in adults. In fact, very little research has been conducted on children and adolescents. Since 1977, there has been a 70% increase in caffeine consumption among children and adolescents (Harnack et al., 1999). The average daily caffeine intake in children

ages 5–18 years was reported to be 38 mg in 1982 (Morgan et al., 1982). A more recent sample of caffeine consumer's ages 12–17 years indicates a mean intake of 69.5 mg/day, which is slightly less than the caffeine contained in one cup of coffee (Frary et al., 2005). When caffeine intake is examined relative to body weight, children ages 2–11 consume 0.4 mg/kg and those ages 12–17 consume 0.55 mg/kg compared to the average adult caffeine intake of approximately 1.3 mg/kg (Frary et al., 2005). Thus children consume about one half the concentration of caffeine as adults, on average. While this may seem harmless, there are two things that are important to consider. First, there is a broad range of caffeine use among adolescents, such that some use considerably more than average. It is this population that may be at particularly high risk for developing other types of high-risk behaviors, as will be discussed later. Second, because of a dearth of empirical research on caffeine use in adolescents, we do not know the minimum "safe" level of caffeine use in this population.

Caffeinated beverage consumption in general, and soda consumption in particular, is of concern because of its potentially negative health effects as well as its established relationship with sleep dysfunction, obesity, and dental caries. For example, children ages 2–18 who consume ≥9 oz. of soda per day drink less milk and fruit juice and ingest ~200 more calories per day when compared to infrequent soda drinkers (Harnack et al., 1999). Studies have shown that soda is the preferred route of caffeine administration among adolescents, however coffee-type drinks and "energy drinks", which contain significantly more caffeine per serving than soda are also becoming more popular within this population (Frary et al., 2005; Harnack et al., 1999; Smiciklas-Wright et al., 2003).

In addition to traditional caffeine-containing products, such as coffee, tea, and soda, people can now get their caffeine fix from a variety of "non-traditional" sources. For example, caffeine has been added to products that people already consume such as water, gum, mints, and candy. Caffeine-containing water (Water Joe™) can be purchased on the Internet and in some retail stores. Caffeinated gum (Jolt™ and Stay Alert™) and mints are also gaining popularity and, as with other new caffeine products, are marketed to children. The Jolt Gum website claims that having 144 pieces of Jolt Gum (equivalent to 72 cups of coffee) will "make you the most popular kid on the block" and that you "may even be able to get an A in art history" because of the "greenish speckles" (Jolt Gum, 2008). The Mars™ Corporation recently released a caffeinated version of the Snickers™ bar, called Snickers Charged™ (Mars, Mount Olive, NJ). Finally, although not likely in your local grocery store, you can find caffeinated potato chips (NRG: "Phoenix Fury"; Golden Flake Snack Foods Inc., Titusville, AL) and oatmeal (Morning Spark Oatmeal; Sturm Foods, Manawa, WI) as well. Caffeine is also added to some non-food products. For example, caffeine-containing tights are marketed to women as a method to locally reduce cellulite (Caffeine tights, 2008). It is also added to makeup and skin care products to "de-puff and reduce swelling while increasing circulation for increased blood flow to alleviate and brighten dark circles" (Caffeine eye cream, 2008). Finally, caffeine can be found in some specialty shampoos that claim to "promote hair growth" and "slow down hereditary hair loss" (Alpecin, 2008). The recent explosion of novel, caffeine-containing products suggests that consumption of caffeine may be increasing. In addition, it appears that consumable caffeine products are being marketed to younger populations, perhaps in an effort to increase use of these products and to get children "hooked" at earlier ages. However, the non-food products highlighted above are targeted to adult populations with concerns about cellulite, aging, and hair loss. This suggests that companies may capitalize on the familiarity that most adults have with the effects of caffeine by using it to promote novel products.

3. Mechanisms of caffeine action

The primary mechanism of caffeine action is antagonism of adenosine receptors (Nehlig, 1999). To date, four adenosine receptors have been identified: the A1, A2 (A and B) and A3 (Fredholm et al., 1999). The A1 and A2 receptors bind caffeine at low doses, but the A2B receptor only binds at high doses and the A3 is caffeine insensitive (Fredholm et al., 1999). The adenosine A1 receptor is distributed ubiquitously throughout the brain with the highest density of receptors in the hippocampus, cortex, and cerebellum (Goodman and Synder, 1982; Mahan et al., 1991; Svenningsson et al., 1997). This receptor is coupled to inhibitory G proteins within the cell (Fredholm et al., 1999). The adenosine A2A receptor is expressed with high density in the striatum, nucleus accumbens, olfactory tubercles and extended amygdala with weaker expression in the globus pallidus and the nucleus of the solitary tract (Rosin et al., 1998). Unlike the adenosine A1 receptor, the A2A receptor is coupled to stimulatory G proteins within the cell (Fredholm et al., 1999). Therefore, binding of caffeine or adenosine to the A1 and A2A receptors has opposing actions within the cell.

Aside from its well-known effects on sleep and arousal, which are primarily mediated by antagonism of the adenosine A1 receptor, caffeine is also known to interact with the dopamine system to exert some of its behavioral effects (Cauli and Morelli, 2005; Fredholm and Svenningsson, 2003). These actions are likely mediated through inhibition of the adenosine A2A receptor, which is primarily localized to dopamine rich areas of the brain (Fredholm et al., 1999). Adenosine A2A receptors are co-localized with dopamine D1 and D2 receptors (Kudlacek et al., 2003) and have been shown to form heterodimers (Fuxe et al., 2003). In addition, activation of adenosine A2A receptors decreases dopamine binding at the D2 receptor (Salim et al., 2000). Through these interactions, caffeine is able to directly potentiate dopamine neurotransmission, thereby modulating the rewarding and addicting properties of nervous system stimuli. In addition, caffeine use, tolerance, and dependence are highly heritable traits, suggesting a genetic component (Kendler and Prescott, 1999). In fact, several studies have reported a link between polymorphisms in the A2A gene with caffeine sensitivity and consumption (Alsene et al., 2003).

4. Physiological, behavioral and psychological effects of caffeine

Caffeine acts as a central and peripheral nervous system stimulant in both animals and humans. One of the primary effects of acute caffeine is to increase arousal (Barry et al., 2005; Flaten and Blumenthal, 1999). In rats, caffeine administration leads to increased locomotor activity (Nehlig et al., 1992), which can be blocked by administration of dopamine receptor antagonists (Garrett and Holtzman, 1994; Kuribara and Uchihashi, 1994). Caffeine can also induce rotational behavior in rats with unilateral lesions of the nigrostriatal dopamine cells in a manner that mimics dopamine (Garrett and Holtzman, 1995; Herrera-Marschitz et al., 1988). Finally, caffeine can potentiate the effects of dopamine on rotational behavior in animals with this same lesion (Jiang et al., 1993). When taken together, these studies suggest that caffeine interacts with the dopaminergic system to produce some of its behavioral effects. In addition to locomotor behavior, caffeine improves performance on learning and memory tasks in both rats and non-human primates (Angelucci et al., 1999, 2002; Howell et al., 1997) as well as improves memory retention in rats (Molinengo et al., 1994). These effects may be due to enhanced memory consolidation, as administration of caffeine after training was more effective than when caffeine was administered immediately before training in one study (Angelucci et al., 2002), although the precise mechanism for this remains unknown.

In humans, acute caffeine has dose-dependent effects on mood, attention, and physiology. For example, moderate doses of caffeine (200–300 mg) often produce enhanced feelings of well-being, improve concentration, and increase arousal and energy (Garrett and Griffiths, 1997; Griffiths et al., 1990b). High doses (>400 mg), however, lead to feelings of anxiety, nausea, jitteriness, and nervousness (Garrett and Griffiths, 1997). It is believed that most habitual caffeine consumers titrate their intake in order to maintain plasma caffeine levels that will maximize the positive effects and minimize the negative ones (Smith, 2002). In fact, some caffeine consumers appear to develop tolerance to the negative effects of caffeine and not to the positive effects, which could lead to increased caffeine reinforcement and intake (Griffiths et al., 1989; Nehlig, 1999). This will be discussed in more detail later. In humans, acute administration of moderate doses of caffeine (200–350 mg) decreases heart rate and increases blood pressure (Bender et al., 1997; Lane and Williams, 1987; Sung et al., 1994; Waring et al., 2003). Acute caffeine at similar doses to those mentioned above also increases skin conductance responses (Davidson and Smith, 1991; Totten and France, 1995). One of the problems with these studies is that the doses and routes of administration are variable, which makes comparison across studies difficult.

Behavioral effects of caffeine in humans have also been well documented. For example, moderate doses of caffeine enhance cognitive performance (Smit and Rogers, 2000), auditory vigilance (Lieberman et al., 1987), and reaction time (Durlach, 1998; Lieberman et al., 1987). These effects can be seen in doses ranging from 32 to 200 mg (Lieberman et al., 1987). Studies investigating caffeine discrimination have shown that a subset of subjects can detect caffeine at doses as low as 10 mg (Griffiths et al., 1990a; Silverman and Griffiths, 1992). Habitual caffeine consumers will self-administer caffeine at a greater rate than placebo in experimental self-administration paradigms (more detail given later (Evans et al., 1994; Hughes et al., 1995). What cannot be determined from these studies is whether people self-administer caffeine for the positive, mood elevating effects or to remove the negative effects, such as headache and fatigue.

Within the caffeine literature, there is an ongoing debate about the motivation for self-administration. Many researchers argue that the primary motivation for caffeine self-administration, in habitual caffeine consumers, is avoidance of withdrawal symptoms (Schuh and Griffiths, 1997). This contention has been supported by studies showing that, in long-term caffeine withdrawn and caffeine-consuming participants, there is no evidence for acute caffeine improving mood and/or performance (James, 1998; James et al., 2005; Garrett and Griffiths, 1998) or reinforcement (Garrett and Griffiths, 1998). However, the suggestion that caffeine administration is used primarily for withdrawal reversal is equivocal for several reasons. First, there are positive effects of moderate caffeine use which may be reinforcing on their own (Smith, 2002). Second, there are infrequent caffeine users who do not exhibit withdrawal symptoms when abstaining from caffeine. Although non-habitual caffeine consumers are rarely studied, the studies that have been done suggest that caffeine administration can stimulate mood and cognitive performance even in moderate and irregular caffeine users (Childs and de Wit, 2006; Haskell et al., 2005) and that a primary reason for infrequent use of caffeine may be the negative physiological and psychological symptoms that can occur (Stern et al., 1989). Third, not all habitual caffeine consumers exhibit withdrawal symptoms (Hughes et al., 1998), thus counteracting withdrawal symptoms, as a motive for caffeine use would not apply to these individuals. It is also possible that there are multiple reasons for caffeine self-administration. In some individuals, it may be primarily for withdrawal reversal, but

in others, it may be for the mild stimulant effects, and in some cases, it may be both. Most epidemiological studies suggest that there is a broad range of sensitivity to caffeine within the population, which may be associated with variability in caffeine self-administration, caffeine tolerance, and caffeine withdrawal and could be mediated, at least in part, by genetic polymorphisms that relate to enzymatic breakdown of caffeine or adenosine receptor function (Cornelis et al., 2007; Retey et al., 2007). These biological differences could mediate susceptibility to withdrawal and/or positive effects of caffeine and, therefore, may underlie motivation for caffeine administration. Finally, it is important to consider that the motivations for caffeine consumption may differ as a function of age. For example, in children and adolescents, caffeine consumption may be driven by peer pressure or enhancement of sports performance (Bramstedt, 2007). These are less likely to be reasons that adults consume caffeine. In addition, because children and adolescents probably consume smaller amounts of caffeine on a less frequent basis than adults, they may be more likely to experience the positive effects of caffeine than adults in whom caffeine use may, in fact, be driven by desire to reverse withdrawal.

There are also potential health risks and benefits of habitual caffeine use. These topics have been reviewed recently and, thus, will only be discussed briefly here (Higdon and Frei, 2006; Nawrot et al., 2003). Regular, high levels of caffeine consumption (>450 mg/day) have been shown to increase the risk of cardio-vascular disease (CVD) in some studies (Greenland, 1993; Panagiotakos et al., 2003). However, there are an equal number of studies that show no relationship between caffeine consumption and CVD (Hart and Smith, 1997; Stensvold et al., 1996). High levels of caffeine use are also associated with calcium excretion and bone loss, which may contribute to osteoporosis (Barger-Lux et al., 1990; Bergman et al., 2000), however, caffeine intake appears to interact with calcium intake, such that the only group in which caffeine consumption increases bone loss is those with low calcium intake (Harris and Dawson-Hughes, 1994; Barrett-Conner et al., 1994). Finally, although the data differ among studies, most agree that high levels of caffeine consumption in women trying to conceive can be associated with low rates of conception (Christianson et al., 1989; Jensen et al., 1998; Stanton and Gray, 1995; Williams et al., 1990) and higher rates of spontaneous abortion (Dlugosz et al., 1996; Fernandes et al., 1998; Srisuphan and Bracken, 1986). As with the other papers reviewed, there is a wide range of doses at which these effects are reported as well as some studies showing no effect of caffeine on fertility (Alderete et al., 1995; Olsen, 1991; Watkinson and Fried, 1985), but the general consensus is that high levels of caffeine consumption may have adverse effects on fertility and the recommendation is for women who are trying to become pregnant to limit caffeine to <300 mg/day (Nawrot et al., 2003).

Despite the potential health risks of caffeine consumption, there are also some reported health benefits. One of the best-characterized benefits of coffee consumption is a reduction in the risk of type 2 diabetes mellitus (Salazar-Martinez et al., 2004; Tuomilehto et al., 2004; van Dam and Hu, 2005). Although the mechanism is not known, it appears to be related to coffee consumption and not to caffeine consumption, as decaffeinated coffee provides similar benefits but tea does not (Salazar-Martinez et al., 2004; van Dam and Feskens, 2002). There is also evidence that the thermogenic effects of caffeine can increase energy expenditure (Astrup et al., 1990; Dulloo et al., 1989), and, perhaps, reduce weight gain over time (Lopez-Garcia et al., 2006). Caffeine also appears to improve sports performance (Jones, 2008), including perceived exertion (Hudson et al., 2008) and endurance (Hogervorst et al., 2008). Finally, there is some evidence of an inverse relationship between caffeine consumption and colorectal cancer (Giovannucci, 1998; Tavani and La Vecchia, 2004) and Parkinson's disease (Hernan et al., 2002; Ross et al., 2000), but the mechanisms for this apparent protection remain unknown.

5. Is caffeine addictive?

One controversial issue in the field of caffeine research is whether or not caffeine is "addictive". Caffeine consumers often report that they are "addicted to caffeine", but the data are inconsistent. The DSM-IV does not classify substances as addictive, but rather sets forth criteria for substance dependence, including: (1) tolerance, (2) substance-specific withdrawal syndrome, (3) substance often taken in larger amounts or over a longer period than expected, (4) persistent desire or unsuccessful efforts to cut down or control use, (5) a great deal of time spent in activities necessary to obtain, use, or recover from the effects of the substance, (6) important social, occupational, or recreational activities given up or reduced because of the substance, and (7) use continued despite knowledge of a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by the substance (APA, 1994). Users of a substance must meet three of the above criteria to be considered dependent. One issue with these criteria is that the effects of caffeine are extremely variable, with some people never developing tolerance or withdrawal symptoms (Alsene et al., 2003; Kendler and Prescott, 1999). In addition, because the use of caffeine is so widespread and socially acceptable, criteria 5–6 are not likely to be relevant for caffeine. Because fewer of the criteria are applicable to caffeine, it may be more difficult to classify caffeine dependence than dependence on drugs of abuse.

Studies in both adult and adolescent populations have shown that anywhere from 20 to 100% of regular caffeine consumers exhibit signs of caffeine dependence (Bernstein et al., 2002; Griffiths et al., 1986; Hughes et al., 1998; Silverman et al., 1992; Strain et al., 1994). This broad range suggests a high degree of variability among studies in findings of caffeine dependence that is likely related to differences among the studies, in methodology, population sampling, and double-blind procedural design. The studies that have reported 100% of the participants exhibiting symptoms of caffeine dependence were conducted in small samples that were preselected for heavy caffeine use (Griffiths et al., 1986; Strain et al., 1994) or in self-reported daily caffeine consumers (Silverman et al., 1992), which may not be representative of the general population. Several studies have used questionnaires to assess frequency of symptoms consistent with caffeine dependence. One such study in 36 adolescent daily caffeine consumers found that 22.2% of the sample could be classified as caffeine-dependent based on their criteria (Bernstein et al., 2002). However, the average daily caffeine consumption in this sample was 244 mg, which is well above the typical consumption for adolescents (and even for adults). Similarly, Hughes and colleagues performed telephone surveys in 162 self-described caffeine users and found that 30% reported three or more symptoms consistent with caffeine dependence (Hughes et al., 1998). In both of these studies, researchers were specifically recruiting caffeine-consuming individuals and, in the case of the Bernstein et al. study, eligibility criteria included reporting more than one symptom of caffeine dependence in a phone interview and, as mentioned above, these study populations are not representative of the general population. Dews and colleagues completed 11,112 telephone interviews of the general population, without regard to caffeine use and found that 61% of the respondents reported daily caffeine consumption (Dews et al., 1999). Of these caffeine consumers, 11% reported withdrawal symptoms upon cessation of caffeine ingestion. In order to empirically determine the extent of caffeine dependence, this

study was carried further and 57 caffeine consumers were asked to participate in an experiment. Participants were randomly assigned to the following conditions, abrupt caffeine withdrawal, gradual withdrawal, and a caffeine maintenance control group. Thirty-eight percent of the abrupt withdrawal group was considered caffeine withdrawn. None of the other participants reported significant symptoms. In addition, an important finding from this study was that less than half of the subjects who reported experiencing severe withdrawal symptoms during the telephone interview also experienced them during the experimental phase of the study. This finding calls into question the accuracy of self-report for caffeine dependence symptoms, in particular when they are not being acutely experienced.

The data reported above suggest that caffeine dependence may occur in a subset of habitual caffeine users. The controversy surrounding caffeine dependence is not limited to discrepancies in the data, but rather in whether the effects of caffeine abstinence are severe and consistent enough to warrant a DSM classification. Supporters of the caffeine dependence classification argue that there is substantial evidence to suggest that caffeine dependence is a real phenomenon that occurs in a subset of individuals and, although more studies are needed, the problem is potentially significant enough to merit DSM classification (Hughes et al., 1998; Juliano and Griffiths, 2004). The opponents argue that, although a subset of caffeine users experience symptoms of caffeine dependence, the percentages vary widely from study to study and often increase as awareness of caffeine abstinence increases (Dews et al., 2002; Satel, 2006). Even in studies that have specifically used deception to avoid awareness of the nature of the experiment (Hughes et al., 1991; Silverman et al., 1992), it may be difficult to maintain double blind experimental procedures, given that caffeine may be detected by taste (James et al., 1997). Another argument against caffeine dependence is that the symptoms of caffeine dependence are often mild to moderate, subside within a short period of time. Finally, the symptoms that occur after cessation of caffeine use are not comparable to those experienced during withdrawal from drugs such as cocaine and heroin (Dews et al., 2002). In fact, Dews and colleagues argue that "…discussing caffeine in terms of drugs of abuse trivializes the dangers of such drugs as cocaine" (Dews et al., 2002).

The majority of the research on caffeine dependence has been conducted in adults. It is important to consider that children may be more likely than adults to develop dependence or may develop dependence at lower doses or frequencies of caffeine use. To date, there have been no longitudinal studies to determine whether caffeine dependence symptoms in youth track to adulthood. Moreover, it is unknown whether children and adolescents who report mild dependence symptoms experience an increase in severity as they get older. Despite the equivocal nature of the data, it is irresponsible to dismiss the classification of caffeine dependence all together when there is so much about caffeine use that is still unknown. At best, researchers should acknowledge that more research needs to be conducted, especially in under-studied populations such as children, before a clinical classification of caffeine dependence is established or dismissed.

Caffeine intoxication is classified as a clinical syndrome in the DSM-IV (APA, 1994). Caffeine intoxication is characterized by the following: recent consumption of caffeine and five or more symptoms that develop during, or shortly after, caffeine use including restlessness, nervousness, excitement, insomnia, flushed face, diuresis, and gastrointestinal complaints. These symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and cannot be attributable to another medical condition or mental disorder. Individuals who are habitual consumers of caffeine may not experience these symptoms due to the development of tolerance. It is more likely that low or non-consumers of caffeine, such as children and adolescents, would be susceptible to Caffeine intoxication.

6. Tolerance to the effects of caffeine

Developing tolerance to a drug is a hallmark of substance abuse and dependence. Tolerance is defined by the American Psychiatric Association as "…a need for markedly increased amounts to achieve the desired effect." (APA, 1994). A further distinction can be made into acute and chronic tolerance based on the time-course of the development of tolerance. Chronic tolerance to caffeine refers to differences in responding to acute caffeine in caffeine deprived state based on a history (weeks to months) of caffeine usage (Kalant and Khanna, 1990). Acute tolerance to caffeine is observed when responses to caffeine administration are attenuated based on recent (within hours) caffeine exposure (Kalant and Khanna, 1990). The majority of experiments in animals and humans suggest that caffeine leads to the development of chronic tolerance. From here forth, when a reference is made to tolerance, it will be chronic tolerance unless otherwise stated.

It is common among substance abusers to develop tolerance to some, but not necessarily all, of a drug's effects and it is well established, in both human and animal models, that tolerance develops to at least some of the effects of caffeine. In animals, tolerance to the locomotor effects of caffeine clearly develops. For example, rats given 75 mg of caffeine daily show no stimulation of rotational behavior (Garrett and Holtzman, 1995). Chronic caffeine administration also eliminates caffeine-induced locomotor behavior (Finn and Holtzman, 1986; Nikodijevic et al., 1993). These effects are specific to effects of caffeine on adenosine receptors, as animals do not show cross-tolerance to dopaminergic drugs (Nikodijevic et al., 1993).

In adults, caffeine-induced tolerance has been shown for some, but not all, effects and only in a subset of habitual caffeine users (Nehlig, 1999). Three to 5 days of consumption of moderate to high doses of caffeine (300–1000 mg) leads to a 90% reduction in caffeine-induced elevations in blood pressure and decreases in heart rate (Ammon et al., 1983; Denaro et al., 1991; Shi et al., 1993). This tolerance is lost after a brief period of caffeine abstinence (Shi et al., 1993). This is likely due to clearing of caffeine from the system as there is an inverse relationship with the level of plasma caffeine and the response to caffeine administration (Robertson et al., 1981). There is also evidence for tolerance to some of the psychological effects of caffeine. For example, caffeine non-users typically report "tension-anxiety", "jitteriness", "nervousness", and "increased energy" after acute caffeine exposure, but caffeine consumers do not report these symptoms (Evans and Griffiths, 1992). Conversely, some of the positive effects of acute caffeine (i.e. ratings of "helpful", "alert", "increased feelings of well-being") occur reliably in caffeine consumers, but are not always found in non-caffeine consumers, suggesting that a subset of positive effects of caffeine actually sensitize, or get stronger, after repeated administration (Schuh and Griffiths, 1997).

It is important to note that not all studies demonstrate complete tolerance to the effects of caffeine. Farag et al. found that participants could be subdivided into low and high tolerance groups based on blood pressure responses to acute caffeine administration (Farag et al., 2005). In addition, a population-based twin-study using a questionnaire to assess tolerance found that only about 15% of the population sampled reported positive responses to the questions (Kendler and Prescott, 1999). Finally, effects of caffeine on sleep, which is the function that appears most sensitive to caffeine, appear to develop only a partial tolerance with 90% of the sleep deficit remaining after 7 days of caffeine administration (Bonnet and Arand, 1992).

To date, no empirical studies have been conducted to test whether children and adolescents develop tolerance to the effects of caffeine. One study, in which researchers assessed caffeine consumption and features of caffeine dependence in teenagers using a phone screen, showed that 41.7% reported symptoms of tolerance and 77.8% reported symptoms of withdrawal (Bernstein et al., 1994). In addition, adolescents who do not regularly consume caffeine tend to report more negative symptoms when given caffeine than those youth who are habitual consumers (Rapoport et al., 1981a). For example, a study in which adolescents who typically consumed either low or high levels (>500 mg/day) of caffeine were given caffeine (10 mg/(kg day)) or placebo for 2 weeks, found that parents of low consumers rated them as more restless, fidgety, and having difficulty sleeping when they were given caffeine. Low consuming children given caffeine also self-rated increased headache, stomachache, nausea, and faintness. By contrast, parents of high consumers reported no negative effects of caffeine and high consuming children only reported feeling faint or flushed (Rapoport et al., 1984).

7. Sensitization and cross-sensitization

Sensitization is the process by which the same dose of drug has stronger effects after repeated administration. Sensitization to at least some of the drug effects occurs with most drugs of abuse (Horger et al., 1990; Kalivas and Duffy, 1993; Lett, 1989) and is believed to result from changes in drug sensitivity that occur within the neural substrate for reward (Carlezon and Nestler, 2002; Vanderschuren and Kalivas, 2000; White and Kalivas, 1998). Thus, the neuronal response to the drug gets stronger after repeated administration, which leads to enhance psychological and physiological effects. Cross-sensitization is the process by which taking one drug enhances the response to that drug as well as other drugs acting at the same neurobiological site. This is one mechanism by which the taking of one drug can act as a "gateway" to administration of another drug. For example, repeated administration of amphetamine sensitizes the reward substrate to the effects of cocaine (Horger et al., 1992). Cross-sensitization is a concern because habitual use of licit drugs, such as caffeine or nicotine, may lead to cross-sensitization to illicit drugs and potentiate substance abuse (Horger et al., 1992; Horger et al., 1991).

7.1. Caffeine and substance abuse

While some caffeine users exhibit many of the characteristics of substance abusers, as mentioned above, caffeine is not considered an addictive substance. Although caffeine does not meet all of the DSM-IV criteria for drug dependence, it has been shown to alter the addictive properties of other drugs of abuse. For example, caffeine pretreatment (Horger et al., 1991) or co-administration (Schenk et al., 1994) increases the rate of cocaine self-administration in rats. In addition, co-administration of cocaine and caffeine increases the preference for the conditioned compartment in a conditioned place preference paradigm relative to either drug alone (Bedingfield et al., 1998). In non-human primates trained to free-base cocaine, a high dose of caffeine (1 mg/kg) pre-exposure led to an increased number of smoke deliveries relative to vehicle treated animals (Schenk et al., 1994). Animal studies have also demonstrated a link between caffeine and nicotine. Rats pre-exposed to caffeine acquired nicotine self-administration significantly faster than controls (Shoaib et al., 1999) and show potentiation of the ability to use nicotine as a discriminative stimulus (Gasior et al., 2002).

In humans, caffeine and nicotine use have a high rate of co-occurrence (Kozlowski et al., 1993; Strain et al., 1994). Caffeine and nicotine have similar physiological and psychological effects when administered intravenously (Garrett and Griffiths, 2001). Cigarette smokers are significantly more likely to habitually consume caffeine than non-smokers (Puccio et al., 1990; Swanson et al., 1994). In addition, in behavioral choice paradigms, subjects are willing to pay significantly more money to receive injections of nicotine when they are also given caffeine as compared to the no caffeine condition (Jones and Griffiths, 2003). Although most of these studies have been conducted in adults, one questionnaire-based study in adolescents found that, similar to adults, high caffeine consumption, defined as four or more caffeinated beverages per day, was associated with daily cigarette use (Martin et al., 2008). These data suggest that habitual caffeine consumption could lead to cross-sensitization for nicotine and, therefore, potentiate nicotine's reinforcing effects. Unlike animal models, there is not a clear relationship between cocaine and caffeine use in humans. If anything, cocaine users are less likely to consume caffeine than non-cocaine users (Budney et al., 1993) and there is no evidence that chronic caffeine use leads to cocaine addiction.

The association between caffeine use and use of other substances, such as nicotine and drugs of abuse (Puccio et al., 1990; Schenk et al., 1994; Swanson et al., 1994) may be due to the effects of caffeine on the neural dopamine system, the neurobiological substrate of reward and reinforcement (Fuxe et al., 2003; Kudlacek et al., 2003; Salim et al., 2000). One potential mechanism is that caffeine primes the dopamine system to respond to cocaine and other drugs of abuse such that drug dependence is established more quickly and, perhaps, at lower doses. Alternatively, caffeine and other drugs could act on parallel neural circuits such that small doses of both could have additive effects (Bedingfield et al., 1998). The studies that demonstrate these associations are typically cross-sectional and correlational in design. To date, there have been no prospective studies linking caffeine usage during adolescence to the usage of other drugs later in life, thus it is unknown whether pre-exposure to caffeine during childhood and adolescence can prime the brain in such a way that it is more sensitive to exposure to other substances later in life. In other words, in children who habitually consume caffeine, is their first exposure to nicotine likely to be a more positive or rewarding experience and, thus, more likely to be repeated? If early caffeine use is a significant risk factor for later drug use, it is imperative to understand this relationship in order to increase awareness of the potential long-term consequences of early caffeine use.

7.2. Caffeine and sugar

In children, the primary vehicle for caffeine is soda, which also contains a large amount of sugar (Frary et al., 2005; Harnack et al., 1999; Smiciklas-Wright et al., 2003). Therefore, during childhood and adolescence, a significant proportion of the population is exposed to repeated pairings of sugar and caffeine. This facilitates the development of caffeine dependence and, perhaps, also contributes to enhance preference for foods and beverages containing added sugar. Sugar is a known "natural reward" that activates similar reward pathways as drugs of abuse, such as cocaine, amphetamine, and nicotine (Robinson and Berridge, 2000). Intermittent access to sugar in food deprived rats leads to both behavioral (Avena and Hoebel, 2003a; Colantuoni et al., 2001) and neurochemical (Avena and Hoebel, 2003b; Colantuoni et al., 2001) similarities to drug addiction. One mechanism by which this occurs is through activation of the dopaminergic system by sugar. Consumption of sucrose decreases the density of dopamine D2 receptors in the nucleus accumbens shell (Bello et al., 2002). Likewise, excessive glucose intake increases the density of dopamine D1 receptors in this same brain region (Colantuoni et al., 2001). Finally, sucrose consumption increases

dopamine turnover in the nucleus accumbens relative to consumption of water (Hajnal and Norgren, 2002). Because of the well-established similarities between sugar and drugs of abuse (reviewed in Avena et al., 2008), the possibility exists that caffeine can potentiate sensitivity to, liking of, and consumption of sugar, just as it does with nicotine (Jones and Griffiths, 2003; Puccio et al., 1990; Swanson et al., 1994). In addition, because caffeine can also activate the dopaminergic system (Fuxe et al., 2003; Kudlacek et al., 2003; Salim et al., 2000), caffeine paired with high levels of added sugar in foods and beverages may act synergistically to release dopamine and, as a consequence, increase the reinforcing properties of sweetened foods and beverages. To date, there have been no studies examining potential links between sugar consumption and caffeine use in children. Furthermore, no studies have examined whether early soda consumption conditions a taste preference for sugary foods and/or promotes the combination of sugar and caffeine in adulthood.

8. Caffeine conditioning and reinforcing value

8.1. Conditioning

Conditioning is a form of associative learning whereby a previously neutral stimulus elicits a given response after repeated pairings with an unconditioned stimulus. Drugs typically act as unconditioned stimuli, as they act directly on the neural substrate for reward and are, therefore, inherently reinforcing. However, conditioned associations can be formed between drug effects and drug-related stimuli, such as needles and pipes, and to the context in which the drugs are taken (Brody et al., 2002; Childress et al., 1999). Because of this learned association, exposure to these conditioned stimuli alone can lead to an increase in drug craving and/or likelihood of taking drugs (O'Brien, 2005; Shaham et al., 2003). Although caffeine is not abused in the same manner as illicit drugs, it is widely used in a habitual manner and becomes associated with other stimuli as well as with specific contexts. For example, people often consume coffee in the morning, perhaps with a donut, at work. Therefore, exposure to a donut at a different time of day might trigger the desire for a cup of coffee. In other words, both sweet foods and coffee are inherently reinforcing to most people, and can each act as conditioned stimuli for the other one. This suggests that sweet foods and caffeine are complementary and their effects may be additive.

It is also important to note that the factors that trigger caffeine consumption may be different from the factors that maintain caffeine consumption. For example, an individual who consumes coffee every morning may do so out of habit, to alleviate or avoid withdrawal symptoms, or to reduce fatigue. These are conditions that support the maintenance of caffeine use. However, this same individual may consume coffee with dessert when dining out at a restaurant, even if this is not a typical time of day to consume coffee or if no withdrawal symptoms are present. This is a situation in which a conditioned association between a sweet food (dessert) and caffeine triggers caffeine consumption, even if this is not a mechanism by which caffeine consumption is maintained.

Soft drink manufacturers state that caffeine is added to enhance the flavor of their beverages (Griffiths and Vernotica, 2000). This is unlikely because the amount of caffeine used in these beverages is below the level of detection reported in most taste studies (James et al., 1997) and because in forced-choice paradigms, most people are unable to distinguish decaffeinated and caffeinated soda based on taste (Griffiths and Vernotica, 2000). It has, therefore, been argued that the popularity of caffeinated-carbonated beverages is not due to the enhanced flavor, but rather the mood-altering and dependence-inducing properties of caffeine.

Another explanation for the popularity of caffeinated soda is that caffeine enhances a conditioned taste preference for foods and beverages containing added sweeteners. Studies have shown that, in moderate caffeine consumers, the presence of caffeine in novel beverages increases the liking of those flavors in adults (Richardson et al., 1996; Yeomans et al., 1998, 2000a,b, 2001). In addition, the absence of caffeine leads to decreased pleasurability ratings of those same beverages. It should be noted that the development of caffeine-induced taste preference and aversion is state-dependent, because when these tests are repeated in non-abstinent caffeine users, caffeine has no effect on taste preferences (Yeomans et al., 2000a, 2002). These results support the theory that caffeine preferences, and subsequent taste preferences induced by caffeine, are driven by the avoidance or alleviation of withdrawal symptoms. To date, all of these studies have been conducted in adults. It is, therefore, unknown whether the relatively moderate amount of caffeine consumed by most children and adolescents is sufficient to condition a taste preference for novel flavored beverages. This is potentially important given that children may be more likely than adults to consume caffeine in a beverage that also contains a large amount of sugar, thus if caffeine conditions a taste preference for soda and energy drinks, this may increase consumption of beverages containing large amounts of soda. Another question that remains for both adults and children is whether these preferences generalize? In other words, if a taste preference is conditioned for beverages containing added sugar, will children also prefer foods with added sugar?

8.2. Reinforcement and self-administration

A reinforcer is a commodity that, when it follows a behavior, will increase the likelihood that behavior will be performed again (Ferster and Skinner, 1957). Reinforcing value can be measured by determining the amount of work an individual is willing to perform to gain access to a particular commodity (Epstein et al., 2007). This is a ubiquitous theoretical construct that can be applied to any reinforcer and is observed in multiple species. There are data to suggest that reinforcing value is a better predictor of consumption than hedonic ratings (Epstein et al., 2007, 2008). For example, if you ask individuals to rate their liking of chocolate on a scale from 1 to 7, most people would rate chocolate liking very highly (6 or 7), but these same individuals may have a very different pattern of chocolate consumption, with some people eating it daily and others eating it rarely. Therefore, the hedonic ratings of chocolate are not predictive of chocolate consumption. On the other hand, if given a task to perform to earn access to portions of chocolate that gets progressively more difficult, individuals willing to work harder for chocolate consume more than those who are not willing to work very hard. The amount of work performed relates to both laboratory and real-world consumption where the harder individuals are willing to work, the more they consume both inside and outside of the laboratory (Epstein et al., 2007, 2008). Another question that needs to be investigated in children and in adults is does caffeine added to soda and energy drinks increase their reinforcing value? By determining how caffeine affects the reinforcing value of beverages and foods, we may gain an understanding of how caffeine affects consumption of caffeine-containing beverages as well as non-caffeine-containing foods that may serve as complements to caffeine use.

Caffeine and drugs of abuse are both considered reinforcing and are both self-administered in naturalistic settings and in the laboratory. In animal models of self-administration, caffeine is administered irregularly, is typically observed after prolonged caffeine exposure followed by abstinence, and is not seen under the same conditions which reliably produce cocaine or amphetamine self-administration (Falk et al., 1994; Griffiths et al., 1979;

Griffiths and Woodson, 1988). In a conditioned place preference paradigm, low doses of caffeine are able to produce a place preference, but higher doses (>30 mg/kg), produce a conditioned place aversion (Brockwell et al., 1991; Patkina and Zvartau, 1998). In this testing paradigm, the reinforcing effects of caffeine are more similar to cocaine and ethanol, although when animals were given a choice between the chamber paired with cocaine and the chamber paired with caffeine, the chamber associated with cocaine was preferred 100% of the time (Patkina and Zvartau, 1998).

In humans, doses as low as 25–50 mg are reliably self-administered in a subset of caffeine consumers, but this is not observed in non-consumers when tested using laboratory self-administration paradigms (Griffiths and Mumford, 1995; Hughes and Oliveto, 1997; Richardson et al., 1996). Caffeine, like other drugs, produces an inverted U shaped dose response curve in humans with optimal self-administration and behavioral effects seen at moderate doses (100–300 mg) (Garrett and Griffiths, 1998; Griffiths et al., 1989). Typically self-administration is only observed after a period of caffeine abstinence and the amount of work individuals are willing to perform to gain access to caffeine is directly proportional to the severity of the withdrawal symptoms (Garrett and Griffiths, 1998; Griffiths et al., 1989). In self-administration paradigms where subjects are given repeated exposure to coffee or capsules containing placebo and caffeine (identified by letters or colors), 47–85% of adult caffeine users reliably self-administer caffeine after a period of repeated exposure to both placebo and caffeine (Evans et al., 1994; Hughes et al., 1995).

Self-administration is not sufficient to demonstrate that a substance has reinforcing properties. Although many researchers have described their work as testing "reinforcing value" or "reinforcement" of caffeine, most used caffeine self-administration as an index of its reinforcing value (Hughes et al., 1995; Rogers et al., 2003). In one study that did measure reinforcing value, high level, habitual caffeine consumers (>1000 mg/day) were required to ride a stationary bike to gain access to caffeinated coffee. On average, participants worked for 10 cups of coffee per day when the amount of cycling per cup was only a few minutes, but when the amount of cycling was increased to >30 min per cup, participants were only willing to work for ~2 cups per day (Griffiths et al., 1989). Although the amount of caffeine consumed decreased as the work required to gain access to it increased, subjects were still willing to perform a significant amount of work (cycling for >60 min) to gain access to some coffee. Because these studies were conducted in habitual caffeine consumers, these effects may have been driven by a desire to avoid and/or alleviate withdrawal symptoms, or negative reinforcement (Schuh and Griffiths, 1997). More research needs to be conducted in both adults and in children to assess the reinforcing properties of caffeine, in particular in low or non-consumers.

9. Why should we be worried about caffeine use in children?

The use of caffeine among children and adolescents is of concern for a number of reasons. First, very few studies have examined the physiological and psychological effects of caffeine use in this population. Although data from adult populations suggest that caffeine is relatively safe, children should not be thought of merely as small adults. Caffeine could have effects on children and adolescents that are different from those seen in adults. Second, childhood and adolescence is a period of rapid growth and the final stage of brain development. In order to maximize growth and development, proper sleep and nutrition are essential. Caffeine use disrupts sleep patterns (Orbeta et al., 2006; Pollak and Bright, 2003) and the excess consumption of soda is

associated with poor diet (Berkey et al., 2004; Blum et al., 2005; Ludwig et al., 2001), excess weight (Berkey et al., 2004; Ludwig et al., 2001), and dental caries (Marshall et al., 2005). Third, childhood and adolescence may be a critical period for the establishment of eating patterns and taste preferences. If caffeine enhances preferences for sweet foods and beverages, this may contribute to excess energy intake and increased risk for overweight and obesity in adulthood. Fourth, there is evidence from animal studies that caffeine can prime the brain to increase responding to subsequent drug exposure, thereby potentiating the reinforcing effects of drugs (Schenk et al., 1994). Children and adolescents may be particularly vulnerable to these effects, as their brains are still undergoing significant development; in particular areas of the brain involved in executive function, impulsivity control, and planning (Giedd, 1999; Sowell et al., 1999).

9.1. Physiological, behavioral and psychological effects of caffeine in children

Studies in children and adolescents suggest that caffeine has similar physiological effects in younger individuals as have been shown in adults. For example, moderate to high doses of caffeine (approximately 100–400 mg) led to increased reports of nervousness, jitteriness, fidgetiness, and decreased reports of sluggishness in children and adolescents (Bernstein et al., 1994; Elkins et al., 1981; Rapoport et al., 1981b). A few studies have examined physiological responses to caffeine in children and adolescents and have shown that caffeine increases ambulatory blood pressure in a dose-dependent manner (Savoca et al., 2004; Savoca et al., 2005). Withdrawal from caffeine also produced similar effects in a subset of adolescent caffeine users as are seen in some adults, such as headache, drowsiness, and fatigue (Bernstein et al., 2002; Hale et al., 1995). However, these effects were seen in fewer children and were much less consistent than what is typically observed in adult caffeine users (Rapoport et al., 1981a,b). This could be due to the fact the children typically consume smaller amounts of caffeine on a less regular basis than adults. In addition, with the studies cited above, there was no standardization of the amount of caffeine consumed, so there was a wide variety of exposure to caffeine when the children were being asked to report their symptoms (Bernstein et al., 2002; Hale et al., 1995). Future studies should focus on controlling for the amount of caffeine exposure.

In adults, caffeine also produces some positive subjective effects, such as enhanced feelings of well-being, self-confidence, and increased talkativeness (Griffiths and Mumford, 1995), but this has not been replicated in children (Bernstein et al., 1994; Elkins et al., 1981; Rapoport et al., 1981a,b). One potential reason for this is that all of these studies used acute doses of caffeine that were 3–10 times higher than the average daily dose of caffeine in children. Although the doses are similar to those that produce positive effects in adults, when the doses are corrected for the lower body weight in children, they are significantly higher and possible high enough to produce negative effects. One study measured self-reported subjective effects in children with usual caffeine consumption on 1 day and no caffeine on another (Goldstein and Wallace, 1997). They found that the high consumers (>50 mg/day) reported more positive effects than the low consuming group (<10 mg/day) when they were able to consume their normal amount of caffeine, but after a day of caffeine abstinence, the high consumers reported more negative symptoms than the low consuming group. On caveat with this study is that the children were aware of the caffeine abstinence, which may have amplified the actual physiological and psychological effects.

The issue of caffeine dependence in adolescents has been specifically addressed in one study of which I am aware. This was a study in 36, 13–17 year olds who self-identified as daily caffeine

consumers and who reported more than one symptom of caffeine dependence on a telephone screen (Bernstein et al., 2002). Twenty-two percent of the sample was found to be caffeine-dependent. Caffeine self-administration has also been tested in a study in adolescents, using a self-administration paradigm designed to mimic realistic consumption. Adolescents were given bottles of soda, either containing caffeine or not, labeled with different letters. They had bottles labeled A 1 day and B the next. For the following 2 days, they were given both A and B bottles and told to drink the one they preferred. The next week, the same procedures were followed except the bottles were labeled with C and D. At the end of 4 weeks, the data revealed that 22% of the children studied reliably, preferentially self-administered the caffeine-containing beverage (Hale et al., 1995). When taken together, these studies suggest that a subset of children may preferentially self-administer coffee and may exhibit symptoms of caffeine dependence, but there is a large degree of variability in the magnitude, severity, and type of caffeine effects that may depend, in part, on the level of habitual caffeine consumption (Hughes and Hale, 1998).

9.2. Caffeine use and brain development

Caffeine is used as a first line treatment for apneic episodes in premature infants (Comer et al., 2001). Although this treatment results in few side effects, the long-term effects of early caffeine treatment on human brain development are unknown. In animal models, perinatal caffeine treatment results in an upregulation of adenosine A1 receptors (Boulenger et al., 1983; Daval et al., 1989) and a reduction in seizure susceptibility (Georgiev et al., 1993; Szot et al., 1987; Tchekalarova et al., 2007). These studies demonstrate that exposure to caffeine during a period of time when brain development is occurring can have long-lasting effects on brain function.

While no one has examined the effects of caffeine consumption on adolescent brain development, the possibility exists that development can be altered during this time period. Studies examining neurological function in adolescents have revealed that a large amount of brain development is still occurring at this time point and, in some brain regions, development occurs beyond the teenage years (Giedd, 1999; Sowell et al., 1999). The areas of the brain that are still developing during adolescence include the orbitofrontal cortex and the temporal lobe (Giedd, 1999; Sowell et al., 1999). These are areas that contain adenosine receptors and therefore have the potential to be modified by caffeine (Svenningsson et al., 1997). In addition, because caffeine acts on brain regions that mediate reward and addiction, it is possible that caffeine consumption could influence the reinforcing properties of certain types of foods and beverages that are paired with caffeine.

9.3. Caffeine use and enhancement

Caffeine is frequently used by children and adolescents as a way to enhance academic and athletic performance, although the empirical data on the success of this strategy is weak. Caffeine is thought to enhance athletic performance by improving muscle contraction efficiency and decreasing perceived effort and fatigue (Cole et al., 1996; Sinclair and Geiger, 2000). The National Collegiate Athletic Association and the International Olympic Committee limit caffeine use among athletes by making the maximum allowable urinary caffeine level 12–15 μg/ml (National, 2006; Schwenk and Costley, 2002), however, in order to achieve this level of caffeine in urine, the athletes would have to ingest 5–6 cups of coffee. At this point the negative physiological effects of caffeine, such as nausea, vomiting, and diarrhea, would outweigh any potential benefit to athletic performance. Thus, it is considered acceptable for athletes to use moderate amounts of caffeine as a

way to enhance performance. To determine the prevalence of caffeine use for performance enhancement among children and adolescents, 16,000 Canadian school children (ages 11–18 years) were surveyed. Of these, 27% admitted to using caffeine to enhance athletic ability, 13% of these children reported being encouraged to do so by their coaches (Canadian Center for Drug Free Sport, 1993). A similar study was conducted on American school children, and the results were almost identical, with 27% of the total sample reporting use of caffeine to enhance athletic performance, and the percentages increasing with age (Forman et al., 1995).

The effects of caffeine on cognitive performance have been studied in both adults and children. Studies in adults show mild improvement on some cognitive tasks, including simple (Attwood et al., 2007) and choice reaction time tests (Attwood et al., 2007; van Duinen et al., 2005), but not on the Stroop task (Deslandes et al., 2005). In addition, studies that demonstrate improvement typically do so in caffeine consumers who are at least mildly deprived of caffeine. Thus, it is difficult to determine if caffeine improves mental performance or if it reverses the negative effects of caffeine deprivation. Few studies have been conducted in children. One study in 9–11 years old found that, after overnight caffeine abstinence, caffeine consumers performed more poorly on a cognitive task when compared to non-consumers (Heatherley et al., 2006). After caffeine administration, the consumers performed as well as the non-consumers, but the caffeine had no effect on performance in the non-consumers. This result is consistent with findings from adults and supports the withdrawal reversal hypothesis. Another study in regular caffeine-consuming children showed that caffeine administration improved manual dexterity and reduced variability in reaction time among boys (Bernstein et al., 1994). Finally, caffeine dose-dependently decreased reaction time in prepubertal boys in another study of regular caffeine consumers (Elkins et al., 1981). In the latter two studies, caffeine-consuming boys were used and caffeine improved performance relative to placebo after caffeine abstinence. However, in the absence of a control group of irregular caffeine consumers, it is not possible to determine whether caffeine enhances performance or whether caffeine reverses performance deficits induced by caffeine withdrawal.

9.4. Caffeine use, poor diet, and overweight in children

Caffeine alone, or in combination with other drugs, has been shown to reduce body weight in animals (Zheng et al., 2004) and, in some studies, reduce weight gain in humans (Lopez-Garcia et al., 2006; van Dam et al., 2006), although it is important to note that several studies have shown no greater weight loss induced by the addition of caffeine to a low calorie diet in humans (Astrup et al., 1992; Kovacs et al., 2004). One trial in obese adolescents showed that a combination of caffeine and ephedrine resulted in greater weight loss than placebo, suggesting that this may be an effective addition to weight loss treatment in children and adolescents (Molnar et al., 2000). Although the issue of caffeine-induced weight loss is equivocal, no human studies have reported weight gain in response to caffeine use, suggesting that caffeine by itself does not lead to increased energy intake. What is important to consider is the vehicle in which caffeine is delivered which, in adults, may be a non-caloric beverage, such as black coffee or diet soda, but in children is more likely to be a beverage that also has high levels of sugar. It is in this context that caffeine may make significant contributions to both poor diet and weight gain.

Caffeine use, in particular in the form of sugar-sweetened carbonated beverages, is associated with higher incidence of overweight in children (Johnson and Kennedy, 2000). Studies have shown that children who consume soda on a regular basis are more likely to be overweight (Ludwig et al., 2001). One study reported

that for every additional serving of sugar-sweetened beverage consumed daily, there is a 60% increase in the odds of becoming obese (Ludwig et al., 2001). The relationship between soda consumption and weight may be mediated by poor diet. Studies show that children who consume more servings of soda per week also consume fewer servings of milk, fruits, and vegetables (Harnack et al., 1999). One possible explanation for this is that parents who allow their children to frequently consume soda may be less concerned with their children's diet in general, and may not encourage healthy eating. Another explanation is that chronic soda consumption leads to a conditioned taste preference for sweetened foods and beverages which contributes to poor eating habits. To my knowledge, neither of these hypotheses has been tested.

9.5. Caffeine use and sleep in children

Children and adolescents are not getting as much sleep as they need. One study reported that 90% of the middle and high school students sampled reported getting less than 8 h of sleep on average, which is the recommended amount of sleep for this population (Seicean et al., 2007). One factor the contributed to shortened sleep duration is caffeine consumption. Studies have shown that moderate to high caffeine consumers have more disturbed and more interrupted sleep than do low or no caffeine consumers (Orbeta et al., 2006; Pollak and Bright, 2003). In addition, caffeine may be used to counteract the effects of poor sleep on daytime wakefulness (Pollak and Bright, 2003). This cycle of caffeine use disrupting sleep, leading to fatigue and subsequent caffeine use to counteract the fatigue may perpetuate poor sleep patterns and heighten caffeine consumption (Goldstein and Shapiro, 1987).

9.6. Combined risk of caffeine use, risk taking, and sensation seeking

The relationship between use of illicit drugs and personality traits, such as risk taking and sensation seeking, has been well established (Ball, 1995; Bickel et al., 1999; Lejuez et al., 2002, 2003). Despite the fact the directionality of these relationships is difficult to determine using cross-sectional studies, the relationships are strong enough that these personality traits alone can be used to identify individuals who have a propensity to use drugs (Sher et al., 2000). There is a growing body of literature that suggests that, like illicit drug and tobacco, caffeine use in adolescents and young adults is associated with impulsivity, sensation seeking, and risk taking behaviors. A study in 60 Introductory Psychology students in a large public University showed that caffeine use greater than 240 mg/day was associated with an increase in impulsivity and sensation seeking (Jones and Lejuez, 2005). In addition, a study conducted in adolescents showed that high caffeine use, defined as consuming four or more caffeinated beverages per day, was associated with daily cigarette use, aggressive behavior, and attention and conduct problems (Martin et al., 2008). Finally, a study by Miller (2008b) examined the relationship between energy drink consumption and problem behaviors in male and female undergraduates and showed that consumption of energy drinks was significantly, positively associated with risk-taking behavior and that this effect was moderated by race, being more pronounced in Caucasian undergraduate students. When taken together, these studies support an emerging theory that individuals with sensation seeking tendencies may use caffeine to increase arousal. Unfortunately, what is not know is whether early caffeine use predisposes these individuals to seek out other methods to increase arousal as they get older, such as risk taking behavior, drug use, or smoking. In addition, due to the correlational nature of these studies, it is not possible to determine cause and effect. It is possible that individuals with high levels of sensation seeking, impulsivity, and conduct disorder use caffeine as a way to "self-medicate".

9.7. Energy drinks

"Energy Drinks", with names like Cocaine™ and Red Bull™, represent the fastest growing segment of the beverage industry accounting for over $3 billion in sales in 2005 (Chandrasekaran, 2006). These drinks contain as much as five times the amount of caffeine in soft drinks and some are marketed specifically to adolescents and young adults. One energy drink, Spark™, which contains 60 mg of caffeine, is recommended for use in children 4 years and older and claims to provide "focused, sustained energy" and to "keep energy levels up" for children involved in physical activity (Advocare, 2005). Another energy drink, XS™, which has 83 mg of caffeine, is packaged in 8.4-ounce cans because, according to the manufacturer, "this size is very comfortable to hold, especially for children" (XSGear.com, 2007). In addition, this same company claims that "XS is recommended by many health professionals as a much better 'treat' for most children than sodas or juices" (XSGear.com, 2007). Finally, new energy drinks that claim to burn calories, such as Enviga™, target individuals with weight concerns and may lead to increased caffeine use as an attempted method of weight control. The growing variety and availability of energy drinks, coupled with their appeal to younger generations, adds to the growing concern of the effects of caffeine on the physiology and behavior of children. The topic of the implications if increased energy consumption was nicely reviewed by Reissig et al. (2009) and will, thus, only briefly be described here.

In addition to high levels of caffeine, typically listed either as 'caffeine' or 'guarana', high levels of sugar (glucose, dextrose, and sucrose) and small amounts of one or more of the following: vitamins, minerals, ginseng, taurine, inositol, or other botanical or herbal extracts. The latter ingredients are present at low levels, so their role, if any, would likely be modulatory (Smit et al., 2004). Few studies have examined the effects of the separate components of energy drinks to determine which ingredients exert their behavioral and physiological effects as well as to determine if the ingredients have synergistic effects. The studies that have focus on the two primary ingredients in energy drinks, caffeine and sugar. Warburton and colleagues showed that a caffeine–taurine-containing beverage significantly improved scores on a battery of cognitive tasks in non-caffeine withdrawn participants compared to sugar-containing and sugar-free control beverages (Warburton et al., 2001). Similarly, two studies by Smit and colleagues demonstrated that energy drinks significantly improve mood and cognitive and psychomotor task performance and that these effects were limited to the entire drink and the caffeine-containing control beverages (Smit et al., 2004; Smith, 2002). Some of the data presented in these studies suggests that sugar content and carbonation can play a small modulatory role in these tasks, but only in the presence of caffeine. Conversely, another study compared the effects of an entire energy drink with the individual glucose, caffeine, and herbal flavoring fractions and showed that the majority of the cognitive and psychomotor improvement was seen only when the entire drink was given and not in the caffeine-only control (Scholey and Kennedy, 2004). This suggests that caffeine and sugar can work synergistically to improve cognitive and psychomotor performance. Discrepancies among these studies may be attributable to differences in the test batteries used, the times of day of the experiments, and/or the other substances contained within the drinks. At any rate, these studies highlight the need for more research on energy drinks and energy drink components to determine their relative costs versus benefits for health and performance.

Energy drink consumption can lead to several adverse consequences, particularly in children and adolescents, due to their high caffeine content. First, children and adolescents may be more susceptible to caffeine intoxication which, as mentioned above, results in a host of physiological and psychological effects and can, in some cases, lead to death (APA, 1994; Walsh et al., 2006). Second, in addition to the adverse effects from energy drinks themselves, energy drinks are often combined with alcohol as a way to increase the positive symptoms of alcohol while counteracting the depressive symptoms of alcohol intoxication (Ferreira et al., 2006; O-Brien et al., 2008; Oteri et al., 2007). This can lead to increased alcohol intake and, consequently, increased alcohol-related adverse events (Oteri et al., 2007). Third, excessive consumption of energy drinks has been associated with engaging in several high risk behaviors, including smoking, drinking, illicit drug use, risky sexual behavior, and fighting (Miller, 2008b). Although the majority of the studies highlighted here are cross-sectional and correlational in nature, they are indicative of a growing trend in energy drink consumption and potential adverse effects, particularly within younger populations.

10. Conclusions

Caffeine use is on the rise among children and adolescents. This has lead many researchers to question the safety of caffeine use within this population, however little empirical data exist on the physiological, psychological, or behavioral effects of habitual caffeine use among children. It is clear that children can and do develop physiological tolerance to caffeine (Bernstein et al., 1994; Rapoport et al., 1984). In adults, this contributes to habitual caffeine consumption (Nehlig, 1999). It is not known whether caffeine paired with sweeteners (as is the case with soda and energy drinks) conditions a taste preference for sugar sweetened foods and beverages in children, as is known to occur in adults (Richardson et al., 1996; Yeomans et al., 1998, 2000a,b, 2001). This is one of the gaps that need to be addressed. The reinforcing value of caffeinated beverages in children is also not well understood, but data from adults (Griffiths et al., 1989) and the rising consumption patterns of caffeine in children (Frary et al., 2005; Harnack et al., 1999; Smiciklas-Wright et al., 2003) lend support to the hypothesis that caffeine added to beverages enhances their reinforcing value. Finally, given the research that has been conducted in animal models (Horger et al., 1991; Schenk et al., 1994), it is possible that habitual caffeine use may lead to cross-sensitization of the neural reward substrate to illicit drugs. Given all of these factors, it is necessary that more research be conducted on caffeine use among children to understand long-term consequences of caffeine exposure during this critical period of development.

Acknowledgements

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