Published in final edited form as:
Horm Behav. 2010 June ; 58(1): 122–137. doi:10.1016/j.yhbeh.2009.10.015.

The Emergence of Gonadal Hormone Influences on Dopaminergic Function during Puberty

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Abstract

Adolescence is the developmental epoch during which children become adults-intellectually, physically, hormonally and socially. Brain development in critical areas is ongoing. Adolescents are risk-taking and novelty-seeking and they weigh positive experiences more heavily and negative experiences less than adults. This inherent behavioral bias can lead to risky behaviors like drug taking. Most drug addictions start during adolescence and early drug-taking is associated with an increased rate of drug abuse and dependence.

The hormonal changes of puberty contribute to physical, emotional, intellectual and social changes during adolescence. These hormonal events do not just cause maturation of reproductive function and the emergence of secondary sex characteristics. They contribute to the appearance of sex differences in non-reproductive behaviors as well. Sex differences in drug use behaviors are among the latter. The male predominance in overall drug use appears by the end of adolescence, while girls develop the rapid progression from first use to dependence (telescoping) that represent a female-biased vulnerability.

Sex differences in many behaviors including drug use have been attributed to social and cultural factors. A narrowing gap in drug use between adolescent boys and girls supports this thesis. However, some sex differences in addiction vulnerability reflect biologic differences in brain circuits involved in addiction. The purpose of this review is to summarize the contribution of sex differences in the function of ascending dopamine systems that are critical to reinforcement, to briefly summarize the behavioral, neurochemical and anatomical changes in brain dopaminergic functions related to addiction that occur during adolescence and to present new findings about the emergence of sex differences in dopaminergic function during adolescence.

Introduction

Adolescence is a critical developmental epoch for addictive disease. Virtually every drug user has his or her first experience with addictive drugs during adolescence. The first regular use of an addictive drug (typically tobacco, alcohol or marijuana) occurs almost always before age 21, and the earlier substance abuse begins, the faster it develops and the more severe it is (Estroff et al. 1989; Myers and Andersen 1991; Clark et al. 1998; Brown et al. 2008; Windle et al. 2008). Adolescence is a time of tremendous change – children are maturing physically,

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emotionally and socially. Brain development is going through a crucial stage, and the hormonal and physical changes of puberty are ongoing. The present review addresses the contribution of puberty to adolescent changes in the behaviors and neurobiological mechanisms that are most important for the development of drug addiction. We have focused on biologic factors (development of specific neural circuits) rather than the social factors like gender roles and peer influences as contributors to substance abuse. Extensive literature about the latter is already available (Dakof 2000; Waylen and Wolke 2004) while biologic factors that influence gender-specific vulnerabilities are much less discussed. The information we review demonstrates that the enhanced vulnerability to addiction during adolescence reflects mainly gender-independent adolescent brain functions, and that pubertal hormonal changes mediate the emergence of the gender-specific risks for various aspects of addiction that appear by the end of adolescence.

In the following sections we will review the sex differences in drug abuse vulnerability, the important endocrine mediators that have been identified in animal models, the ontogeny of behaviors that enhance addiction risk across adolescence, adolescent development of the dopaminergic neurons innervating the basal ganglia and frontal cortex which mediates drug reinforcement and how puberty influences these processes. Finally, we will provide new preliminary data about the emergence of sex differences in dopaminergic function during adolescence. The chapter ends with a brief mention of several critical neurobehavioral functions including executive function, regulation of emotional behavior and stress-sensitivity which are critical for drug addiction but relatively uncharacterized during puberty. These represent an important target for future research.

Part 1: Sex, Gonadal Steroids and Addiction in Adults

Sex Differences in Addiction Vulnerability

Sex differences in Drug Abuse in Humans—Sex differences in drug sensitivity, drug use patterns and the role of reproductive hormones in these differences have been reviewed in previous articles in the Volume and so these will only be briefly summarized here. There are two sex differences in drug abuse in human populations that are consistently reported. First, more adult males use and abuse addictive drugs than females across most drug classes, including alcohol, psychostimulants and narcotics (NHSDUH 2007; Tetrault et al. 2008). However, women develop addiction more quickly, demonstrating a “telescoping” between initial use and dependence for most drugs including alcohol, psychostimulants and narcotics and experience a higher incidence of psychiatric disease, history of physical or sexual abuse (Ross et al. 1988; Brady et al. 1993; Brady and Randall 1999; Van Etten et al. 1999; Brecht et al. 2004; Diala et al. 2004). However, these differences are diminishing rapidly, as changing social and cultural factors strongly influence drug taking behavior. There is considerable debate but little concrete information about the role of biologic factors in either of these phenomena.

Sex Differences in Drug Self-Administration in Non-Human Primates—Sex differences in vulnerability to addiction have been characterized more extensively in animals. These have also been summarized in previous articles in this volume and so only the main issues which are relevant to adolescence will be mentioned here. We will cover the brief literature on non-human primates first, and then the more extensive literature which used rodent models.

The literature on sex differences in drug self-administration in non-human primates is sparse and reviewed elsewhere (Lynch et al. 2002; Carroll et al. 2004), but some highlights will be presented here. The findings vary by drug and by experimental paradigm. While many self-administration studies conducted in non-human primates include both males and females, few utilize subject numbers large enough to detect sex differences. Findings for ethanol are

especially contradictory. Sex differences in acquisition of ethanol-self administration were not observed in non-human primates (Grant and Johanson 1988). Females have been reported to drink more ethanol under free-drinking conditions but less ethanol under operant conditions (Juarez and Barrios de Tomasi 1999; Vivian et al. 2001). Careful consideration of differences in self-administration of cocaine based on dose, sex and menstrual cycle phase has showed that female cynomolgous monkeys will work to higher break points on a progressive ratio during the follicular phase of the cycle, but that otherwise males and females respond similarly (Mello et al. 2007). Female monkeys were reported to consume more phencyclidine than males (Carroll et al. 2005). In general, the study of sex differences in drug self-administration in non-human primates is inadequate to provide any definitive characterization.

Sex Differences in Addiction Vulnerability in Rodent Models—The majority of studies exploring sex differences use rodents although there is a growing literature with non-human primates. Animal models of the reinforcing effects of addictive drugs include locomotor activation and its sensitization, conditioned place preference (CPP) and self-administration. Locomotor activation estimates sensitivity to the activation of dopaminergic neurons projecting to the forebrain by addictive drugs but does not provide a direct measure of the reinforcing effects. CPP provides a more direct assessment of the reinforcing effects of drugs, and self administration provides the current "gold standard' of voluntary drug intake. All of these have provided some insight into the emergence of sex differences in the effects of addictive drugs that occur across adolescence because robust and consistent sex differences exist for all of these measures.

Locomotor stimulation, locomotor sensitization, CPP and acquisition of self administration of psychostimulants, narcotics, nicotine and ethanol occur faster, at lower doses and/or are greater in magnitude in females than males (Donny et al. 2000; Carroll et al. 2004; Hu et al. 2004; Chaudhri et al. 2005; Craft 2008; Yararbas et al. 2009). During short access, fixed ratio responding, females and males self-administer comparable amounts of cocaine (Caine et al. 2004). However, females will work harder for psychostimulants under a progressive ratio, escalate use faster and bar press more during extinction than males (Lynch et al. 2002; Carroll et al. 2004; Lynch 2006; Quinones-Jenab 2006; Becker and Hu 2008). The latter findings have been interpreted to indicate that motivation to take drugs is stronger in females. During relapse to cocaine self administration, females are comparable to males after cocaine while they exhibit less reinstatement during cue-induced relapse (Fuchs et al. 2005). These latter characteristics are thought to be a better model of drug-taking characteristics that are relevant for human addiction than simple self-administration (Vanderschuren and Everitt 2004). Sex differences in several nonpharmacological controls of self-administration also have been reported. Self-administration of nicotine is more affected by non-drug stimuli in females than males and responding during time-out periods and during extinction are greater in females than males (Chaudhri et al. 2005). These differences could reflect sex differences in regulation of operant behavior. The finding with nicotine may be particularly relevant to humans, as women are reported to be more sensitive to conditioned cues associated with smoking than men (Perkins et al. 1999). In general, females show behaviors that can be interpreted as transitioning into compulsive phases of addiction faster, much as has been noted in humans.

Gonadal Steroid Influences on Addiction

Gonadal Steroid Influences in Humans and Non-human primates—Ovarian steroids are thought to influence the effects of addictive drugs in women, but often in subtle ways. One method that has been used to demonstrate these effects is to measure drug effects or consumption across the menstrual cycle. Women experience greater subjective effects of many addictive drugs during the follicular phase of the menstrual cycle (Terner and de Wit 2006). However, there are some notable exceptions including ethanol, for which neither

subjective effects nor consumption vary with the menstrual cycle (Sofuoglu et al. 1999; Holdstock and de Wit 2000; Evans et al. 2002). Suppression of subjective effects of cocaine by progesterone has been reported in several studies (Sofuoglu et al. 2002; Sofuoglu et al. 2004; Evans 2007). These observations have initiated studies of a possible therapeutic use for progesterone, which might mediate the decreased subjective effects during the luteal phase of the cycle. These findings are discussed at length elsewhere in this volume.

Gonadal Steroid Influences on Addictive Behaviors in Rodent Models—A more extensive literature from studies conducted in rodents supports a facilitatory role for estradiol in self-administration of several drugs, and a suppressive role for progesterone. Estrogen facilitates acquisition, increases responding under a progressive ratio, and enhances responding during drug-induced relapse although negative reports exist (Grimm and See 1997). In contrast, progesterone suppresses these same behaviors (Feltenstein and See 2007; Feltenstein et al. 2009). The role of testicular steroids is less convincing. Castrating male rats does not change psychostimulant-enhanced dopamine release or rotational behavior after amphetamine (Becker 1999) or change cocaine self administration (Hu and Becker 2003; Hu et al. 2004). However, other studies show that castration of male rats causes a delayed increase in cocaine-stimulated locomotion (Long et al. 1994; van Luijtelaar et al. 1996; Walker et al. 2001). In general, ovarian steroids modulate addiction-related behaviors significantly : estrogen consistently enhances behaviors in rats that are relevant to addiction, while progesterone suppresses the same behaviors. Testosterone is either inactive or slightly suppresses the same behaviors.

Gonadal Steroid Effects on Dopaminergic Functions Relevant to Addiction

Dopamine and Reinforcement—Gonadal steroid effects on drug self administration are mediated in part by effects on dopaminergic neurons. The dopaminergic neurons that project from the substantia nigra and ventral tegmental area to the caudate nucleus, nucleus accumbens (dorsal and ventral striatum) and frontal cortex play a prominent role in both normal reinforcement and the initiation of drug addiction in adult animals and perhaps the transition into habitual use (Le Moal and Simon 1991; Kalivas and O'Brien 2008; Carlezon and Thomas 2009; Dalley and Everitt 2009). All drugs that humans self-administer activate these dopaminergic neurons, including nicotine, alcohol, opiates and psychomotor stimulants like cocaine and amphetamine (Di Chiara et al. 2004). Developmental changes in and gonadal steroid hormone effects on the dopaminergic neurons which project from the substantia nigra and ventral tegmental area will be focus of the present review. Although gonadal steroids strongly modulate hypothalamic dopaminergic neurons which regulate hormone release and sexual behavior (Hull et al. 1999; Ben-Jonathan and Hnasko 2001; Dominguez and Hull 2005), the contribution of these neurons to drug addiction has not been studied extensively and it will not be discussed here.

Sex Differences in Dopaminergic Function in Humans and Non-Human Primates—Sex differences in dopaminergic function exist which likely contribute to sex differences in drug self-administration (reviewed by Jill Becker in this Volume, and see also (Becker 1999; Becker and Hu 2008; Morissette et al. 2008). The available literature about humans and non-human primates is discussed first, followed by information about rodents.

Although sex differences in the neurochemistry and neuroanatomy of forebrain dopaminergic neurons have not been thoroughly studied in humans and non-human primates, some evidence indicates sex differences do exist. Fundamental data derive from studies of disease risk: females are significantly less likely to develop Parkinson's disease, and do so at a later age (Baldereschi et al. 2000; Wooten et al. 2004). These studies suggest that dopaminergic innervation of basal ganglia may be different in men and women. However there has been little anatomical study of this question. Imaging studies of dopamine release are mixed: some studies show that women

exhibit greater dopamine release in response to psychostimulants, and others show that men do so (Munro et al. 2006; Riccardi et al. 2006). Therefore, the literature is inconclusive about the nature of sex differences in dopaminergic function in humans.

Sex Differences in Dopaminergic Function in Rodents—Sex differences in both presynaptic function (release of dopamine) and postsynaptic function (expression and regulation of dopamine receptors) have been extensively characterized. These have been studied most widely in rodents. It has been proposed that the integration of basal dopamine release, capacity to stimulate dopamine release and receptor sensitivity contribute to the enhanced dopamine response of females (Castner and Becker 1996) that translates into an enhanced behavioral reactivity (Becker and Hu 2008). Basal dopamine release does not differ in males and females: studies utilizing microdialysis or low frequency stimulation with fast scan cyclic voltammetry show that males and females have roughly comparable levels of extracellular dopamine when they are gonadally intact (Becker and Ramirez 1981b; Castner et al. 1993; Walker et al. 2000; Walker et al. 2006). Similarly, the numbers of D1 and D2 receptors in dorsal and ventral striatum are fairly similar in males and females, and one study even reports greater D1 receptor density in males (Becker and Ramirez 1981b; Festa et al. 2006). However, females show consistently higher dopamine release in response to electrical stimulation or psychostimulants in dorsal striatum. Our laboratory has shown that maximal, electrically stimulated dopamine release in dorsal striatum in females is almost double that observed in males (Walker et al. 2000). These findings are consistent with the report that amphetamine causes the greatest c-fos responses (an immediate early gene response that reflects the sum of both pre- and post-synaptic stimulation) in proestrous females (Castner and Becker 1996). It has been postulated that female rodents in a high estrogen state exhibit dopaminergic responses to pharmacologic stimuli that exceed males as well as females in other endocrine states.

An extensive literature supports an important role for estrogen in augmenting both pre- and postsynaptic dopaminergic function. Estrogen augments dopamine release, increases both D1 and D2 receptor number by slowing receptor degradation rates and enhances DAT production (Morissette et al. 1990; Levesque and Di Paolo 1991; Morissette and Di Paolo 1993; Morissette and Di Paolo 1993; Becker and Hu 2008; Morissette et al. 2008). Multiple hypotheses have been proposed to explain how estrogen augments dopaminergic function. One hypothesis is that estradiol reduces GABA-mediated inhibition of dopaminergic terminals (Hu et al. 2006). In contrast, most studies of adult males suggest that testosterone does not regulate dopaminergic function in dorsal or ventral striatum (Becker 1999; Becker 2009). However, frontal cortex dopaminergic circuits that are important for executive function and working memory are facilitated by androgen (Adler et al. 1999; Kritzer 2000; Kritzer et al. 2001; Kritzer 2003; Kritzer et al. 2007), and these processes may contribute significantly to addiction vulnerability. Androgen actions on these brain functions represent an important gap in our knowledge about gonadal steroid effects on addictive behaviors.

Gonadal Steroid Effects on the Anatomy of Dopamine Systems

Gonadal Steroid Hormone Effects on Anatomy of Dopamine Systems in Humans and Non-Human Primates—Gonadal steroids may influence the morphology of dopaminergic neurons as well as expression of key dopaminergic proteins and afferent regulation of dopamine release. Convincing evidence supporting this possibility was the report that ovariectomy of female primates caused a permanent decrease in dopamine cell number in the substantia nigra that could be prevented by estradiol replacement (Leranth et al. 2000). In primates, estradiol and progesterone both increase the density of terminal arborization of dopaminergic neurons in some areas including the dorsolateral (sensory association areas) of the dorsal striatum as well as the frontal cortex (Kritzer and Kohama 1998; Kritzer et al.

2003). Estradiol also has functional effects on dopamine release in monkeys: estradiol replacement of Parkinsonian monkeys can enhance dopamine release even after a prolonged period of estrogen deprivation (Morissette and Di Paolo 2009).

Gonadal Steroid Hormone Effects on Anatomy of Dopaminergic System in Rodents—Numerous studies suggest that estradiol has a trophic role in maintaining dopaminergic neurons, especially in response to neurotoxic injury (Morissette et al. 2008). Recent studies from our own laboratory have shown that female rodents have more dopaminergic neurons in both the substantia nigra and ventral tegmental area, and that estradiol maintains dopamine cell number in both rats and mice, primarily through actions on estrogen receptor beta (Johnson 2009a). Our studies have also suggested a role for testicular steroids in this phenomenon, as castration of male rats resulted in an unexpected increase in the number of dopaminergic neurons (Johnson 2009b). Although other studies have not reported such a difference (Dewing et al. 2006; McArthur et al. 2007), the latter studies did not employ unbiased stereologic counting, which is the most rigorous standard in the field. These differences in the number of dopaminergic neurons may contribute to reported differences in dopaminergic function after manipulation of gonadal steroid hormone levels. Surprisingly, sex differences in dopaminergic innervation of the dorsal and ventral striatum have not been reported. However, dopaminergic innervation of the frontal cortex has been studied, and androgen may contribute significantly in this region. Kritzer showed that androgen reduces terminal density in cortex of rodents (Adler et al. 1999; Kritzer 2000; Kritzer 2003).

The existence of strong regulation by estradiol and modest regulation by testosterone are concordant with the reported expression of gonadal steroid hormone receptors in dopaminergic neurons. A significant percentage of the dopaminergic neurons in the midbrain express androgen receptors, while only a small percentage express either of the two main estradiol receptors (ERα and ERβ) (Kritzer 1997; Creutz and Kritzer 2002; Creutz and Kritzer 2004; Kritzer and Creutz 2008). These anatomical differences represent an important potential mediator of hormonal effects on dopaminergic function. They could be especially relevant as mediators of developmental changes.

Estrogen as a Mediator of Sex Differences in Addiction

The enhancement of dopaminergic function in the forebrain by estradiol has generated the hypothesis that this effect contributes to sex differences in drug self-administration across mammalian species (Lynch et al. 2002; Carroll et al. 2004; Lynch 2006; Becker and Hu 2008). The commonality of this finding may reflect the fundamental organization of how motivation is tied to reproductive state in males and females. Regulation of dopaminergic neurons projecting to the forebrain by ovarian but not testicular steroids is speculated to allow males to seek out sexual partners (using this dopaminergic system) at any time, while females will only seek out sexual partners when they are fertile (Becker and Taylor 2008) although this may not reflect specificity for sexual behavior per se (Paredes and Agmo 2004).

The well-described decrease in sexual motivation (among other deficits) in Parkinson's disease and the emergence of inappropriate sexual behavior during treatment with dopaminergic agonists suggests that dopamine contributes to these behaviors in humans (Meco et al. 2008). However, the relative contribution of specific gonadal steroids is notoriously species-specific and recent studies in humans showed that hypogonadism impaired sexual function in both men and women, but that testosterone restored function in men but estradiol did not do so in women (Czoty et al. 2009). Furthermore, studies of dopamine release in dorsal and ventral striatum of humans show inconsistent sex differences. Two studies of dopamine release have been published in humans which report opposite gender related findings: one reports that release

was greater in males, and another that it was greater in females (Munro et al. 2006; Riccardi et al. 2006)

Gonadal steroids also regulate sexual motivation in primates although non-hormonal (social) cues play a significant role (Wallen and Zehr 2004). Female non-human primates coordinate sexual behavior with the time of menstrual cycle (mid cycle) that is associated with high fertility (Bonsall et al. 1978). Furthermore, dopamine release may be regulated by ovarian steroids in non-human primates, as a recent PET study showed that basal DA release may be lower during the luteal than follicular phase in non-human primates (Schmidt et al. 2009).

Part 2: Adolescence and Addiction

Adolescence as a Developmental Epoch Critical for Addiction in Humans— Adolescence is the final developmental epoch which marks the transition to adulthood (Spear 2000; Windle et al. 2008). For the purposes of this review, we will use the age ranges described in these two reviews. In humans, it spans roughly from years 10-25. This age range is larger than that typically given. However, recent brain imaging studies suggest that the brain is not fully mature until the mid-twenties (Lenroot and Giedd 2006).

The completion of brain and somatic development interact with the dramatic cultural and social changes occurring as children shift their sphere of influence from family to peers. Recent studies have shown that brain structure is undergoing final maturation during this period. Gray matter density falls, perhaps reflecting an offsetting increase in myelin although the trajectory for individual brain regions varies (Isralowitz and Rawson 2006; Paus et al. 2008; Giedd et al. 2009) and synaptic density falls slowly during late adolescence, at least in non-human primates (Bourgeois et al. 1994).

Brain function is also completing critical final stages of development during which executive functions like delayed gratification (Casey et al. 2000; Steinberg et al. 2008; Astle and Scerif 2009) and processing of reward and aversive stimuli finally mature at the end of adolescence (Ernst et al. 2006; Ernst and Mueller 2008; Ernst and Fudge 2009). The immaturity of reward processing by the dopaminergic system and of cortical circuits that inhibit behavior are particularly critical for addiction vulnerability in adolescence. Imaging studies in humans suggest that adolescents may be more sensitive to reward, less sensitive to aversive stimuli and less able to inhibit responses because frontal cortex circuits which regulate behavior are immature compared to adults (Crews and Boettiger 2009; Geier and Luna 2009). Impulsivity and sensation seeking are high during adolescence (Spear 2000; Steinberg et al. 2008). A substantial literature points to these behavioral traits or related psychological constructs like “neurobehavioral disinhibition” as significant risk factors for the development of drug dependence, especially in adolescence (Dawes et al. 2000; Crews et al. 2007; Everitt et al. 2008; Perry and Carroll 2008; Crews and Boettiger 2009; Volkow et al. 2009). In summary, the state of adolescent brain development may place adolescents at risk for substance abuse for several reasons: they may respond to rewarding stimuli more than aversive stimuli relative to adults, they relatively discount future outcomes, and they are sensation seeking and impulsive. There are several excellent reviews in this area (Crews et al. 2007; Brown et al. 2008; Windle et al. 2008).

Adolescence as a Developmental Epoch for Addiction in Rodents—In rodents, adolescence spans from postnatal day (PN) 25 to early adulthood on PN60 (Spear 2000). This time frame includes but is not restricted to pubertal development. As with humans, brain development continues until the end of the time frame, and PN60 should be viewed as the earliest time that adult brain function exists, and it is likely that the latest developing functions

mature somewhat after this arbitrary cutoff (Rice and Barone 2000; McCutcheon and Marinelli 2009).

Although the literature on behavioral development is less abundant, when the appropriate postnatal age is considered, similar behavioral development occurs in rodents and humans during adolescence. Risk-taking and sensation seeking are high in rodents, as they are in humans (Spear 2000; Laviola et al. 2003). A smaller but emerging animal literature supports the same dominance of rewarding over aversive effects of addictive drugs during adolescence (Laviola et al. 2003; Schramm-Sapyta et al. 2009). The commonality of these processes suggest that rodent models can provide a useful tool for exploring brain mechanisms that are important for the development of addiction.

In summary, several behaviors that are critically involved in the development of drug addiction change rapidly during adolescence. Neural circuits involved in processing reward as well as those that control executive functions that inhibit behavior may be the most relevant to the adolescent vulnerability to addiction, as adolescents are possibly more sensitive to reinforcement, and show less ability to inhibit responses based on future outcomes.

Addiction-Related Behaviors during Adolescence

Animal models provide a crucial insight into how addiction-related behaviors change during adolescence, as experimental studies in humans are ethically impermissible, and naturalistic studies are seriously confounded by socioeconomic, environmental and genetic complexities that require an analysis that is beyond the scope of the present review. The majority of these studies have been conducted in rodents; these studies will be reviewed below.

The characteristic behavioral effects of many addictive drugs change as adolescents mature, and the changes generally tend to be consistent across drugs for a given behavior. The one exception may be locomotor activity, as the changes in locomotor response across adolescence are somewhat drug specific. These studies are reviewed by Schramm-Sapyta (Schramm-Sapyta et al. 2009). Amphetamine and methamphetamine stimulate locomotion less in early adolescents than adults, while locomotor stimulation by cocaine is greater during early adolescence than adulthood. Nicotine has been reported to decrease or increase locomotion in a developmentally specific way, depending upon the dose or species under study. Decreases in locomotion result from nicotine treatment of mice, and this decrease is less in adolescents (Lopez et al. 2003). In rats, nicotine is reported to increase locomotion, and adolescents are more rather than less sensitive to this effect (Faraday et al. 2001).

Locomotor sensitization, which is thought to reflect neuroplastic events during early addictive drug exposure, gradually increases across adolescence after treatment with amphetamine, cocaine or methylphenidate: sensitization is low when treatment is initiated during the perinatal period, becomes more robust during adolescence but is greater in adulthood than in adolescence (Kolta et al. 1990; McDougall et al. 1994; Ujike et al. 1995; Bowman et al. 1997; Laviola et al. 1999; Tirelli et al. 2003; Frantz et al. 2007). One exception may be sensitization following single drug exposures, as our laboratory has observed enhanced single-dose sensitization in adolescents compared to adults (Caster et al. 2007). Nicotine sensitization produced by treatment of adolescent rats is less than that observed after a comparable treatment of adult rats, although cross-sensitization to cocaine and amphetamine were both greater in adolescent males than adult males (Collins and Izenwasser 2004; Collins et al. 2004; Cruz et al. 2005; McQuown et al. 2009).

CPP for most addictive drugs including nicotine, cocaine and amphetamine is enhanced during adolescence (Vastola et al. 2002; Belluzzi et al. 2004; Badanich et al. 2006; Kota et al. 2007; Torres et al. 2008; Brenhouse and Andersen 2008a; Schramm-Sapyta et al. 2009; Shram and

Le 2009; Zakharova et al. 2009) although conflicting findings have been reported for both cocaine and amphetamine (Adriani and Laviola 2003; Tirelli et al. 2003; Schramm-Sapyta et al. 2004). Conflicting data exist for ethanol CPP in rats and mice (Philpot et al. 2003; Dickinson et al. 2009) and the cannabinoid agonist WIN5512-2 causes CPP at lower doses in adult than adolescent rats (Pandolfo et al. 2009). In summary, CPP is enhanced in adolescents compared to adults while sensitization is less in animals treated repetitively with psychostimulants in adolescence than those treated as adults. These divergent results suggest that adolescents experience both the reinforcing and neuroplastic effects of addictive drugs, but that the latter may be diminished relative to adults while the former are exaggerated. The enhanced reinforcing effects of most addictive drugs in adolescent rodents is consistent with the increased response to reward reported above that has been observed both in humans and rodents.

The standard for evaluating the addiction liability of drugs of abuse is self-administration. Animal studies in which self-administration starting in adolescence and adulthood were compared have yielded consistent findings for some drugs, but contradictory findings for other drugs. In general, acquisition of self administration of ethanol is consistently faster in adolescents (Bell et al. 2003; Brunell and Spear 2005; Doremus et al. 2005; Bell et al. 2006; Vetter et al. 2007). Faster acquisition of nicotine self-administration has been reported in adolescents compared to animals that begin self-administration as adults (Chen et al. 2007; Levin et al. 2007) and adolescent but not adult mice will voluntarily drink nicotine-containing solutions (Adriani et al. 2002). However, adolescents self-administer less nicotine than adults on demanding reinforcement schedules, and show faster extinction and less relapse than adults (Shram et al. 2008; Shram et al. 2008). Some of these inconsistencies in reports of nicotine self -administration in adolescents and adults may reflect the relative importance of reward and withdrawal at different ages. While adolescents tend to be more sensitive to the rewarding effects of nicotine (see above), they tend to exhibit less pronounced dependence (O'Dell et al. 2004; O'Dell et al. 2006; Wilmouth and Spear 2006; O'Dell et al. 2007; Shram et al. 2008). Finally, findings with self-administration of cocaine have been the most equivocal. Although faster acquisition of self-administration has been observed at least for animals with low saccharin preference (Perry et al. 2007), several other studies have shown that stable self-administration does not differ based on whether self-administration begins during adolescence or adulthood (Frantz et al. 2007; Kantak et al. 2007; Kerstetter and Kantak 2007; Li and Frantz 2009). Most of these studies employ traditional fixed-ratio schedules which do not test for the key transitions to compulsivity and escalation that are tested by escalation regimens (Vanderschuren and Everitt 2004). In general, the literature suggests that adolescents may be more sensitive to the reinforcing effects of drugs of abuse, but no data exist yet to assess whether adolescents escalate use and progress to compulsive use faster than adults.

Maturation of Forebrain Dopaminergic Function during Adolescence

The important role of dopaminergic neurons in sexual and drug reinforcement and the important pubertal events which initiate sexual motivation suggest that the developmental changes in dopaminergic neurons during puberty may be a key event for drug abuse vulnerability. The studies cited above suggest that activation of dopaminergic neurons by reinforcers including drugs might be greater during adolescence compared to adults. In the next section, we will review what is known about the ontogeny of dopaminergic neurons and present new data about the emergence of sex differences in dopaminergic function.

Maturation of Forebrain Dopaminergic Function in Humans—Non-human primate and human dopaminergic systems develop similarly. Dopamine content, tyrosine hydroxylase and anatomic measures of dopaminergic innervation of frontal cortex rise to a peak just before adolescence and fall in non-human primates (Goldman-Rakic and Brown 1982; Rosenberg and Lewis 1994; Rosenberg and Lewis 1995; Erickson et al. 1998). Striatal dopamine content

increases through adolescence in humans (Haycock et al. 2003) although other synaptic markers including tyrosine hydroxylase, the vesicular transporter (VMAT2) and the plasma membrane transporter (DAT) peak just at the beginning of adolescence (Meng et al. 1999; Haycock et al. 2003).

Although all of the neurochemical "machinery" for dopaminergic transmission is present soon after birth, a number of indices of dopaminergic function change markedly during adolescence. Many indices reach peak levels of expression during late adolescence or early adulthood followed by a fall to adult levels. Changes in postsynaptic receptors have been described most thoroughly. Overexpression of D1 and D2 receptors early in development and subsequent *decreases* during adolescence have been reported in several studies (Meng et al. 1999; Seeman 1999). A recent study in humans shows a similar loss of presynaptic markers during early adolescence (Haycock et al. 2003).

Maturation of Forebrain Dopaminergic Function in Rodents—The ontogeny of dopaminergic neurons innervating the forebrain in rodents is quite similar to that reported above for non-human primates and humans. Dopaminergic neurons which eventually innervate the dorsal and ventral striatum and frontal cortex in rats undergo their final division during mid-gestation (Lauder and Bloom 1974). All molecular markers of dopaminergic neurons are expressed at significant levels before birth, but the explosive growth of dopamine innervation of the forebrain occurs after birth in the rat. From PN5 to PN40, most markers including dopamine content, tyrosine hydroxylase, D1 and D2 receptors and dopamine transporter increase markedly in striatum, n. accumbens and frontal cortex (Coyle and Axelrod 1972; Porcher and Heller 1972; Nomura et al. 1976; Kirksey and Slotkin 1979; Giorgi et al. 1987; Gelbard et al. 1989; Broaddus and Bennett 1990; Broaddus and Bennett 1990; Rao et al. 1991; Coulter et al. 1997; Tarazi et al. 1999). A dramatic rise in all of these dopaminergic markers occurs between two to three weeks postnatally, just before adolescence, but maturation continues until at least PN60. Frontal cortex innervation in the rat lags slightly behind that of more caudal regions, with almost all dopaminergic innervation arriving postnatally and achieving adult levels by PN60 (Kalsbeek et al. 1988).

Dopamine receptors in rodents undergo a rise followed by adolescent pruning like that reported in humans (Huttenlocher 1979; Giorgi et al. 1987; Gelbard et al. 1989; Teicher et al. 1995; Montague et al. 1999; Tarazi et al. 1999; Andersen et al. 2000; Tarazi and Baldessarini 2000; Andersen et al. 2002). Although marked pruning of presynaptic markers was not observed in the one rat study that used narrow windows (Tarazi et al. 1998), the radioligand used in these studies (GBR12935) binds in a different way to the DAT than WIN 35,428, a radioligand which shows better correlation between binding and uptake inhibition (Xu et al. 1995). These studies suggest that pruning of critical connections from weaning to adulthood could play a role in behavioral changes.

Extracellular dopamine levels parallel the reported increases in innervation density that occurs throughout adolescence. Basal extracellular dopamine levels as measured by voltammetry or microdialysis are lower during adolescence than adulthood (Gazzara et al. 1986; Stamford 1989; Andersen and Gazzara 1993; Laviola et al. 2001).

Activity of Forebrain Dopaminergic Neurons during Adolescence—The previous description provides the impression that dopaminergic innervation of forebrain targets is deficient in early adolescence, becomes fully functional during later adolescence, followed by some "pruning' back as animals become fully adult. However, measures of dopaminergic neuron activity suggest that these neurons are extremely active during this time frame. Functional studies show that dopaminergic neurons achieve nearly adult levels of function during early adolescence, at about the time that stimulant-induced behavioral activation peaks.

Dopaminergic neurons attain adult firing patterns including autoreceptor function and bursting pattern of firing just before or during adolescence (Pitts et al. 1990; Tepper et al. 1990; Lin and Walters 1994; Wang and Pitts 1995; Marinelli et al. 2006; McCutcheon and Marinelli 2009). Microdialysis and neurotransmitter turnover studies have shown that axonal transection, gamma hydroxybutyrate, and psychomotor stimulants can activate dopaminergic neurons well before weaning (Erinoff and Heller 1978; Cheronis et al. 1979). Single unit studies of dopamine cell firing show that the firing rate is higher during adolescence, perhaps because it is less restrained by autoreceptor inhibition (Marinelli et al. 2006). Our laboratory has shown that cocaine-induced dopamine overflow is greater in dorsal striatum in adolescent than adult rats even though maximal dopamine release (which reflects terminal stores) is significantly less (Walker and Kuhn 2008). The traditional turnover measure of HVA/DA ratio also is significantly higher in adolescent than adult rats (see Figure 1). Similar findings have been reported in a study that compared 18, 30 and 110 day old rats (Teicher et al. 1993). These data all suggest that dopaminergic neurons that project to forebrain targets relevant to addiction may not have complete, adult levels of innervation, but if anything are more responsive to neuronal inputs.

Enhanced activation of dopaminergic neurons in early adolescence may not extend to the dopaminergic neurons that innervate the cerebral cortex. An elegant series of studies in rat brain slices showed that both D1 excitatory and D2 inhibitory influences on interneuron function were absent in cortex during the same phase of development that is described above (Tseng and O'Donnell 2005; Tseng and O'Donnell 2007). However, these studies employed a different model system, and comparable end points have not been assessed in dorsal or ventral striatum during adolescence. It is possible that cortical dopaminergic inputs may mature at a slightly different pace than the striatal inputs.

Part 3: Sex, Gonadal Steroids and Addiction in Adolescence

Emergence of Sex Differences in the Use of Addictive Drugs by Humans

Sex differences in drug use by humans appear during adolescence. However, generational cohort effects influenced by changing social roles for women and other factors highly influence these findings. Initiation in drug use has almost equalized in boys and girls (Johnston et al. 2007; NHSDUH 2007). Young adolescent females are as likely to drink alcohol, use marijuana and other illicit drugs and to use multiple drugs as young adolescent males (Johnston et al. 2007; NHSDUH 2007; Palmer et al. 2009). Use of tobacco, alcohol, marijuana and other illicit drugs increases linearly across adolescence in a parallel way in males and females. The significant differences emerge later in adolescence, when males are slightly more likely to be alcohol dependent and females to smoke (Young et al. 2002; Cropsey et al. 2008). Other studies that include older teenagers show that males' use of marijuana and other illicit drugs exceeds that of females (Terry-McElrath et al. 2008) although cohorts vary and in some studies, use of even “hard” drugs like heroin and cocaine are comparable in adolescent males and females (Gerra et al. 2004). In general, the two major sex differences in drug use (more frequent drug use by males and the “telescoping” of progression from use to abuse in females) appear by the end of adolescence (Nolen-Hoeksema 2004; Ridenour et al. 2006).

Puberty as an Influence on Vulnerability to Addiction in Adolescence?

Puberty as a Critical Aspect of Adolescent Brain Development—Puberty is superimposed upon and contributes to adolescent brain development. The animal models are so concordant with studies in humans, that these will be discussed together in this section. In humans, pubertal development occurs over a wide age range depending on ethnic background, culture and health of the individual, but in the developed world, girls generally attain adult estradiol and progesterone levels by age 14-15 (when they are menstruating) and boys attain

adult testosterone levels a year later, by age 16-17 (Styne and Grumbach 2008). Similarly, in rodents, females have adult cyclic gonadal steroid hormone levels by about postnatal day PN35 when they experience their first estrus, while males experience a liner increase in testosterone from PN25 until about PN60. At this age, puberty is generally complete in both sexes and animals are reproductively mature (Lee et al. 1975; Korenbrot et al. 1977; Ojeda et al. 1980; Ojeda et al. 1986).

Both activational and organizational effects of gonadal steroids contribute significantly to changes in brain structure and function during puberty. During puberty, both males and females attain adult levels of reproductive hormones, which then regulate their targets on an ongoing basis: this process provides the activational effects of gonadal steroids which regulate brain function in an ongoing and reversible fashion. However, there is a growing appreciation that the rise of gonadal steroids during puberty in both males and females contribute to the completion of sexual differentiation of the brain by triggering irreversible processes – the organizational effects of gonadal steroids (Cooke et al. 1998; Becker et al. 2005; Schulz et al. 2009).

Sexual dimorphisms in brain structure that emerge during puberty are also influenced by gonadal steroids. In fact, human brain structure is sexually dimorphic even at birth (Gilmore et al. 2007) and the trajectory of change in brain structure across adolescence varies in girls and boys well before puberty. Girls attain peak gray matter density 1-2 years before boys (Giedd et al. 2006). This trajectory is further influenced by pubertal stage (De Bellis et al. 2001). The changes in some brain structures including amygdala and hippocampus reflect the stage of pubertal development and gray matter changes depend on circulating estradiol in girls and testosterone in boys (Peper et al. 2009). The sexual dimorphisms in brain structures in rodents have been well described and are well beyond the scope of the present review. Several excellent reviews exist (MacLusky and Naftolin 1981; Cooke et al. 1998; Morris et al. 2004; Ahmed et al. 2008).

Puberty and Behavioral Change during Adolescence—The increased secretion of gonadal hormones during puberty contribute to maturation of behavior as well as brain structure and function. In females, pubertal increases in both estradiol and progesterone are necessary for the appearance of the full complement of female behaviors and in males, both testosterone and estradiol formed from aromatization of testosterone contribute to activational and organizational effects. Several recent reviews of how gonadal steroids contribute to the development of reproductive function and sexual behaviors during puberty have been published (Romeo et al. 2002; Romeo 2003; Sisk et al. 2003; Sisk and Zehr 2005; Schulz and Sisk 2006). Testicular and ovarian steroids permit the onset of sex- appropriate social behavior, aggression, and parental behavior as well as reproductive behaviors. While the majority of these data have been collected in mice, rats and hamsters, similar findings have been reported in humans who experience precocious puberty (reviewed in (Sisk and Zehr 2005).

Gender differences in behavior which are relevant to addiction also emerge during puberty (Windle et al. 2008). Sensation seeking is expressed at higher rates and often more strongly associated with drug abuse in men than women (Butkovic and Bratko 2003; Nolen-Hoeksema 2004). Sensation seeking is highest during mid/late puberty in both boys and girls compared to similarly-aged children at an earlier pubertal stage (Quevedo et al. 2009). Furthermore, pubertal hormone levels contribute to these events. Testosterone has been positively correlated with sensation-seeking in both adult males (Coccaro et al. 2007) and adolescent males (Martin et al. 2004) while high estradiol has been associated with lower levels of sensation seeking (Balada et al. 1993) although pubertal changes have not been reported. Finally, testosterone levels during puberty are positively correlated with sensation seeking and concurrent drug use (Martin et al. 2002) Although it is likely that hormonal events in both males and females

contribute to the emergence of sex differences in addiction-critical behaviors, the study of pubertal influences on these critical developmental events is in its infancy

Emergence of Sex Differences in the Action of Addictive Drugs

The well-established stimulation of dopaminergic function by estradiol reviewed above suggests the rise in estradiol that occurs with the onset of estrous cyclicity should trigger an increase of dopamine release and in the behavioral response to addictive drugs. In fact, sex differences in multiple addiction-related behaviors do appear during adolescence in rodents, and in the very small number of primate studies that exist. However, emerging evidence indicates that both ovarian and testicular steroids might contribute to these changes.

Our laboratory has shown that young adolescent male rats exhibited greater cocaine-stimulated locomotion, more activation of downstream signaling pathways in the dorsal striatum (as measured by c-fos activation), and greater single-dose sensitization of locomotor behavior than adult (Caster et al. 2005; Caster et al. 2007). Comparison of cocaine-stimulated locomotion in adolescent and adult males and females has shown that adolescent males and females respond similarly to cocaine, and that the sex difference in cocaine-stimulated locomotion appears during adolescence. The sex difference reflects in part the decline in cocaine-stimulated activity in males as well as an increase in cocaine-stimulated locomotion in females (Parylak et al. 2008). A similar developmental change in the locomotor response to methylphenidate has been reported: while male and female adolescents exhibited comparable locomotor stimulation, methylphenidate stimulated significantly more locomotor activity in adult females than in males (Wooters et al. 2006). Morphine-induced locomotor stimulation showed a somewhat different pattern: adolescent males exhibited more locomotor stimulation than adult males, but adolescent and adult females were equivalent to adult males – there was a sex difference during adolescence but not adulthood (White et al. 2008). The greater sensitivity of male mice to inhibition of locomotion by nicotine relative to females appears after adolescence (Lopez et al. 2003) Finally, locomotor stimulation associated with low doses of ethanol increases as adolescent monkeys become adult (Schwandt et al. 2007).

Sex differences in sensitization also emerge during adolescence. Cross-sensitization between nicotine and the psychostimulants cocaine and amphetamine are greater in male than female adolescent rats (Collins and Izenwasser 2004; Collins et al. 2004). Sex differences in ethanol sensitization in mice similarly have been reported in adult but not adolescent mice, suggesting that these differences emerge during puberty (Itzhak and Anderson 2008). Ethanol-induced locomotor sensitization in female but not male non-human primates has been reported during adolescence (Schwandt et al. 2008).

Sex differences in the reinforcing effects of addictive drugs also appear during adolescence. The greater sensitivity of females to cocaine CPP emerges during adolescence (Zakharova et al. 2009). Adult but not adolescent female mice experience greater CPP to cocaine than age-matched males (Balda et al. 2009). One study reported no sex difference in either morphine or cocaine CPP when adolescent and adult rats were compared, but the number of experimental subjects was small enough that it would be been unlikely to detect such a difference unless it had been extremely large (Campbell et al. 2000).

Sex differences in self-administration of many addictive drugs appear during adolescence. We have shown that adult but not prepubertal female rats ingest more cocaine and two laboratories have reported the appearance of faster acquisition of cocaine self administration during adolescence (Perry et al. 2007; Carroll et al. 2008; Lynch 2008; Walker et al. 2009). While both adolescent male and female rats acquire nicotine self administration faster than adults, levels of self-administration actually fall in males as they enter adulthood, while females maintain levels of intake (Levin et al. 2003; Levin et al. 2007). Females and males exhibit

comparable nicotine self administration under a progressive ratio schedule early in adolescence but by the end of adolescence, females take more nicotine than males (Lynch 2009). Finally, adolescent mice self-administered fewer doses of oxycodone than adults, but this result was interpreted as greater sensitivity to the effects of oxycodone on dopaminergic neurotransmitter because they demonstrated an exaggerated increase in dopamine in the ventral striatum at the end of self administration (Zhang et al. 2009).

Emergence of sex differences in alcohol ingestion have been reported in both rodents and non-human primates, although the specific sex differences depend upon species. Female rats ingest more alcohol than male rats, and this sex difference appears during adolescence (Lancaster and Spiegel 1992; Lancaster et al. 1996). The one primate study that exists shows that males and females ingested equal amounts of ethanol in these studies (Schwandt et al. 2008).

Developmental changes in responses to amphetamine differ from the other drugs that have been studied and so these are described separately. Both male and female adolescent rats acquired amphetamine self administration faster than adults in a study by Shabazi (Shahbazi et al. 2008). Adolescent males in this study took less amphetamine under a progressive ratio schedule than adult males, while young adult females took more than older adult females. In another study, adolescent females exhibited greater sensitization to amphetamine than adult females or males of either age, but no sex differences were observed in either amphetamine-induced locomotion or CPP in this study, which diverges from the literature (Mathews and McCormick 2007). One important caveat in interpreting sex differences in amphetamine self-administration is that amphetamine metabolism is enhanced by testosterone, and thus likely changes across adolescence (Meyer and Lytle 1978; Becker et al. 1982; Milesi-Halle et al. 2005).

There are some notable gaps in our information about sex differences in the effects of addictive drugs in adolescent animals. There is little information about the reinforcing effects of cannabinoids. Higuera-Matas investigated the adult consequences of treating male and female rats with the CB1 agonist CP55,940 from PN28-38 and showed that females showed enhanced cocaine self-administration (Higuera-Matas et al. 2008; Higuera-Matas et al. 2009). Wiley and colleagues have compared the acute effects of THC on the cannabinoid tetrad: of catalepsy, hypolocomotion, analgesia and hypothermia as well as tolerance and sensitization following repeated THC. They found that female adolescents were less sensitive than female adults to catalepsy, antinociception and hypothermia and tended to show less tolerance, while adolescent males were more sensitive to the inhibition of locomotion than adult males (Wiley et al. 2007). Most importantly, there are no studies of changes in the actions of addictive drugs during adolescence in non-human primates excluding the two reported for ethanol.

Gonadal Steroid Role in the Emergence of Sex Differences in the Effects of Addictive Drugs in Adolescence

Studies of the sexual differentiation of reproductive as well as non reproductive behaviors have shown that puberty represents a second “critical period” in which organizational effects of gonadal steroids produce irreversible effects on sexually dimorphic brain structures and function (see above). Activational effects of gonadal steroids also begin during puberty, and so both processes can contribute to the emergence of sexual dimorphisms in vulnerability to addiction during adolescence. These studies indicate that an early developmental window just before and after birth contributes to the organizational effects of gonadal steroids on the actions of addictive drugs.

Behavioral studies support a role for ovarian and testicular steroids in sexual differentiation of the behavioral response to addictive drugs, but the relative contribution of organizational and activational effects is far from clear. Several studies support a role for organizational effects

of gonadal steroids on the effects of addictive drugs. Ovariectomy or masculinization of female rat pups by androgen treatment right after birth prevented the appearance of the enhanced responses of females to the locomotor stimulant effects of amphetamine (Forgie and Stewart 1993; Forgie and Stewart 1994). A single study of the weak estrogen bisphenol showed that even gestational exposure could influence the ontogeny of dopaminergic neurons, as bisphenol exposure during prenatal days 11-18 suppressed amphetamine-induced CPP in female offspring (Laviola et al. 2005).

Recent studies from our laboratory suggest that puberty may represent an additional window during which the organizational effect of gonadal steroids influences the effects of addictive drugs. In a series of studies we have compared the effects of pre- and post-pubertal ovariectomy or castration. Ovariectomy either in adulthood or before puberty suppressed cocaine-stimulated locomotion. However, pre- but not postpubertal castration significantly increased cocaine-stimulated locomotion in males (Kuhn et al. 2001; Walker et al. 2001; Parylak et al. 2008). The pre-pubertal surgery was conducted on PN25, after the well described perinatal sensitive period of steroid hormone effects on brain organization. These data both supported a role for ovarian hormones in females, but also suggested that a previously unrecognized organizational effect of androgen contributed to the normal developmental fall in cocaine-stimulated behavior in males. These findings suggest that gonadal steroids augment addiction-related behaviors in females and suppress them in males during adolescence.

Emergence of Sex Differences in Dopaminergic Function during Adolescence

The behavioral studies reviewed above demonstrate that locomotor activation, drug-related reinforcement and drug self administration become sexually dimorphic in rodents during adolescence. Given the demonstrated importance of drug-induced activation of dopaminergic neurons in these sex differences, it is logical to propose that sexual differentiation of dopaminergic function mediates these effects.

Sex differences in the anatomy of dopaminergic projections to the forebrain emerge prenatally in rodents. Ovtsharoff (Ovtscharoff et al. 1992) showed that females have higher density of dopaminergic fiber innervation in the caudate prenatally. It has further been suggested that genetic sex rather than circulating hormone levels influences dopaminergic neurons in female rodent brain (Beyer et al. 1991; Kolbinger et al. 1991). The demonstration that the testis-determining gene sry is expressed in dopaminergic neurons where it may regulate tyrosine hydroxylase expression independent of hormone levels further supports the likelihood that sex-specific regulation of dopaminergic neurons exists (Dewing et al. 2006), although this is an emerging area with little data.

There is little evidence yet about the effect of gonadal steroids on dopaminergic function during the critical periods during early postnatal and pubertal development. However, behavioral data suggest that exposure of males to androgen perinatally or during puberty and exposure of females to estrogen during puberty provide the critical hormonal cues (see recent review by Becker (Becker 2009)). The only existing study is the demonstration that gonadal steroids do not contribute to the adolescent pruning of D2 receptors (Andersen et al. 2002).

Gonadal Steroid Contribution to Changes on Dopaminergic Function during Adolescence

Our laboratory has begun to characterize the emergence of sex differences in dopaminergic cell bodies in the substantia nigra and ventral tegmental area and their terminal projections in order to understand the potential contribution of dopaminergic function to changing addiction vulnerability during puberty. Our previous findings showed that cocaine enhanced dopamine overflow in the dorsal striatum is 3 fold higher in young adolescent than adult male rats. This developmental difference is regionally selective, as it does not occur in the core of the nucleus

accumbens (Walker and Kuhn 2008). Our behavioral studies predicted that the onset of estrous cyclicity in females during adolescence might prevent a similar developmental decrease in cocaine-stimulated dopamine overflow in females.

To investigate this possibility, we measured stimulated dopamine overflow at various times after cocaine administration (10 mg/kg) in adolescent (day 28) and adult (day 65) male and female rats using fast-scan cyclic voltammetry as previously described in both adolescents and adults (Walker et al. 2000; Walker et al. 2006; Walker and Kuhn 2008). Figure 2 shows the percent increase in dopamine relative to baseline stimulation at 20 Hz. Cocaine-stimulated dopamine overflow was greater in adolescent rats of both sexes compared to adults, and adolescent males and females were comparable to each other. Although cocaine-stimulated dopamine overflow was less in adulthood than in adolescents of both sexes, the decline from adolescence to adulthood in females was less than that observed in males (Walker et al. 2000; Walker et al. 2006). These findings suggest that dopaminergic function falls during adolescence in a sex-specific way. However, this study could not determine the contribution of organizational or activational effects of gonadal steroids to these changes in dopamine release.

The literature in adults suggests that activational effects of estradiol are the primary gonadal steroid influence on dopaminergic function in adult rats. However, our behavioral data (Parylak et al. 2008) indicated that important organizational effects of ovarian or testicular steroids might contribute to adolescent changes in endocrine function. To investigate this possibility, we conducted prepubertal castration or ovariectomy on PN25, and evaluated cocaine-stimulated dopamine overflow 30 days later, to match our previous behavioral studies. The results of these experiments are shown in Figures 3 and 4. As expected, prepubertal ovariectomy decreased cocaine-stimulated overflow (Figure 3). Surprisingly, prepubertal castration caused a significant increase in cocaine-stimulated dopamine overflow (Figure 4). Given the well-described effects of estradiol on dopaminergic function, it is difficult to discriminate the relative contribution of activational and organizational effects to the results in females. However, the weight of literature demonstrating the lack of androgen effects on dorsal striatal dopamine release in adult animals suggests that androgen may have a previously undescribed organizational effect on dopaminergic functions during puberty. This result matches the behavioral findings that we described above, which demonstrated a significant augmentation of cocaine-stimulated behavior after prepubertal but not adult castration.

The mechanisms by which both ovarian and testicular steroids influence dopaminergic function across adolescence are not known. Since we have recently shown that estradiol augments dopaminergic responses to psychostimulants in part by maintaining dopaminergic neuron number, we conducted a pilot study to determine whether sex differences in dopaminergic neuron number emerged during puberty. To investigate this possibility, we killed matched cohorts of male and female rats on PN21, 28, 42 and 65 and counted dopaminergic neuron number in the substantia nigra and ventral tegmental area, the nuclei from which dopamine projections to the forebrain arise, using unbiased stereology.

Animals were deeply anesthetized and transcardially perfused with 10% neutral buffered formalin. After perfusion, the brains were extracted and post-fixed overnight in 10% formalin, equilibrated in a 30% sucrose cryoprotectant solution and stored at 4°C. Serial coronal sections (30 μm) were cut on a cryostat, thaw-mounted onto slides and dried overnight at 37°C. Sections were rinsed in PBS and incubated in 0.3% hydrogen peroxide-methanol for 30 minutes, rinsed and blocked in 0.5% BSA + 0.3% Triton X-100 for 15 minutes at room temperature. After blocking, sections were incubated in primary antibody diluted in blocking buffer (1:10000, Immunostar, Inc., Hudson, WI) overnight at 4°C. The next day, sections were rinsed and incubated in a biotinylated horse anti-mouse secondary antibody (1:1000, Vector Labs,

Burlingame, CA) for 1 hour at room temperature. The sections were then rinsed and incubated in avidin-biotin complex for 1 hour at room temperature, rinsed and stained with DAB (Vector Labs). Sections were rinsed, dehydrated through graded alcohols, counterstained with cresyl violet, mounted and coverslipped. Unbiased stereological estimation of the total number of TH-IR and TH-IN cell bodies in the SNpc and VTA was performed using the optical fractionator method (West et al. 1991). A computerized counting system containing a Nikon Optiphot-2 microscope, a camera (Dage) and motorized stage (Ludl) was used to estimate the total number of cells. Individual cell bodies were visualized with a 100× oil immersion lens (numerical aperture = 1.3). Enough cells were counted to achieve a coefficient of error that was ≤ 0.10. This study was conducted without heat-mediated antigen retrieval, and cell numbers were lower than can be detected with the latter technique. However, a clear and unexpected pattern emerged from this experiment. As shown in Figure 5, a dramatic fall in DA cell number occurred during adolescence. This fall seemed to plateau in females by day 65, when the characteristic sex difference emerged.

These findings suggest that a significant wave of dopaminergic cell death occurs during adolescence in rats, in both males and females. Two earlier waves of apoptotic cell death occur right after birth and on about PN14 (Jackson-Lewis et al. 2000; Burke 2003; Burke 2004). The relevance of the fall during adolescence to dopaminergic function is not clear, as it occurs during the same time that innervation density in the terminal areas is increasing (see above). It has been suggested that the cells that undergo apoptosis were those which did not reach their target appropriately and so did not receive trophic input from target neurons (Oo et al. 2003; Burke 2004). The emergence of the sex difference in the number of dopamine neurons only after puberty supports our initial hypothesis that trophic effects of estradiol might contribute to maintenance of dopaminergic neurons in adult life. It is intriguing that the changes in the number of dopaminergic neurons parallel the changes in cocaine's effects on dopamine release that we saw: a dramatic decline across adolescence, only part of which was sexually dimorphic. We are currently investigating whether anatomic changes in cell body and/or terminal areas contributes to gonadal steroid regulation of addiction-related behaviors.

Significance of Adolescent Changes in Forebrain Dopaminergic Function for Addiction

The studies reviewed above show that dopaminergic function in the dorsal striatum undergoes its final maturation followed by a “pruning back” to adult function as adolescents develop. Sex differences in dopaminergic function and in behaviors regulated by dopamine appear during this time frame. These effects seem to reflect both the onset of activational effects of estradiol to augment dopaminergic function in females and possibly an organizational effect of androgen which suppresses dopaminergic function in males. Figure 6 summarizes one potential scheme that could explain the present findings. From left to right, the figure demonstrates three phases of dopaminergic neuron development. The leftmost panel shows dopamine neurogenesis. The middle panel depicts the period of axon outgrowth and innervation of targets that occurs during postnatal life and through adolescence. The final phase of dopaminergic neuron development is depicted on the right panel, as receptors “prune” back. Dopaminergic neurons are lost at every stage of the process, based on data in the present study and that published previously (Burke 2003;Burke 2004). We hypothesize that during adolescence, the final phase of apoptotic cell death of dopaminergic neurons in the midbrain is augmented by androgen and offset by trophic effects of estradiol. This is indicated by fewer cells in the middle and right panel for males, and a gray neuron in the bottom panel indicating population of neurons maintained by estradiol in females. A gray neuron is also included in the leftmost panel, as studies in culture have suggested that females may have more neurons at early phases of development, although we did not detect such differences by the beginning of adolescence (Beyer et al. 1991). By the end of adolescence/puberty, females have more dopaminergic neurons, which we hypothesize contributes to the sex enhanced dopamine function observed in females. However, additional

effects beyond those on the number of dopaminergic cell bodies likely contribute to the emergence of sex differences in dopaminergic function. Potential candidates include the appearance of cyclic effects of estradiol on DAT and receptors as well as activational effects of androgen on cortical neural circuits involved in executive function. In addition, afferent input (perhaps GABAergic feedback on dopaminergic neurons, indicated in the bottom right panel) may also contribute to additional regulation of dopaminergic functions in females.

There is one caveat in interpreting the relevance of these findings for addiction. The main adolescence-related changes in dopaminergic function we have observed occurred in dorsal striatum. The dopaminergic neurons that project from the VTA to the nucleus accumbens may be more important for the initial phases of drug reinforcement (Koob 1996; McBride et al. 1999; Di Chiara 2002). However, dopamine increases in the dorsal striatum are thought to be critical for the transition from voluntary drug taking to habit learning, a crucial phase in the development of addiction (Vanderschuren and Everitt 2004; Volkow et al. 2006; See et al. 2007; Dalley and Everitt 2009). One implication of these findings is that while the reinforcing effects of drugs may not be uniformly greater during adolescence, the transition to addictive patterns of behavior may occur more quickly in people who use drugs in early adolescence.

The emergence of sex differences in dopaminergic function was superimposed on normal developmental influences. These data are again consistent with the epidemiologic literature showing that adolescents of both genders are at greater risk to experiment with and become dependent upon addictive drugs but that gender-specific issues also emerge as adolescents mature. The behavioral significance of the attenuated dopaminergic function that develops across adolescence in males remains an important question. Is it associated with increased or decreased vulnerability to addiction? Epidemiologic studies do indicate that the earlier drug use starts (in early adolescence, at the beginning of pubertal development in males), the greater the risk of future drug dependence. How does rising testosterone influence drug taking behaviors? Intriguing studies that testosterone itself is self-administered through actions that involve both androgens and estrogens suggests an important role for androgen that has not yet been characterized (Wood 2004; Sato et al. 2008; Wood 2008). Animal studies which explore drug self-administration in males that have received prepubertal castration may help to answer these questions.

Endocrine Influences on Non-Dopaminergic Systems

This review has focused on one aspect of addiction that has proven relevance to addiction: the maturation of dopaminergic neurons involved in regulation of reinforcement. However, other elements of neural function critical to adolescence also change during adolescence. Maturation of executive function in the frontal cortex including the noradrenergic and serotonergic influences that are critically involved in attention and inhibition of behavior are key events of adolescent brain development (Chambers et al. 2003). We reviewed above evidence that androgen regulates frontal cortex dopaminergic circuits. Rising testosterone levels during puberty could influence frontal cortex functions like response inhibition, but the contribution of pubertal hormonal changes to these critical brain functions have not been studied either in humans or animal models.

Summary

Addiction vulnerability is high in adolescence. A significant component of this vulnerability reflects developmental stage not sex. Human studies show that both males and females who use addictive drugs early in adolescence have higher risk of addiction than those who start as adults. The dramatic fall in cocaine-induced dopamine release that we observed as adolescent males and females matured into adulthood suggests that important developmental changes in forebrain dopaminergic systems occur during adolescence in a sex-independent way. However,

we also showed that well described sex differences in dopaminergic function emerge during adolescence, and could likely contribute to the sex differences in drug use patterns that emerge during late adolescence in humans.

Acknowledgments

Support by NIDA grant DA019114 and 009079 is gratefully acknowledged. All animal experiments were conducted in accordance with animal protocols approved by the Duke University IACUC.

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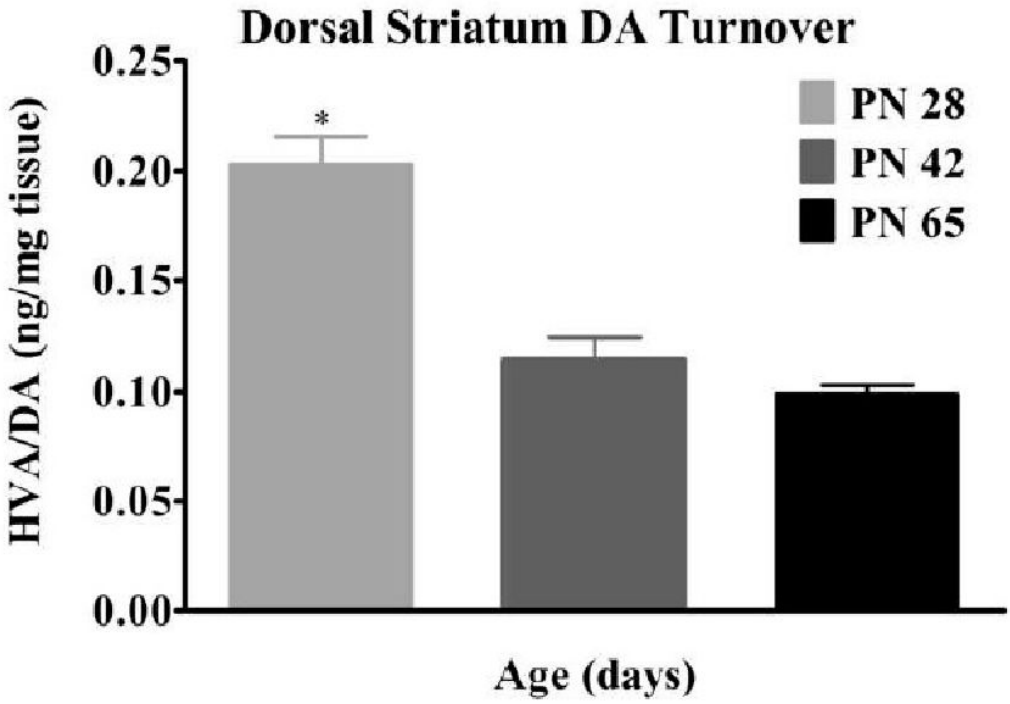

Figure 1.
HVA:DA ratio in dorsal striatum across adolescence in male rats. N = 10-12/group. ANOVA indicate P < .01 for significant effect of age. Rats were killed, brain regions frozen and DA and metabolites assessed by HPLC.

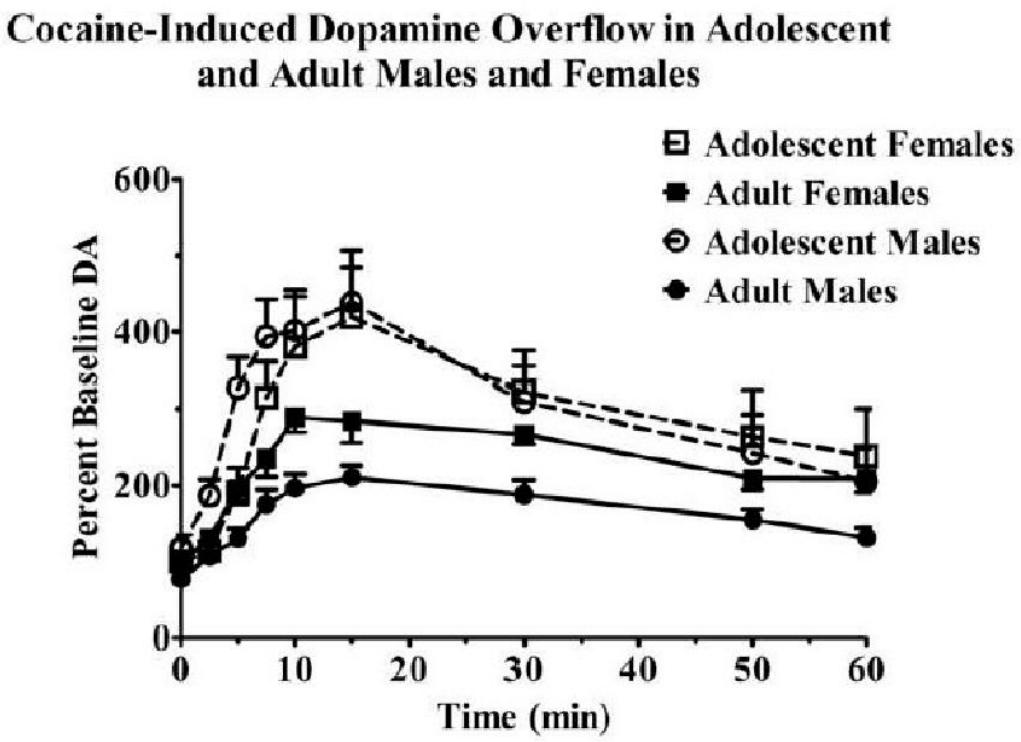

Figure 2.

Time course of cocaine-induced dopamine overflow in adolescent (PN28) or adult (PN65-75) male and female rats. Data show percent increase in extracellular dopamine at various times after cocaine (10 mg/kg). N = 5-9/group. ANOVA indicated $P < .001$ for an effect of time, $p < .001$ for an effect of age and $p < .001$ for sex × age × time. Lower level ANOVAS indicated that $p < .008$ for an effect of age in males but no effect of age was found in females. ANOVA conducted in adults showed that females exceeded males ($p < .008$).

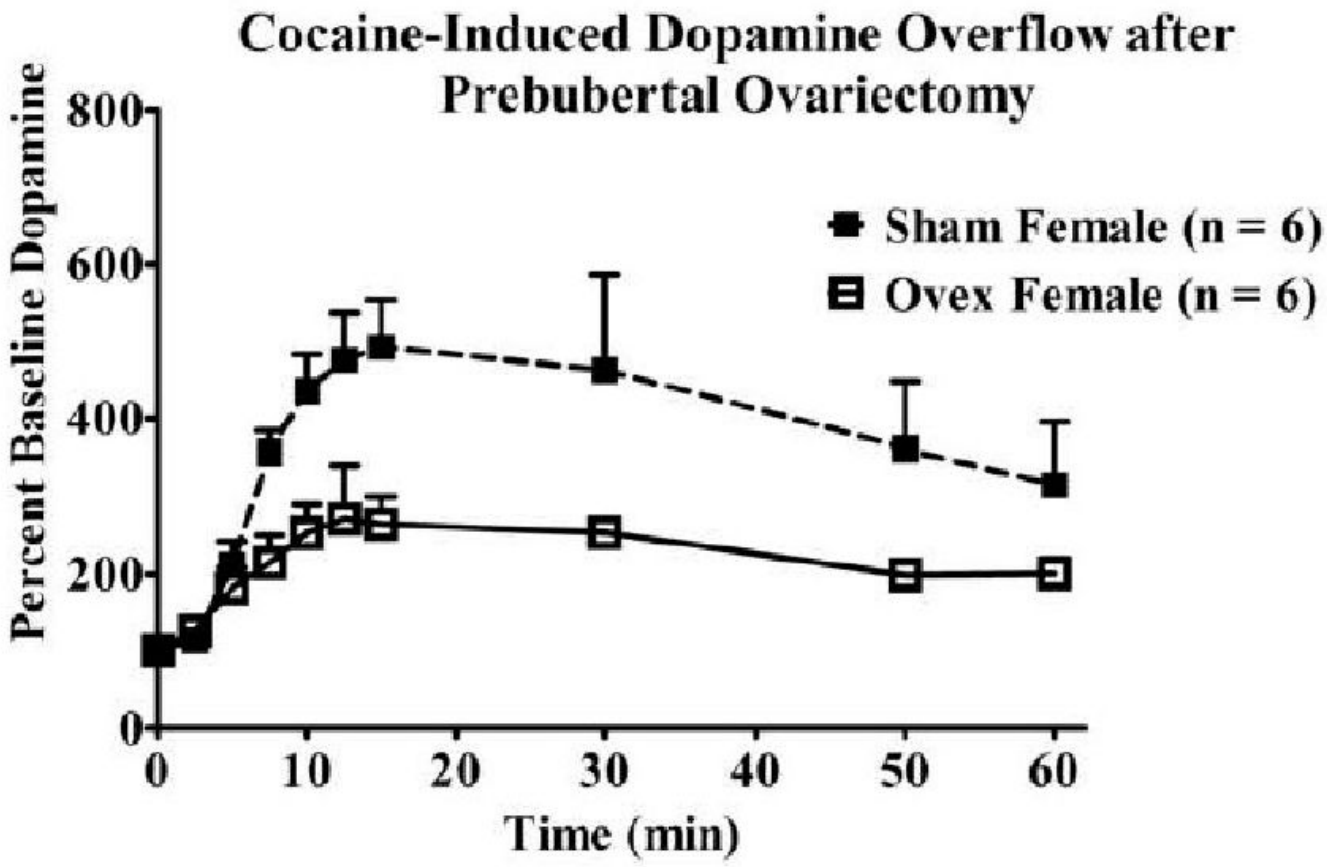

Figure 3.
Cocaine-stimulated dopamine overflow in female rats 1 month after prepubertal (day 25) sham or active ovariectomy. Data were collected as described in Figure 3. N = 4-5/group. ANOVA indicated $P < .001$ for an effect of time and $p < .001$ for an effect of surgery.

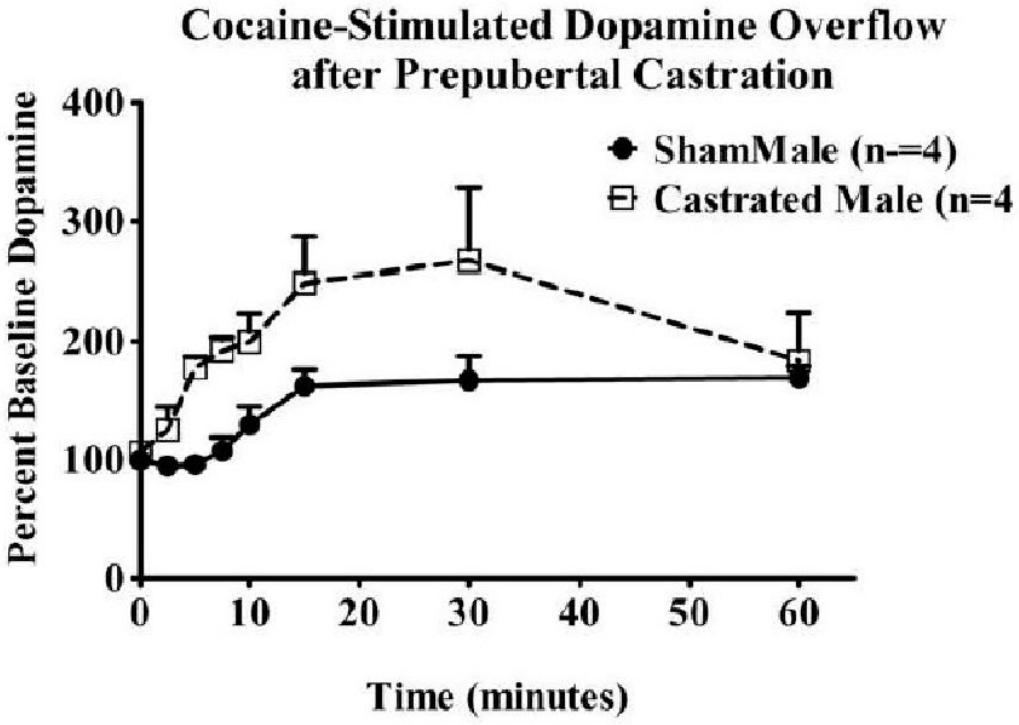

Figure 4.

Cocaine-stimulated dopamine overflow in male rats 1 month after prepubertal (day 25) sham or active castration. Data were collected as described in Figure 3. N = 4-5/group. ANOVA indicated $P < .001$ for an effect of time and $p < .001$ for an effect of surgery.

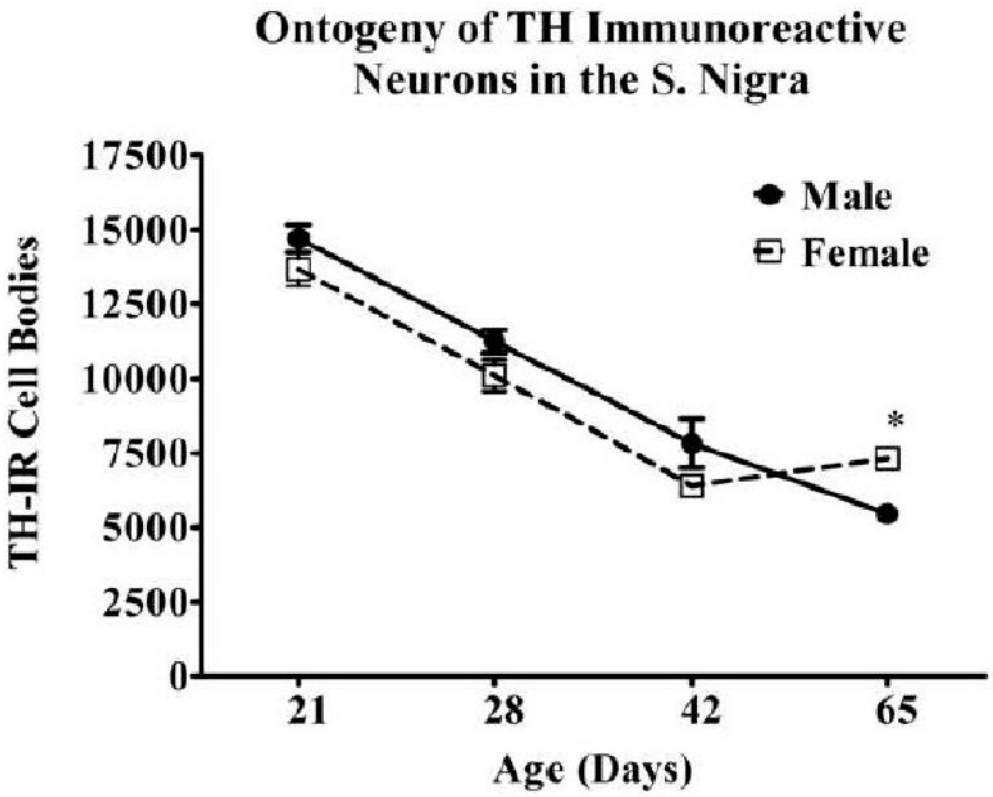

Figure 5.
Tyrosine hydroxylase immunoreactive neurons in substantia nigra across postnatal age. N = 5-7/group. ANOVA indicates $p < .001$ for an effect of age and $p < . 01$ for interaction of age × gender.

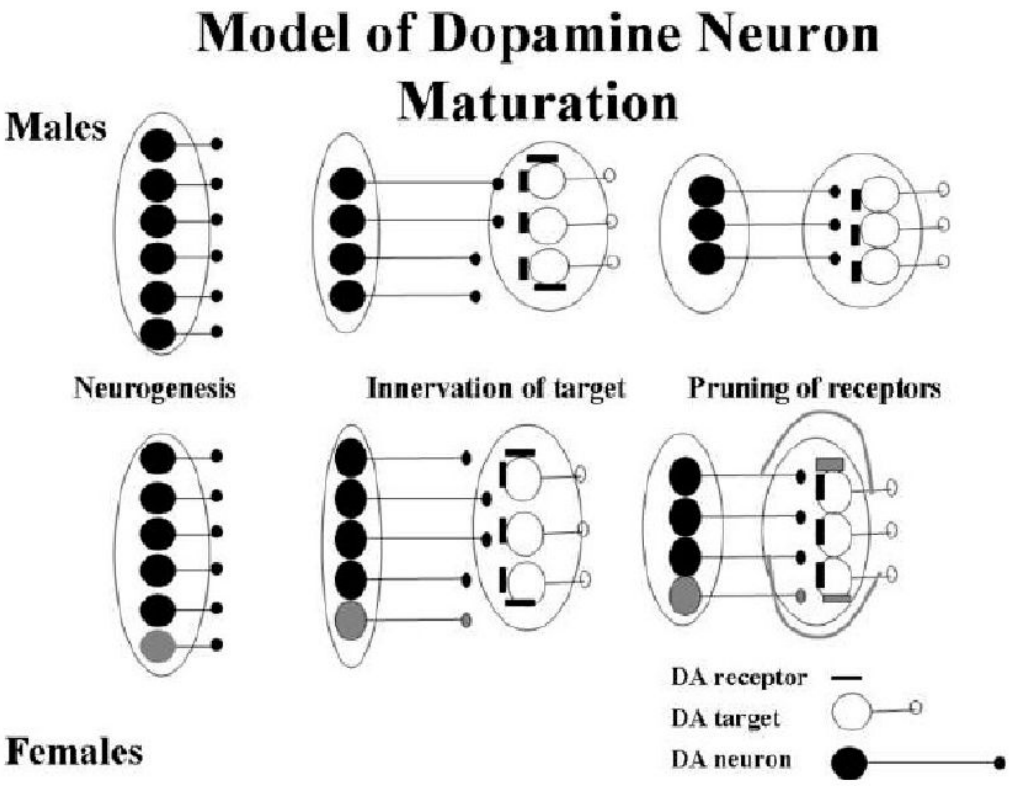

Figure 6.
Hypothetical model of how estradiol and testosterone influence the ontogeny of forebrain dopamine systems.