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Early sexual experience alters voluntary alcohol intake in adulthood

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HIGHLIGHTS

- Sexual experience during adolescence but not adulthood increases alcohol self-administration.
- Sexual experience increased anxiety- and depressive-like behaviors.
- Adolescent experiences have enduring effects on adult phenotype.

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ABSTRACT

Steroid hormones signaling before and after birth sexually differentiates neuronal circuitry. Additionally, steroid hormones released during adolescence can also have long lasting effects on adult behavior and neuronal circuitry. As adolescence is a critical period for the organization of the nervous system by steroid hormones it may also be a sensitive period for the effects of social experience on adult phenotype. Our previous study indicated that early adolescent sexual activity altered mood and prefrontal cortical morphology but to a much smaller extent if the sexual experience happened in late adolescence. In humans, both substance abuse disorders and mood disorders greatly increase during adolescence. An association among both age of first sexual activity and age of puberty with both mood and substance disorders has been reported with alcohol being the most commonly abused drug in this population. The goal of this experiment was do determine whether sexual experience early in adolescent development would have enduring effects on adult affective and drug-seeking behavior. Compared to sexually inexperienced hamsters and those that experienced sex for the first time in adulthood, animals that mated at 40 days of age and were tested either 40 or 80 days later significantly increased depressive- but not anxiety-like behaviors and increased self-administration of saccharine-sweetened ethanol. The results of this study suggest that an isolated, though highly relevant, social experience during adolescence can significantly alter depressive-like behavior and alcohol self-administration in adulthood.

Sexual development of the brain and behavior has long been conceptualized as a two-stage process wherein steroid hormone exposure during the prenatal and early postnatal period permanently organizes neural circuitry and establishes the manner in which these circuits will respond to steroid hormones later in life [24]. As originally conceived, this organizational–activational hypothesis has provided deep insights into explaining the role of hormones in sexually differentiated behavior; more recently, this hypothesis has been expanded to include persistent effects of steroid hormones outside of the early life critical periods [5,30,32]. As an example, exposure to androgenic steroids during the peripubertal period appears necessary for the full expression of male-typical sex behavior in adulthood [20,27–29]. Specifically, if male hamsters are deprived of androgens during puberty, male-typical levels of sexual or aggressive behavior in adulthood do not occur even when treated with testosterone [28]. Similarly, if male Siberian hamsters mate with a sexually receptive conspecific during adolescence, a manipulation that increases circulating testosterone, adult affective behavior, gene expression, and neuronal morphology is altered in adulthood [21]. Additionally, many of these effects were recapitulated by exogenous testosterone administration [21].

Adolescence is the developmental period that includes onset of puberty and subsequent sexual and neurological development [29]. Puberty begins in the brain with increased production and release of gonadotropin releasing hormone (GnRH) [29,31]. Importantly, during this period there is significant maturation of the nervous

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system in general and the prefrontal cortex in particular [14,23]. For instance, there is a marked increase in the volume of gray matter, the numbers of synapses, and overall myelination in addition to greater pruning of prefrontal synapses [33,36,40]. Additionally, this period is marked by an increase in the dopaminergic input to the prefrontal cortex, as well as in dopamine receptor density and transporter activity [15,34]. Importantly, sex steroid hormones including testosterone can modulate many of these processes [18]. One potential side effect of this rapid neuronal development is that environmental stimuli, (including those that alter HPG axis physiology) during this period may have long lasting and far-reaching consequences on adult phenotype [1].

In humans, both substance abuse disorders and mood disorders greatly increase during adolescence [11]. An association among both age of first sexual activity and age of puberty with both mood and substance disorders has been reported [3,19,37]. Alcohol is the most frequently used and abused drug among adolescents, and it is the leading cause of mortality and morbidity in this age group; more than all other drugs collectively [22]. Our previous study indicated that adolescent sexual activity altered mood and prefrontal cortical morphology in adulthood apparently by increasing circulating testosterone (and potentially estrogens via aromatization) during this developmental epoch but to a much smaller extent if the sexual experience happened in late adolescence [21]. Therefore we hypothesized that early, but not later, adolescent sexual experience, which could potentially recapitulate the effects of early puberty, would increase voluntary alcohol intake and induce a depressive- and anxiety-like phenotype in adult Siberian hamsters.

1. Materials and methods

1.1. Animals

Siberian hamsters (*Phodopus sungorus*) used in this study were bred in our colony at The Ohio State University from a wild-bred stock originally obtained from Dr. K. Wynne-Edwards (Kingston, Ontario, Canada). Hamsters were housed in polypropylene cages ($28 \times 17 \times 12$ cm) with a nestlet and 1 cm of corncob bedding. Hamsters were weaned at approximately 21 days in a long photoperiod (16:8 LD; with lights-off at 1500 Eastern Standard Time [EST]) and housed within this room for the duration of the study. All hamsters had ad libitum access to food (Harlan Teklad Rodent Diet 8640, Indianapolis, IN, USA) and filtered tap water, except where experimental protocol dictated otherwise. Animal rooms were held at constant temperature and humidity ($21 \pm 2^{\circ}$C and $50 \pm 10\%$, respectively). All procedures were conducted in accordance with the US National Institute of Health (1986) Guide for the Care and Use of Laboratory Animals, The Ohio State University Institutional Animal Care and Use Committee, and the international ethical standards described previously by Portaluppi et al., [25].

At 40 or 80 days of age males were paired with an ovariectomized hormone-primed female (see below) or kept isolated (control condition). The females were removed after 6 h and mating behavior was recorded to ensure that copulation took place. Hamsters were provided with a sexual experience at 40 or 80 days of age, and then were tested 40 or 80 days later (40×40 vs. 40×80 vs. 80×40 vs. 80×80 groups). All behavioral testing was conducted between 15:00 and 18:00 h and hamsters were each given 30 min to habituate to the test room before initiation of testing. Tests were performed in the following order: (1) elevated-plus maze, (2) forced swim test, then (3) ethanol intake test (Figs. 1 and 2).

1.2. Sexual experience

The stimulus females were introduced to the males and allowed to copulate for a maximum of 6 h. Sexual behavior was induced between intact males and ovariectomized females. Female OVX hamsters were implanted with a 5 cm long estrogen capsule 2 weeks prior to the beginning of experiments. OVX females were brought into behavioral estrus by subcutaneous injections of progesterone 6 h prior to being sexually paired with a male. Bouts of mating behavior were conducted in a rectangular box measuring $50 \times 75 \times 50$ cm ($D \times W \times H$), the front wall of which was transparent. Sexual contact was monitored and videotaped in the dark under red light, and tests were conducted between 15:00 and 21:00 h and recorded on-video tape to ensure that copulation had occurred.

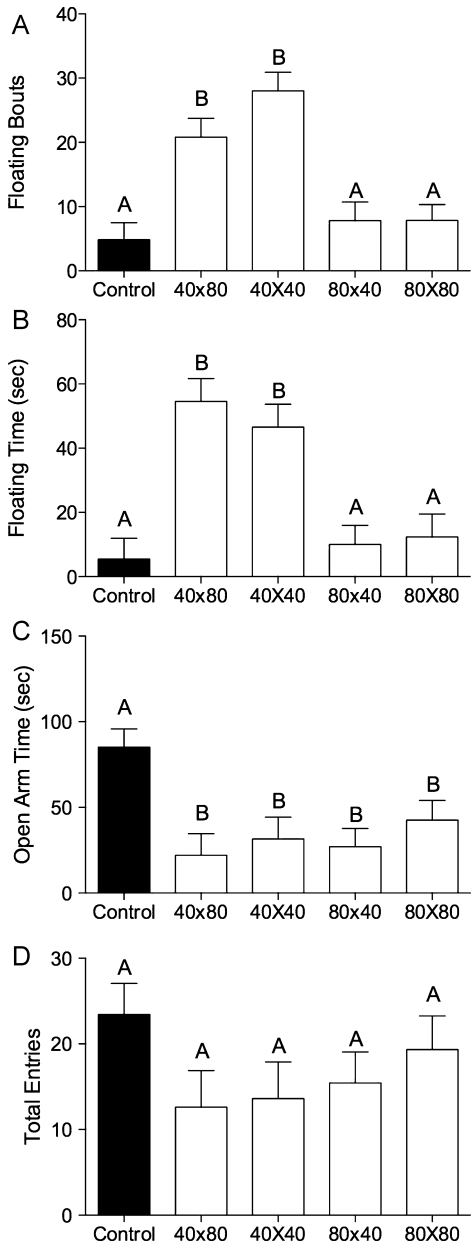

Fig. 1. Adolescent sexual activity alters behavioral parameters (recapitulated). Effects of adolescent sexual activity on behavioral responses (mean ± SEM) in the behavioral measure. (A) Total number of arm entries in the testing arena. (B) Percentage of time spent in the open arm of the elevated plus maze. (C) Percentage of time spent floating in the forced swim test. Bars sharing the same letters are not statistically different from each other. Control: no sexual experience; 40×80: mated at 40 days tested 80 days later; 40×40: mated at 40 days and tested 40 days later; 80×40 mated at 80 days and tested 40 days later; 80:80 mated at 80 days and tested 80 days later.