Psychoneuroendocrinology (2013) 38, 2758—2769

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Long-term programming of enhanced aggression by peripuberty stress in female rats

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Received 4 March 2013; received in revised form 22 June 2013; accepted 10 July 2013

KEYWORDS
Female aggression;
Maternal behavior;
Stress reactivity;
Puberty;
Violence;
Oxytocin;
Vasopressin;
Corticosterone;
Long-term effects;
Cohabitation female—male

Summary Human literature has linked adverse early life experiences with an increased risk to develop violent behaviors in both boys and girls. We have previously shown that male rats submitted to stress during the peripuberty period display as adults abnormal aggressive behavior against both male intruders and female partners. In the present study, we examined whether the same stress protocol would affect the development of aggressive behaviors in female rats. We evaluated the behavior of these peripuberty stressed female rats when confronted, at adulthood, with either female or male intruders, and during their cohabitation with male partners. Given that estrus cycle influences mood and aggressive behaviors, female aggressive behavior was assessed at different estrus cycle phases: estrus and diestrus, and during pregnancy and lactancy. Additionally, we evaluated postpartum plasma levels of vasopressin, oxytocin and corticosterone, hormones associated with aggression and the regulation of social behavior. Compared to control females, females submitted to stressful events during puberty exhibited higher and more sustained rates of aggression during adulthood independently on the estrus cycle or the sex of the intruder, and they had higher levels of plasma vasopressin. Significant correlations between plasma levels of vasopressin and corticosterone and aggressive behavior were also found. Strikingly, our results showed opposite intragroup correlations suggesting a different role of these hormones on aggression depending on life experiences. We provide here an animal model, devoid of cultural influences strongly supporting a role for biological factors in the development of aggressive behaviors following exposure to stressful events at puberty in females.

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0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2013.07.005

1. Introduction

Puberty is a critical developmental period characterized by increased levels of gonadal steroid hormones with brain organizational influences, and increasing connectivity in social- and emotion-related areas (Blakemore, 2012). Many psychiatric disorders such as personality and mood disorders, addiction and schizophrenia start during adolescence, suggesting that the neurobiological events involved in remodeling neural circuits that occur during this period render the adolescent developing brain highly vulnerable to experiential input (Paus et al., 2008). Importantly, exposure to high rates of stress around puberty has been related to an increase of violent behaviors and personality disorders (PD) [note that a very high percentage of individuals that commit violent repeated offenses suffer PD (Putkonen et al., 2003)]; although this is typically reported in men (Wolff and Shi, 2012) evidence is also available in women (Foy et al., 2012). Animal research has shown that exposure to stressful events during puberty increases agonistic behaviors during adolescence and adulthood in several species (Delville et al., 2003; Sachser, 1993).

Since the physiological systems that sustain aggression (Albert and Walsh, 1984; Umukoro et al., 2012) and stress (de Kloet, 2010) are highly preserved throughout evolution, several animal models have been proposed to study the development of human aggressive behavior using rodents. However, very few models have included non-lactating females, possibly because aggressive behavior in female rodents is considered in general rare unless the females are protecting their offspring (for review, see Umukoro et al., 2012). Although the patterns of aggressive behavior differ between males and females (Blanchard et al., 1980), female rodents display non-reproduction related aggressive behavior as well (DeBold and Miczek, 1984). Furthermore, it is known that certain conditions and treatments increase aggressive behavior in both sexes, such as for example, electrical stimulation in the hypothalamus (Kruk et al., 1984), ethanol administration (Blanchard et al., 1987), or isolation (Malick, 1979; More, 2008). Differences between the degree to which male and female rodents react to environmental experiences affecting aggressive behavior have been reported as well. For instance, in rats, aggressive behavior measured after exposure to a single or repeated immobilization stress was found to be increased in females (Albonetti and Farabollini, 1993b) and decreased in males (Albonetti and Farabollini, 1993a); while exposure to maternal separation in early life led to increased aggression at adulthood in males (Veenema et al., 2006) and reduced aggression in females (Boccia and Pedersen, 2001). Therefore, these findings prevent the generalization of the effects of stress on aggressive behavior from males to females and highlight the need to investigate them in animals of both sexes.

We have previously shown that male rats submitted to stress — consisting of fear-inducing experiences — during the peripuberty period display as adults abnormal aggressive behavior against both male intruders (Marquez et al., 2013) and female partners (Cordero et al., 2012). In the present study, we examined whether the same stress protocol would affect the development of aggressive behaviors in female rats exposed to stress experiences during puberty. We evaluated the behavior of these peripuberty stressed female rats when confronted, at adulthood, with either female or male intruders, and during their cohabitation with male partners. Given that, in females, fluctuant levels of ovarian hormones related to the estrus cycle influence mood and aggressive behaviors (Lovick et al., 2005); female rats were submitted twice during adulthood to the resident intruder test, first in diestrus and the second exposure during estrus. Different protocols have been used to induce maternal aggression in female rats, including the exposure to an unfamiliar female (Bosch et al., 2010) or to a sexually naïve male intruder (Parmigiani et al., 1988; Johns et al., 1998). As the latter has been reported to induce more severe aggression and in order to assess inter-sexual aggressive behavior with low influence of mating and sexual behavior, maternal aggression against a male intruder was performed on postpartum day 7. Further, we evaluated plasma corticosterone levels, given the link between glucocorticoids and aggression (Haller et al., 2004) and the neuropeptides arginine vasopressin (AVP) and oxytocin (OXT) given their role in the regulation of social behavior and, particularly, aggression and maternal behaviors (Bosch and Neumann, 2012).

2. Methods and materials

2.1. Animals

The female experimental subjects were the offspring (F0) of Wistar Han rats (12 females and 12 males) purchased from Charles River Laboratories (Lyon, France) that were bred in our animal house. Taking into account that human studies have often found a high prevalence of psychopathology among first-degree relatives, in order to study the potential role of the stress in exacerbating pre-existent aggressive behavior, sisters were submitted to a different experimental condition, control or stress. In this way, at weaning, from each litter (with the exception of one litter that only had one female offspring) a pair of females of equivalent weight were separated and placed in a new home—cage together with two more females of equivalent weight from two other different litters (3 females per cage, no siblings between them). Efforts were made to ensure that each couple of cages was equally matched with three other females from the same three different litters. From these matched cages, all the animals from one of the cages were submitted to the same control or stress condition, while females from the other matched cage were submitted to the other experimental condition [$N = 12$ females per group; matched siblings between the groups: 11 pairs; note that as one female had no siblings, in order to maintain similar housing conditions for all the animals (namely three females per cage) one female from another litter had to be added to one cage, and therefore one pair of females (one in the control group and one in the stress group) were not siblings between them].

The male subjects (used either in the maternal aggression tests or as partners) were naive Wistar rats acquired at 10 week-old from Charles River Laboratories. Ovariectomized (OVX) females 3-month old, used as intruders in the resident-intruder test, were obtained from Charles River. Ovariectomies were performed by the supplier (Charles River Laboratories) one week before shipment. Animals were maintained