Experimental Physiology

Adolescent stress and neural plasticity in hamsters: a vasopressin–serotonin model of inappropriate aggressive behaviour

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Animal studies show that arginine vasopressin facilitates aggression, while serotonin (5-HT) inhibits aggression by blocking the activity of the vasopressin system. Clinical studies report that subjects with a history of 'fighting and assault' show a significant positive correlation between cerebrospinal fluid concentrations of vasopressin and aggression in the presence of a hyporeactive 5-HT system. Thus, in animals and humans, a hyporeactive 5-HT system may result in enhanced vasopressin activity and increased aggression. Can the stress of emotional and physical insult, i.e. threat and attack, during adolescence affect the development of the vasopressin and 5-HT systems and alter normal aggressive behaviour in early adulthood? Adolescent male golden hamsters were weaned at postnatal day 25, and stressed for 2 weeks by daily 1 h bouts of threat and attack by adult hamsters. Male littermates were run in a parallel stress study using daily 1 h trials of isolation in a novel environment. During early adulthood, on postnatal day 45, 3 days after the cessation of stress trials, animals were tested for aggression in a resident : intruder model. The results show a context-dependent change in aggression. Animals with a history of abuse show exaggerated attack behaviour toward smaller males compared to littermates with a history of isolation stress. Conversely, when confronted by males of equal size, animals with a history of abuse show diminished aggression and increased submission compared to controls. It was determined that the density of vasopressin fibres and neurones in the hypothalamus is lower in abused animals compared to controls. In contrast, the number of 5-HT terminals within the hypothalamus is higher in abused animals compared to controls. These results provide evidence in an animal model that stress in the form of threat and attack during adolescence can alter the balance between vasopressin and 5-HT in the brain, resulting in inappropriate aggressive behaviour in early adulthood.
Experimental Physiology (2000) **85S**, 85*S*–90*S*.

There is compelling evidence in numerous mammalian species showing stress during the perinatal period can have long-lasting negative consequences on aggressive behaviour. For example, infant rhesus monkeys isolated from their mother in early life show monoamine deficits, altered regulation of the stress response and a dysfunctional autonomic nervous system as young adults (Kraemer & Clarke, 1990; Higley *et al.* 1991; Clarke, 1993). Animals stressed in this manner have arrested behavioural development, diminished social skills, and increased vulnerability for long-term psychopathology (Higley & Suomi, 1989). Often their aggressive behaviour is unpredictable, inappropriate and excessive (Harlow *et al.* 1971). Self-injurious behaviour is not uncommon (Kraemer & Clarke, 1990).

Unlike the perinatal period, there is little information on the long-term neurobiological and behavioural consequences of stress during the peripubertal period or 'adolescence.' Following weaning, peripubertal animals are confronted with new stressful situations, many involving agonistic social interactions as they compete for food, territory, social status and mates with other conspecifics. The work discussed in this review examines the long-term changes in neurobiology and behaviour in response to social subjugation, i.e. stress of threat and attack by conspecfics, in adolescence. In particular, this review focuses on arginine vasopressin and serotonin (5-HT), their control of aggression, and how they are affected by adolescent stress.

Neural regulation of aggression

Vasopressin in the anterior hypothalamus facilitates aggression

Vasopressin innervation to the anterior hypothalamus plays a fundamental role in the regulation of offensive aggression; i.e. initiation of attacks and bites, in Syrian golden hamsters (*Mesocricetus auratus*). Blockade of vasopressin V_{1A} receptors with a selective vasopressin receptor antagonist in the anterior hypothalamus inhibits offensive aggression by resident male hamsters toward smaller intruders (Ferris & Potegal, 1988).

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Similar blockade of V_{1A} receptors inhibits aggression between hamsters tested in a neutral arena for dominant/subordinate behaviour (Potegal & Ferris, 1990). Conversely, activation of V_{1A} receptors by microinjection of vasopressin into the anterior hypothalamus facilitates offensive aggression in hamsters (Ferris *et al.* 1997).

The anterior hypothalamus has a dense plexus of vasopressin fibres colocalized with V_{1A} receptors (Ferris *et al.* 1997). Microdialysis in this area shows release of vasopressin by resident hamsters during agonistic encounters with intruders (C. Ferris, unpublished observation). There is evidence those vasopressin neurones localized to the medial supraoptic nucleus and nucleus circularis are the source of innervation to the anterior hypothalamus, releasing neuropeptide and facilitating aggression (Ferris *et al.* 1991). Lesion of these neurones causes a reduction in agonistic behaviour (Ferris *et al.* 1990).

The role of vasopressin in the regulation of aggression is not limited to hamsters but includes other species, including humans. In rats, aggressive behaviour is enhanced by microinjection of vasopressin in the lateral septum and amygdala (Koolhaas *et al.* 1990, 1991). In prairie voles, vasopressin injections within the cerebral ventricles activate aggressive behaviour (Winslow *et al.* 1993). In humans and in rats, high indexes of aggressivity correlate with high concentrations of vasopressin in the cerebrospinal fluid (Haller *et al.* 1996; Coccaro *et al.* 1998).

Serotonin inhibits aggression

In contrast to vasopressin, the 5-HT system is associated with the inhibition of aggressive behaviour (Olivier & Mos, 1990). In hamsters, microinjection of 5-HT_{1A} receptor agonist 8-OH-DPAT into the anterior hypothalamus causes a dose-dependent reduction in offensive aggression (Ferris *et al.* 1999). Peripheral treatment with fluoxetine, a 5-HT re-uptake inhibitor, blocks offensive aggression of a resident toward an intruder and suppresses vasopressin-facilitated attacks and bites (Delville *et al.* 1995; Ferris *et al.* 1997). Furthermore, peripheral fluoxetine treatment inhibits vasopressin release within the anterior hypothalamus (Ferris, 1996). These findings support the notion that peripheral fluoxetine can alter aggression by suppressing the release of vasopressin and/or by blocking the activity of vasopressin on afferent neurones.

Neuroanatomical findings corroborate the neurochemical data showing an interaction between these two neurotransmitter systems. The anterior hypothalamus has a high density of 5-HT_{1A} receptors overlapping the V_{1A} binding site in this area (Ferris *et al.* 1999). There is a high density of 5-HT terminals and synaptic boutons throughout the anterior hypothalamus. In the areas of the medial supraoptic nucleus and nucleus circularis these synaptic boutons are closely associated with the primary dendrites of vasopressin neurones (Ferris *et al.* 1997). Fluoro-Gold injections in anterior hypothalamus label neurones in the dorsal, median and caudal linear raphe nuclei, a portion of which also contain tryptophan hydroxylase immunoreactivity (Ferris *et al.* 1999). Presumably, the release of 5-HT into the anterior hypothalamus by these neurones acts through 5-HT_{1A} receptors to inhibit vasopressin-facilitated offensive aggression. A model of vasopressin–5-HT interaction in the control of offensive aggression is shown at the top of Fig. 1.

The notion that vasopressin facilitates aggression and 5-HT suppresses aggression, in part, by inhibiting the activity of the vasopressin system appears to translate to humans. Patients with personality disorder characterized by a history of fighting and assault show a negative correlation for prolactin release in response to d-fenfluramine challenge (Coccaro *et al.* 1998). The blunted prolactin response in these patients is suggestive of a hyporesponsive 5-HT system. These patients showed a significant positive correlation between cerebrospinal fluid concentrations of vasopressin and aggression. Hence, a hyporesponsive 5-HT system may contribute to enhanced central release of vasopressin, facilitating impulsive and aggressive behaviour in humans.

Social subjugation in adult animals

In adult animals, losing fights and being relegated to low social status is very stressful. Social subjugation can alter circulating levels of steroid hormones and many of the neurotransmitter systems in the central nervous system including vasopressin and 5-HT (Bronson & Eleftheriou, 1964; Rose *et al.* 1975; Eberhart *et al.* 1980, 1983; Yodyingyuad *et al.* 1985; Ferris *et al.* 1989; Huhman *et al.* 1991; McKittrick *et al.* 1995). Studies on adult male hamsters show depressed concentrations of testosterone and elevated concentrations of glucocorticoids following repeated defeat by dominant conspecifics (Huhman *et al.* 1991). Subordinate hamsters exposed to daily bouts of threat and attack by dominant conspecifics present with lower levels of vasopressin in the anterior hypothalamus and fewer vasopressin neurones in the nucleus circularis (Ferris *et al.* 1989). In a laboratory setting, an individually housed hamster will routinely attack and bite an equal or smaller sized intruder placed into their home cage (Ferris & Potegal, 1988). However, following repeated defeat by a dominant conspecific, a resident hamster will be defensive or fearful of equal-sized non-aggressive intruders (Potegal *et al.* 1993). The generalization of submissive behaviour toward non-threatening, novel-stimulus animals is an example of 'conditioned defeat.' (Potegal *et al.* 1993). Conditioned defeat in adult hamsters is not permanent, as the flight and defensive behaviours disappear over many days. This disappearance of overt conditioned defeat appears to be time dependent and not a function of repeated exposure to novel non-aggressive intruders.

Social subjugation in adolescent animals

While there is a large literature on the neurobiological and behavioural consequences of social subjugation in adult animals, there are few studies on the effects of social stress during adolescence. In humans, adolescence is defined as a period of pronounced physical, cognitive and emotional growth. This period usually begins just before puberty and ends in early adulthood with sexual maturity, social awareness and independence (Ingersoll, 1992). In golden hamsters, there

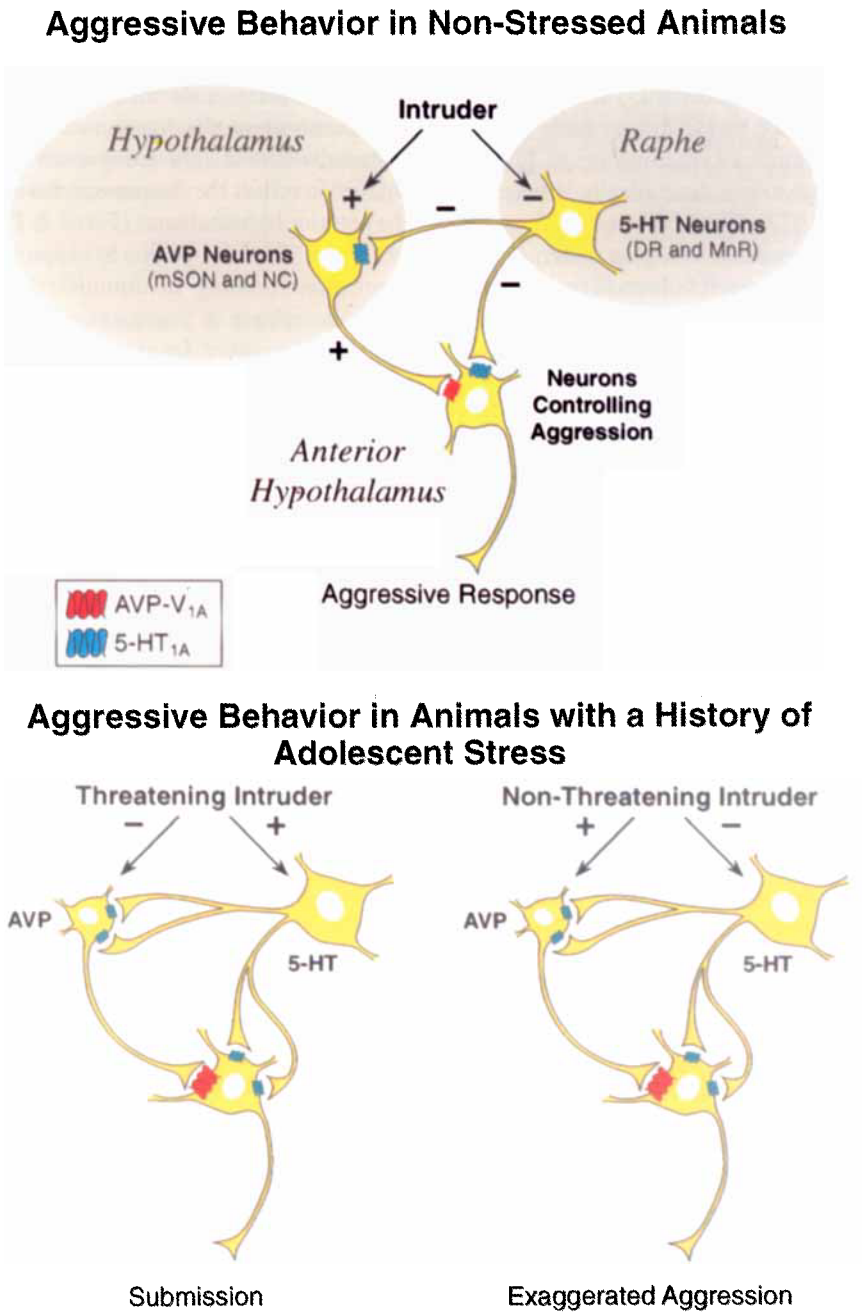

Figure 1

Top panel, schematic diagram depicting the interaction between the vasopressin (AVP) and serotonin (5-HT) systems in the regulation of aggressive behaviour at the level of the anterior hypothalamus. Adult resident animals without a history of adolescent stress response to an intruder with activation (+) of vasopressin neurones in the medial supraoptic nucleus (mSON) and nucleus circularis (NC) exciting neurones involved in the facilitation of aggression. The presence of an intruder also inactivates (−) 5-HT neurones removing an inhibitory drive on vasopressin neurones and neurones in the anterior hypothalamus controlling aggression. The net result is enhanced aggressive responding toward intruders. DR, dorsal raphe nucleus; MnR, median raphe nucleus. Bottom panel, schematic diagrams depicting the interaction between the vasopressin (AVP) and serotonin (5-HT) systems during agonistic encounters between a resident with a history of adolescent stress and threatening and non-threatening intruders. The diagrams and description match that show in the top panel, but include changes in neuronal morphology and receptor size to reflect the hypothesized changes in neurobiology that occur with adolescent stress.

is a developmental period analogous to adolescence. In the wild, hamsters wean around postnatal day 25 (P-25), leave the home nest, forage on their own, and establish nest sites, and defend their territory (Schoenfeld & Leonard, 1985). Hamsters can begin to establish dominance hierarchies as early as P-35 (Whitsett, 1975), and have a minimal breeding age of 42 days. Androgen concentrations start to rise dramatically between P-28 and P-35 (Miller *et al.* 1977). Thus between P-25 and P-42, as hamsters achieve independence from the maternal nest, they double their weight and size, reach full sexual maturity and reproductive competence and establish social relationships. This period between P-25 and P-42 is designated as adolescence in golden hamsters.

Recent studies on social subjugation in adolescent hamsters revealed unique neurobiological and behavioural outcomes compared to adult animals (Delville *et al.* 1998). Male golden hamsters weaned at P-25, were exposed daily to aggressive adults from P-28 to P-42, and tested for offensive aggression as young adults several days later after the cessation of stress. Animals with a history of social subjugation showed a context-dependent alteration in their aggressive behaviour. They showed typical conditioned defeat, fleeing from non-aggressive intruders of comparable age and size. In this respect, they were similar to socially subjugated adult male hamsters. However, when confronted by a smaller, weaker intruder they were exceedingly aggressive, displaying short attack latencies and high number of bites compared to sibling controls that were not subjugated during adolescence.

This exaggerated aggressive response in animals displaying conditioned defeat was unexpected. Equally surprising, the basal testosterone concentrations in young adult hamsters exposed to the daily stress of threat and attack throughout adolescence were comparable to control siblings (C. Ferris, unpublished observation). Moreover, following an agonistic encounter with an aggressive, larger conspecific, animals stressed in adolescence show much lower cortisol concentrations than their sibling controls. Hence the anticipated decrease in circulating concentrations of testosterone and increase in glucocorticoids with repeated defeat reported in many studies on adult animals (Bronson *et al.* 1964; Rose *et al.* 1975; Eberhart *et al.* 1980, 1983) including hamsters (Huhman *et al.* 1991) do not replicate in adolescent hamsters.

Young adult hamsters with a history of adolescent stress also have changes in the neurochemical systems regulating aggressive behaviour. In addition to the decrease in vasopressin levels as noted in adult hamsters, there is an increase in serotonin (5-HT) innervation to the anterior hypothalamus compared to their sibling controls (Delville *et al.* 1998). As noted earlier, 5-HT decreases aggressive behaviour, in part, by inhibiting the activity of the vasopressin system at the level of the anterior hypothalamus. Thus it is possible that the stress of threat and attack in adolescence alters the interaction between the vasopressin–5-HT systems affecting the regulation of aggression and possibly the context-dependent nature of the aggressive response.

A model of this hypothesis highlighting the imbalance in vasopressin–5-HT systems and the context-dependent nature of the aggressive behaviour in animals with a history of adolescent stress is shown at the bottom of Fig. 1. Following adolescent stress the interaction between vasopressin–5-HT systems is altered. The vasopressin neurones have been made smaller to reflect the decrease in vasopressin concentrations in the anterior hypothalamus (Ferris & Potegal, 1988; Delville *et al.* 1998). This may be due to suppression of vasopressin gene expression resulting in diminished release of neuropeptide. With less release of vasopressin, there is upregulation of V_{1A} receptors (depicted by the larger receptor) measured by an increase in B_{max} or a decrease in K_d. Stress is associated with an activation of 5-HT release and/or turnover in the brain (De Souza & Van Loon, 1986; Adell *et al.* 1988; Blanchard *et al.* 1993). Conversely the increase in the density of 5-HT immunoreactive boutons in the anterior hypothalamus (Delville *et al.* 1998) may suggest an increased release of this neurochemical signal. With more 5-HT release there is a downregulation of the 5-HT_{1A} receptor (depicted by the smaller receptor) measured by a decrease in B_{max} and an increase in K_d. The downregulation of serotonin receptors in response to social stress has been reported previously (Bolanos-Jimenez *et al.* 1995; McKittick *et al.* 1995). An intruder of similar size and age may be perceived as a potential threat inhibiting the vasopressin system and driving the 5-HT system (lower left). The subsequent inhibition of aggressive behaviour extends into submissive postures and flight behaviour, given the resident's past history of social subjugation by more aggressive larger males, resulting in conditioned defeat (Potegal *et al.* 1993). However, when the intruder is smaller and younger and offers no potential threat, the behaviour is dramatically different (lower right). The vasopressin system is activated, releasing vasopressin onto highly sensitive receptors. Serotonin release is inhibited, removing an inhibitory pathway that was blunted already by the down-regulation of 5-HT_{1A} receptors. Consequently, the aggressive response is exaggerated.

Summary

The 1978 study of national child abuse and neglect by the American Humane Association reported a high incidence of abuse toward adolescents between the ages 12 and 17; in fact, recent evidence indicates that the incidence of adolescent abuse equals or exceeds that of all other age groups (Schellenbach & Guerney, 1987). While much attention has been paid to victimization of infants and children, less is known about the behavioural and biological consequences of abuse during adolescence. This is surprising because of the incidence of physical abuse rises dramatically during this developmental period (Lourie *et al.* 1979).

The preclinical studies discussed in this review provide evidence of a highly plastic nervous system in adolescence. The neural systems involved in the regulation of agonistic behaviour, i.e. vasopressin and 5-HT, are affected by the daily stress of threat and attack by older conspecifics. As young

adults, animals with a history of adolescent stress show inappropriate and excessive aggressive behaviour. In the presence of adult hamsters, they are very submissive; however, a smaller, younger hamster elicits intense biting attacks. These findings underscore the context-dependent nature of aggressive behaviour and the neurobiological and behavioural consequences of stress in adolescence.

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Acknowledgements

These experiments were supported by grants MH 52280 from the NIMH awarded to C.F.F. The contents of this review are solely the responsibility of the author and do not necessarily represent the official views of the NIMH.