Available online at www.sciencedirect.com
SCIENCE DIRECT
Pharmacology, Biochemistry and Behavior 83 (2006) 169–174
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Orally active vasopressin V1a receptor antagonist, SRX251, selectively blocks aggressive behavior

Craig F. Ferris [a,e,*], Shi-fang Lu [b], Tara Messenger [a], Christophe D. Guillon [c], Ned Heindel [c], Marvin Miller [d], Gary Koppel [e], F. Robert Bruns [f], Neal G. Simon [b,e]

[a] *Center for Comparative Neuroimaging, University of Massachusetts Medical School, Worcester, MA, USA*
[b] *Department of Biological Sciences, Lehigh University, Bethlehem, PA, USA*
[c] *Department of Chemistry, Lehigh University, USA*
[d] *Department of Chemistry and Biochemistry, University of Notre Dame, South Bend, IN, USA*
[e] *Azevan Pharmaceuticals, Inc., Bethlehem, PA, USA*
[f] *Eli Lilly and Co., Indianapolis, IN, USA*

Received 29 September 2005; received in revised form 5 January 2006; accepted 11 January 2006
Available online 28 February 2006

Abstract

Arginine vasopressin functions as a neurochemical signal in the brain to affect social behavior. There is an expanding literature from animal and human studies showing that vasopressin, through the vasopressin 1A receptor (V1A), can stimulate aggressive behavior. Using a novel monocylic beta lactam platform, a series of orally active vasopressin V1a antagonists was developed with high affinity for the human receptor. SRX251 was chosen from this series of V1a antagonists to screen for effects on serenic activity in a resident-intruder model of offensive aggression. Resident, male Syrian golden hamsters were given oral doses of SRX251 or intraperitoneal Manning compound, a selective V1a receptor antagonist with reduced brain penetrance, at doses of 0.2 μg, 20 μg, 2 mg/kg or vehicle. When tested 90–120 min later, SRX251, but not Manning compound, caused a significant dose-dependent reduction in offensive aggression toward intruders as measured by latency to bite and number of bites. The reduction in aggression persisted for over 6 h and was no longer present 12 h post treatment. SRX251 did not alter the amount of time the resident investigated the intruder, olfactory communication, general motor activity, or sexual motivation. These data corroborate previous studies showing a role for vasopressin neurotransmission in aggression and suggest that V1a receptor antagonists may be used to treat interpersonal violence co-occurring with such illness as ADHD, autism, bipolar disorder, and substance abuse.

Keywords: Arginine vasopressin; Hamster; Serenic; Impulsive aggression; Violence; Resident-intruder; Flank marking; Sexual motivation

1. Introduction

Interpersonal violence in the context of antisocial behavior comorbid with DSM-defined illnesses, e.g., manic/depression, ADHD, PTSD, autism, and substance abuse, presents a significant health problem (Cloninger et al., 1997; Connor, 2002). The standard medications used to treat many of these mental disorders do not effectively reduce the co-occurring impulsive aggressive behavior (MTA Cooperative Group, 1991; Aman et al., 2004). Efforts to develop drug intervention strategies for controlling violent behavior in psychiatric patients have been unsuccessful as most treatments (e.g., neuroleptics and benzodiazepines) are nonspecific and arrest aggression by diminishing general activity (Karper and Krystal, 1997).

Can drugs be developed that block impulsive aggression without interfering with other behaviors? These hypothetical drugs, called *serenics* (Olivier and Mos, 1990), would reduce or delay the rapid onset of anger. Serenics would not impair initiative, interfere with normal social relations, or prevent adequate defense from challenges or threats. Two classes of potential therapeutics with "serenic" activity are serotonin (5-

* Corresponding author. Department of Psychiatry, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester MA, USA. Tel.: +1 508 856 5530; fax: +1 508 856 6426.
E-mail address: craig.ferris@umassmed.edu (C.F. Ferris).

0091-3057/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2006.01.001

HT) receptor agonists and 5-HT re-uptake inhibitors. Serotonin is recognized as a critical chemical signal in the control of aggressive responding because many studies across a wide range of animals show that increases in 5-HT neurotransmission reduce aggression (Simon, 2002; Simon and Lu, 2005). Even medications such as lithium, carbamazepine, and beta blockers that reduce aggression, do so by indirectly affecting 5-HT activity in the brain (Middlemis, 1984; Post et al., 1992).

There is accumulating evidence showing 5-HT suppresses aggression, in part, by checking the activity of vasopressin (VP) neurotransmission in the brain. Vasopressin is a neuropeptide released in the brain that can enhance arousal and aggression (Ferris, 2005). The medial basal hypothalamus, a key neural substrate in the control of aggressive responding and the primary site of VP regulation, has a high density of 5-HT binding sites and receives dense innervation of 5-HT fibers and terminals (Ferris et al., 1997). The VP neurons in the hypothalamus involved in the control of aggression appear to be preferentially innervated by 5-HT (Ferris et al., 1997, 1999). Treatment with the 5-HT re-uptake inhibitor fluoxetine blocks aggression facilitated by the microinjection of VP in the hypothalamus (Delville et al., 1995; Ferris et al., 1997). Fluoxetine elevates 5-HT and reduces VP levels in hypothalamic tissue of rats, and hamsters (Altemus et al., 1992; Ferris, 1996). Kia and coworkers (1996) reported intense immunocytochemical staining for 5-HT_{1A} receptors in the VP system of rats supporting the notion that activation of 5-HT_{1A} receptors can influence the activity of VP neurons. However, data also suggest that 5-HT can block the activity of VP following its release in the hypothalamus as evidenced by the dose-dependent diminution of aggression with injections combining VP and 5-HT_{1A} receptor agonist (Ferris et al., 1999). Enhanced aggression caused by activation of VP V1a receptors in the hypothalamus is suppressed by the simultaneous activation of 5-HT_{1A} receptors in the same site.

The animal studies examining the interaction between VP and 5-HT are particularly relevant since Coccaro and coworkers (1998) reported a similar reciprocal relationship in human studies. Personality disordered subjects with a history of fighting and assault show a negative correlation for prolactin release in response to D-fenfluramine challenge, indication of a hyposensitive 5-HT system. Moreover, these same subjects show a positive correlation between CSF levels of VP and aggression. Thus, in humans, a hyposensitive 5-HT system may result in enhanced CNS levels of VP and the facilitation of aggressive behavior.

The activity of centrally released VP appears linked to the 5-HT system, which provides a mechanism for enhancing and suppressing aggressive behavior. Consequently, a potential approach to the treatment of impulsive aggression is the use of selective V1a receptor antagonists. A new class of non-peptidic compounds targeted to the human V1a receptor was developed using a monocyclic beta lactam platform (US Patent 6204260 B1 Non-peptidyl vasopressin V1a antagonists). SRX251 was chosen from a library of these compounds because it is orally active, effectively penetrates the blood–brain barrier, and exhibits picomolar affinity for the human V1A receptor and low nanomolar affinity for rat, mouse, and hamster V1a receptor by in vitro receptor binding and inhibition of phosphoinositol turnover assays. The present studies examined SRX251 for serenic activity in the golden hamster resident/intruder model of offensive aggression. The results showed that SRX251 caused dose-dependent decreases in several measures of aggressive behavior without affecting motor activity, olfactory communication, and sexual motivation.

2. Methods

2.1. Hamster model of aggression

Agonistic behavior can be classified as either offensive or defensive aggression (Blanchard and Blanchard, 1977). Offensive aggression is characterized by the aggressor initiating an attack on an opponent, while defensive aggression lacks active approach. Both types of aggression have their own unique neurobehavioral systems. The stimuli that elicit offensive and defensive attack are different, as are the sequences of behaviors that accompany each agonistic response. While much of the empirical data supporting the notion of unique offensive and defensive neural networks have been collected from animal models, there are interesting and compelling similarities in human aggression that suggest a similar neural organization (Blanchard, 1984). Offensive aggression is easily studied using male golden hamsters tested in a resident/intruder paradigm, an established model of offensive aggression (Ferris and Potegal, 1988). Placing an unfamiliar male hamster into the home cage of another male hamster elicits a well-defined sequence of agonistic behaviors from the resident that includes offensive aggression.

2.2. Animal care

Male Syrian golden hamsters (*Mesocricetus auratus*) (140–150 g) obtained from Harlan Sprague–Dawley Laboratories (Indianapolis, IN) were housed individually in Plexiglas cages (24 × 24 × 20 cm), maintained on a reverse light:dark cycle (14 L:10 D; lights on at 19:00 h), and provided food and water ad libitum. Animals were acclimated to the reverse light:dark cycle for at least two weeks before testing. All behavioral tests were conducted during the dark phase of the circadian cycle. The animals were acquired and cared for in accordance with the guidelines published in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publications, 1985).

2.3. Behavioral measures and analysis

Hamsters are nocturnal and as such behavioral tests were performed during the first four hrs of the dark phase under dim red illumination. The resident was scored for offensive aggression, e.g., latency to bite the intruder, the total number of bites, total contact time with the intruder and flank marking over a 5 min test period (Ferris and Potegal, 1988). Flank marking is a form of olfactory communication in which a

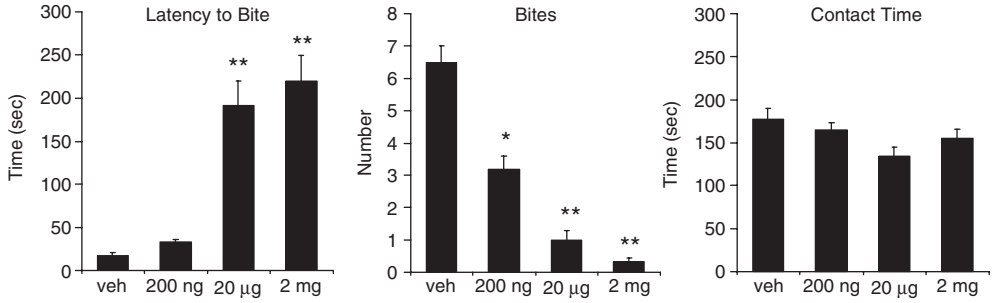

Fig. 1. Oral SRX251 Reduces offensive aggression. Shown are the mean scores of latency to bite, number of bites and contact time of residents toward intruders. There are dose-dependent increases in the latency to bite and decreases in the number of bites, 90–120 min after oral treatment with SRX251. Vertical lines denote SEM. Significant differences (*$p<.05$; **$p<.01$) are in comparison to vehicle.

hamster arches its back and rubs pheromone producing flank glands against objects in the environment (Johnston, 1985). Flank marking frequency is greatly enhanced during aggressive encounters and is particularly robust in dominant animals initiating and winning fights (Ferris et al., 1987). To test for behavioral specificity, hamsters were observed in an open field that consisted of a large clean Plexiglas cage (48×32×40 cm) devoid of any bedding. This open field was delineated into equal quadrants by tape on the underside of the cage. Animals were scored for motor activity by counting the number of quadrants traversed in 1 min. In addition, animals were scored for latency to mount a receptive female as a measure of sexual motivation.

SRX251 was administered by oral gavage at concentrations of 200 ng, 20 µg, or 2 mg/kg in cyclodextrim/lactic acid vehicle 92:8 v/v) or vehicle in a volume of 200 µl. Sixteen animals were tested over four observation periods separated by 48–72 h. Animals were tested 90–120 min after oral gavage. Treatments were counter-balanced with each animal being administered each drug concentration. Data were analyzed with a two-way, repeated measures ANOVA followed by Bonferroni post hoc tests.

2.4. Central vs. peripheral activity of V1A blockade

In a separate study, Manning compound (MC), [1-β-mercapto-β,β-cyclopentamethylene propionic acid 2-[0-(methyl) tyrosine] arginine vasopressin, a selective V1A receptor antagonist, was tested for serenic activity following intraperitoneal administration. MC is not orally active and has reduced brain penetrance when given peripherally. MC blockade of V1A receptors in hamsters lasts for over 12 h (Ferris et al., 1988). Twenty hamsters were divided into four groups of five animals each and given MC in doses of 20 µg, 200 µg, 2 mg/kg or vehicle and scored for behavior 90–120 min later as described above. These doses of MC were chosen because they exceed the dose (10 µg/kg) reported for peripheral blockade of V1A receptors in blood pressure studies (Landulpho et al., 2003; Ackermann and Asisi, 2000). Data was analyzed with a one-way ANOVA followed by Bonferroni post hoc tests.

2.5. Biological time course

SRX251 was administered to four groups of eight animals each by oral gavage at 2 mg/kg in a volume of 200 µl (based on the results of Experiment 1). Hamsters were tested during the first four hrs of the dark phase at 30 min, 2, 6, and 12 h following drug administration. Data were analyzed with a one-way ANOVA followed by Bonferroni post hoc tests.

3. Results

3.1. Effects on offensive aggression

The latency to bite was significantly different between drug concentrations ($F_{(3,12)}=487.22$; $p<0.001$) (Fig. 1). SRX251 given at 20 µg and 2 mg effectively blocked the onset of biting

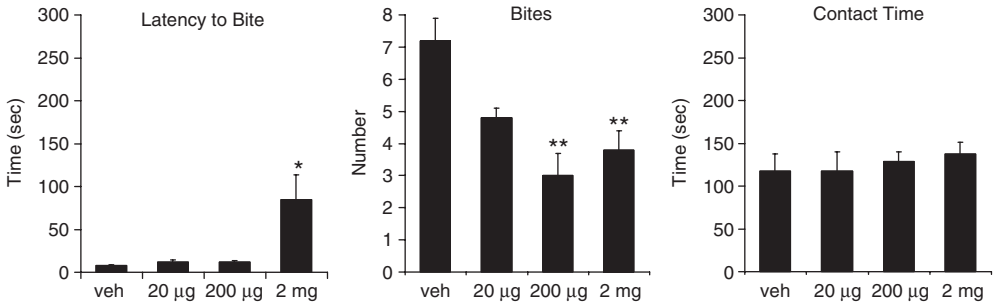

Fig. 2. Effects of Intraperitoneal Manning compound, a Peripheral V1A Antagonist, on Offensive Aggression. Shown are the mean scores of resident hamsters for latency to bite, number of bites and contact time towards intruders. Vertical lines denote SEM. The significant difference (*$p<.05$) for latency to bite is in comparison to vehicle and the lower drug doses. The significant difference (**$p<.01$) for bites is in comparison to vehicle as there were no differences between doses.

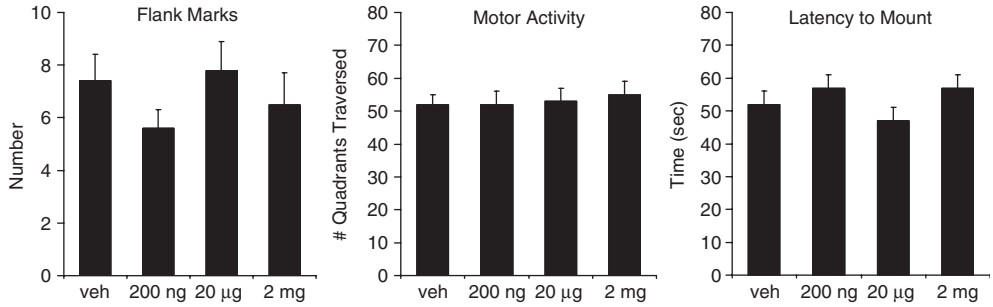

Fig. 3. Oral SRX251 Shows Behavioral Specificity. Shown are mean scores of resident hamsters for flank marks, general motor activity and time to mount a receptive female 90–120 min following different doses of SRX251. Vertical lines denote SEM. There are no significant differences from vehicle.

as compared to control ($p<.01$). There was a significant dose-dependent decrease in the number of bites ($F_{(3,12)}=63.6$; $p<0.001$).

With MC there was no dose-dependent decrease in either the latency to bite or the number of bites (Fig. 2). Treatment at the 2 mg dose significantly delayed the latency to bite ($F_{(3,16)}=6.17$; $p<0.01$), but this delay in biting attacks was only 1.5 min as compared to 3 min for SRX251. Treatment with 200 µg and 2 mg of MC significantly reduced the number of bites to ca. 3–4 over a five min period ($F_{(3,16)}=9.35$; $p<0.001$), but this was not a dose-dependent effect as there was no significant difference in the number of bites between any of the three doses tested.

3.2. Behavioral specificity

There was no significant difference in contact time among any of the four drug treatments. Flank marking, motor activity in an open field, and sexual motivation as measured by latency to mount a receptive female were unchanged by drug treatment (Fig. 3).

3.3. Duration of action

The latency to bite ($F_{(3,28)}=7.36$; $p<.001$) and number of bites ($F_{(3,28)}=16.4$; $p<.001$) was significantly different between time points (Fig. 4). There was no effect on offensive aggression at 30 min. By 2 and 6 h post treatment, there was a significant increase in bite latency and reduction in bites. Aggressive behavior was fully recovered by 12 h post treatment. There was no significant difference in contact time between any of the four time points ($F_{(3,28)}=2.37$; $p<.09$).

4. Discussion

These studies using an orally active V1a receptor antagonist, SRX251, show a dose-dependent reduction in offensive aggression following drug treatment in male Syrian golden hamsters. The data corroborate and add to the growing body of literature showing a substantive role for VP in the regulation of aggression. Microinjection of VP into the hypothalamus of resident hamsters significantly increases the number of biting attacks on intruders (Delville et al., 1995; Ferris et al., 1997; Caldwell and Albers, 2004). Infusion of VP into the amygdala or lateral septum facilitates attack behavior in castrated rats (Koolhaas et al., 1990, 1991). Prairie voles show a dose-dependent increase in aggression toward intruders following intraventricular administration of VP (Young et al., 1997). In prairie voles, VP treatment increases aggressive behavior (Winslow et al., 1993). Data from rats and humans show high indices of aggressivity correlate with high concentrations of VP in cerebrospinal fluid (Haller et al., 1996; Coccaro et al., 1998).

In hamsters, a selective V1a receptor antagonist microinjected into the hypothalamus caused a dose-dependent inhibition of aggression by a resident male toward an intruder (Ferris and Potegal, 1988). Treatment with V1a receptor antagonist prolongs the latency to bite an intruder and reduces the number of bites, but does not alter other social or appetitive behaviors. Vasopressin receptor antagonist also blocks

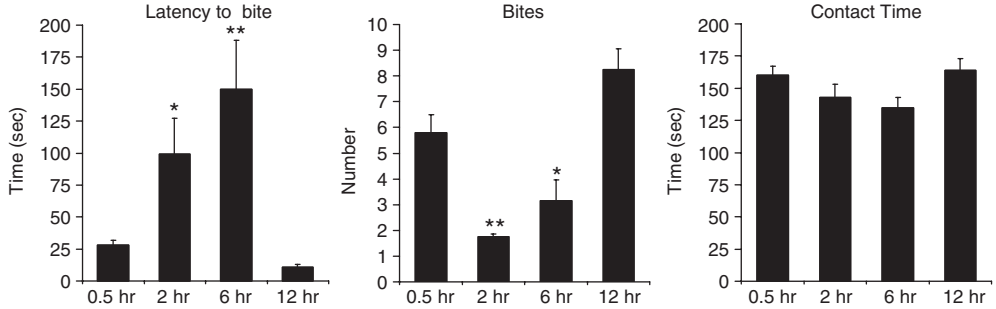

Fig. 4. Time Course of Serenic Activity Following Oral SRX251. Shown are the mean scores of latency to bite, number of bites and contact time of residents toward intruders at 0.5, 2, 6 and 12 h after SRX251. There are time-dependent changes in the latency to bite and number of bites at 2 and 6 h. Vertical lines denote SEM. There were no significant differences between the 2 and 6 h time points for any of the three measures. The significant differences (*$p<.05$; **$p<.01$) noted are between 2 and 6 h in comparison to 0.5 and 12 h.

aggression associated with the development of dominant/subordinate relationships (Potegal and Ferris, 1990). In male prairie voles, intraventricular injection of V1a receptor antagonist reduces aggression toward male intruders (Winslow et al., 1993).

In all prior studies to date using V1a antagonists to block aggression, it was necessary to administer the drugs directly into the brain because they were unable to effectively cross the blood–brain-barrier. SRX251 is the first example of an orally active V1a antagonist with central nervous system activity. However, it is possible that the anti-aggressive effect of oral SRX251 was due, in part, to the blockade of V1a receptors in peripheral tissues like the liver and blood vessels. To control for this possibility, MC a selective V1a antagonist with reduced brain penetrance, was tested for anti-aggressive activity at doses exceeding that reported to block peripheral V1a receptors (Landulpho et al., 2003; Ackermann and Asisi, 2000). While an oral dose of 20 μg/kg of SRX251 effectively blocked aggressive behavior, an intraperitoneal dose of 20 μg/kg of MC had no significant effect on latency to bite or number of bites. Only when MC was given in much higher doses was there a significant reduction in aggression. However, this reduction appears to be non-specific as there was no dose-dependent change in behavior.

While the present study confirms that aggressive behavior is under the control of the V1a receptor, there is recent evidence that the V1b receptor, also localized in the limbic system, may be involved in the regulation of agonistic behavior. V1b receptor knock out mice show reduced aggressive behavior (Wersinger et al., 2002), while treatment with a selective V1b antagonist SSR149415 reduced offensive aggression of resident male hamsters toward intruders (Blanchard et al., 2005). This raises the possibility that SRX251 may reduce aggression by interacting with V1b receptors. However, this is unlikely since SRX251 has a very low affinity (>1 μm; G. Koppel et al., unpublished data) for the V1b receptor and the sensitivity and behavioral profile of V1a and V1b receptor blockade are different. SSR149415 is orally active but only effective in doses of 10 mg/kg or greater as compared to the 20 ug/kg of the V1A antagonist given in the present studies. Furthermore, V1b receptor blockade significantly reduces olfactory investigation (contact time in our studies) and flank marking, while SRX251 has no such effects.

The VP system is plastic and can be sensitive to hormonal and environmental conditions that promote the expression of inappropriate aggression (Ferris, 2000). For example, treating adolescent hamsters with androgenic anabolic steroids increases the density of VP immunoreactive fibers and neuropeptide content in the hypothalamus and enhances VP mediated aggression as adults (Harrison et al., 2000; DeLeon et al., 2002). Testosterone treatment in castrated hamsters increases V1a receptor density in the hypothalamus and VP-induced aggression (Delville et al., 1996). Conversely, social subjugation of adolescent hamsters reduces VP immunoreactivity in the hypothalamus resulting in inappropriate aggressive behavior. Hamsters subjugated in adolescence are highly aggressive toward non-threatening, smaller intruders but submissive towards equal sized intruders (Delville et al., 1998). Interestingly, adolescent hamsters exposed to cocaine develop a highly aggressive phenotype as adults (Jackson et al., 2005). The increased offensive aggression is associated with enhanced released of VP in the hypothalamus and can be blocked by the central administration of the V1a receptor antagonist, MC. Submissive hamsters in adult dominant/subordinate dyads also have reduced levels of VP in the hypothalamus (Ferris et al., 1989), while dominant partners show higher levels of V1a binding in the hypothalamus (Cooper et al., 2005). The highly aggressive California mouse (*Peromyscus californicus*) has greater VP staining in the bed nucleus of the stria terminalis and V1a receptor density in the lateral septum as compared to the less aggressive white-footed mouse (*Peromyscus leucopus*) (Bester-Meredith et al., 1999). However, when California mice are cross-fostered with white-footed parents, they show a reduction in aggression in a resident-intruder paradigm and lower levels of VP in the bed nucleus as compared to their unfostered siblings (Bester-Meredith and Marker, 2001). Collectively, these studies show that androgen hormone levels, drugs of abuse, stressful environments and maternal care can affect VP neurotransmission and aggressive behavior. While speculative, this involvement of VP in conditions associated with heightened aggression raises the possibility that in the future V1a receptor antagonists may be used to treat interpersonal violence co-occurring with such illness as ADHD, autism, bipolar disorder and substance abuse.

Acknowledgements

These experiments were supported by grants R42 HD37290 (NICHD) and MH 52280, MH59300 from the NIMH. The contents of this paper are solely the responsibility of the authors and do not represent the official views of the NIMH. Drs. Ferris, Lu, Koppel, and Simon hold equity in Azevan Pharmaceuticals, Inc. Drs. Miller and Heindel are consultants to Azevan Pharmaceuticals, Inc.

References

Ackermann U, Asisi N. Increased central AT(1)-receptor activation, not systemic vasopressin, sustains hypertension in ANP knockout mice. Am J Physiol Regul Integr Comp Physiol 2000;278:R1441–5.

Altemus M, Cizza G, Gold PW. Chronic fluoxetine treatment reduces hypothalamic vasopressin secretion in vitro. Brain Res 1992;593:311–3.

Aman MG, Binder C, Turgay A. Risperidone effects in the presence/absence of psychostimulant medicine in children with ADHD, other disruptive behavior disorders, and subaverage IQ. J Child Adolesc Psychopharmacol 2004;4:243–54.

Blanchard DC. Applicability of animal models to human aggression. Biological perspectives on aggression. Alan R. Liss, Inc.; 1984. p. 49–74.

Blanchard RJ, Blanchard DC. Aggressive behaviour in the rat. Physiol Behav 1977;1:197–224.

Blanchard RJ, Griebel G, Farrokhi C, Markham C, Yang M, Blanchard DC. AVP V1b selective antagonist SSR149415 blocks aggressive behaviors in hamsters. Pharmacol Biochem Behav 2005;80:189–94.

Bester-Meredith JK, Marker CA. Vasopressin and aggression in cross-fostered California mice (*Peromyscus californicus*) and white-footed mice (*Peromyscus leucopus*). Horm Behav 2001;40:51–64.

Bester-Meredith JK, Young LJ, Marker CA. Species differences in paternal behavior and aggression in *Peromyscus* and their associations with vasopressin immunoreactivity and receptors. Horm Behav 1999;36:25–38.

Caldwell HK, Albers HE. Effect of photoperiod on vasopressin-induced aggression in Syrian hamsters. Horm Behav 2004;46:444–9.

Cloninger RC, Bayon C, Przybeck TR. Epidemiology and axis I comorbidity of antisocial personality. In: Stoff DM, Breiling J, Maser JD, editors. Handbook of antisocial behavior. New York: John Wiley & Sons, Inc.; 1997. p. 12–21.

Coccaro EF, Kavoussi RJ, Hauger RL, Cooper TB, Ferris CF. Cerebrospinal fluid vasopressin levels correlates with aggression and serotonin function in personality-disordered subjects. Arch Gen Psychiatry 1998;55:708–14.

Connor DF. Aggression and antisocial behavior in children and adolescents: research and treatment. New York: The Guilford Press; 2002.

Cooper MA, Karom M, Huhman KL, Elliot Albers H. Repeated agonistic encounters in hamsters modulate AVP V1a receptor binding. Horm Behav 2005;48:545–51.

DeLeon KR, Grimes JM, Melloni Jr RH. Repeated anabolic–androgenic steroid treatment during adolescence increases vasopressin V(1A) receptor binding in Syrian hamsters: correlation with offensive aggression. Horm Behav 2002;42:182–91.

Delville Y, Mansour KM, Ferris CF. Serotonin blocks vasopressin-facilitated offensive aggression: interactions within the ventrolateral hypothalamus of golden hamsters. Physiol Behav 1995;59:813–6.

Delville Y, Mansour KM, Ferris CF. Testosterone facilitates aggression by modulating vasopressin receptors in the hypothalamus. Physiol Behav 1996;60:25–9.

Delville Y, Melloni Jr RH, Ferris CF. Behavioral and neurobiological consequences of social subjugation during puberty in golden hamsters. J Neurosci 1998;18:2667–72.

Ferris CF. Serotonin inhibits vasopressin facilitated aggression in the Syrian hamster. In: Ferris CF, Grisso T, editors. Understanding aggressive behavior in children, vol. 794. New York, N.Y: New York Academy of Sciences; 1996. p. 98-103.

Ferris CF. Adolescent stress and neural plasticity in hamsters: a vasopressin/serotonin model of inappropriate aggressive behavior. Exp Physiol 2000;85:85–90.

Ferris CF. Vasopressin/oxytocin and aggression. In: Goode Jamie, editor. Molecular mechanisms influencing aggressive behaviours, vol. 268. Novartis Foundation Symposium; 2005.

Ferris CF, Potegal M. Vasopressin receptor blockade in the anterior hypothalamus suppresses aggression in hamsters. Physiol Behav 1988;44:235–9.

Ferris CF, Axelson JF, Shinto L, Albers HE. Scent marking and the maintenance of dominant/subordinate status in male golden hamster. Physiol Behav 1987;40:661–4.

Ferris CF, Axelson JF, Martin AM, Roberge LR. Vasopressin immunoreactivity in the anterior hypothalamus is altered during the establishment of dominant/subordinate relationships between hamsters. Neuroscience 1989;29:675–83.

Ferris CF, Melloni Jr RH, Koppel G, Perry KW, Fuller RW, Delville Y. Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. J Neurosci 1997;17:4331–40.

Ferris CF, Stolberg T, Delville Y. Regulation of aggressive behavior in male golden hamsters (*Mesocricetus auratus*). Behav Neurosci 1999; 113:804–15.

Haller J, Makara GB, Barna I, Kovacs K, Nagy J, Vecsernyes M. Compression of the pituitary stalk elicits chronic increases in CSF vasopressin, oxytocin as well as in social investigation and aggressiveness. J Neuroendocrinol 1996;8:361–5.

Harrison RJ, Connor DF, Nowak C, Nash K, Melloni Jr RH. Chronic anabolic–androgenic steroid treatment during adolescence increases anterior hypothalamic vasopressin and aggression in intact hamsters. Psychoneuroendocrinology 2000;25:317–38.

Jackson D, Burns R, Trksak G, Simeone B, Deleon KR, Connor DF, et al. Anterior hypothalamic vasopressin modulates the aggression-stimulating effects of adolescent cocaine exposure in Syrian hamsters. Neuroscience 2005;33:635–46.

Johnston RE. Communication. In: Siegel HI, editor. The hamster reproduction and behavior. New York: Plenum Press; 1985. p. 121–54.

Karper LP, Krystal JH. Pharmacotherapy of violent behavior. In: Stoff DM, Breiling J, Maser JD, editors. Handbook of antisocial behavior. New York: John Wiley & Sons, Inc.; 1997. p. 436–44. Chpt 41.

Kia HK, Miquel M-C, Brisorgueil M-J, Daval G, Riad M, El Mestikawy S, et al. Immunocytochemical localization of serotonin 1A receptors in the rat central nervous system. J Comp Neurol 1996;365:289–305.

Koolhaas JM, Van den Brink THC, Roozendal B, Boorsma F. Medial amygdala and aggressive behavior: interaction between testosterone and vasopressin. Aggress Behav 1990;16:223–9.

Koolhaas JM, Moor E, Hiemstra Y, Bohus B. The testosterone-dependent vasopressinergic neurons in the medial amygdala and lateral septum: involvement in social behaviour of male rats. In: Jard S, Jamison R, editors. Vasopressin.-Londres: Is.NSERM. John Libbey Eurotext Ltds.; 1991. p. 213–9.

Landulpho CD, Dias AC, Colombari E. Cardiovascular mechanisms activated by microinjection of baclofen into NTS of conscious rats. Am J Physiol Heart Circ Physiol 2003;284:H987–93.

Middlemis DN. Stereoselective blockade of [3H]5-HT binding sites and at the 5-HT autoreceptor by propranolol. Eur J Pharmacol 1984;101:289–93.

MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention deficit hyperactivity disorder. Arch Gen Psychiatry 1991;56:1073–86.

Olivier B, Mos J. Serenics, serotonin and aggression in: current and future trends in anticonvulsant, anxiety, and stroke therapy. Wiley-Liss, Inc.; 1990. p. 203–30.

Post RM, Weiss SRB, Chuang DM. Mechanisms of action of anticonvulsants in affective disorders: comparisons with lithium. J Clin Psychopharmacol 1992;12:23S–35S.

Potegal M, Ferris CF. Intraspecific aggression in male hamsters is inhibited by vasopressin receptor antagonists. Aggress Behav 1990;15:311–20.

Simon NG. Hormonal processes in the development and expression of aggressive behavior. In: Pfaff D, Etgen A, Fahrbach S, Rubin R, editors. Hormones, the brain, and behavior. San Diego: Academic Press; 2002.

Simon NG, Lu S. In: Nelson R, editor. Aggressive behavior. Oxford Press; 2005. p. 537–82.

Winslow J, Hastings N, Carter C, Harbaugh C, Insel T. A role for central vasopressin in pair bonding in monogamous prairie voles. Nature 1993;365:545–8.

Wersinger SR, Ginns EI, O'Carroll AM, Lolait SJ, Young III WS. Vasopressin V1b receptor knockout reduces aggressive behavior in male mice. Mol Psychiatry 2002;7:975–84.

Young LJ, Winslow JT, Nilsen R, Insel TR. 1997. Species differences in V1a Receptor gene expression in monogamous and nonmonogamous voles: behavioral consequences. 111:599-605.