Involvement of vasopressin 3 receptors in chronic psychological stress-induced visceral hyperalgesia in rats

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Submitted 18 September 2008; accepted in final form 14 November 2008

Abstract

Stress-related effects of AVP [including modulation of the hypothalamic-pituitary-adrenal (HPA) axis and behavioral responses] are mediated through vasopressin V₃ signaling in the hypothalamus (11, 16, 30), behavioral, and possibly autonomic, responses to stress are mediated by extrahypothalamic AVP/V₃ signaling in limbic structures, including the amygdala, hippocampus, and lateral septum (25, 52). Although in acute stress responses CRF is the main activator of ACTH secretion, the AVP/V₃ system seems to play a major role during the adaptation to chronic stress conditions (1, 19, 26). During chronic stress, it has been shown that the hypothalamic content of AVP and V₃ receptor expression in the brain increases (2) and the peptide becomes the main modulator of the HPA axis (1, 13, 15, 19). SSR149415 is a recently characterized, highly selective, centrally acting nonpeptide antagonist of the V₃ receptor. SSR149415 inhibits various V₃-mediated AVP effects in in vitro systems as well as AVP- and stress-induced ACTH secretion in vivo (47, 48, and

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V. Martinez, unpublished observations). More importantly, SSR149415 exhibits a mixed anxiolytic/antidepressant profile in animal models generally used to model generalized anxiety disorder, panic attack, acute stress disorder, and major depressive disorder (47, 48).

Given the association between stress and anxiety (32, 33) and (to a lesser degree) depression and IBS (49), one can speculate that AVP/V3 mechanisms might be involved in some aspects of IBS pathophysiology. For example, preclinical and clinical data suggest that AVP signaling may be involved in stress- and CRF-induced modulation of intestinal motility (10, 21, 54). However, a role of AVP/V3 signaling in stress-induced visceral hyperalgesia has not been demonstrated.

In the present study, we used the selective V3 receptor antagonist SSR149415 to assess the possible involvement of AVP/V3 signaling in a chronic stress-induced rodent model of visceral hypersensitivity with high-face and construct validity for IBS. We selected this model because it exhibits sustained visceral hyperalgesia and anxiety-like behaviors and has previously been shown to be sensitive to CRF1 receptor antagonists (8, 46). Specifically, we wanted to address the following questions: 1) Does daily application of the V3 receptor antagonist prevent the development of visceral hyperalgesia during repeated stress? 2) Does the antagonist block the expression of visceral hyperalgesia once induced by chronic stress? 3) Does the antagonist affect the development of visceral hyperalgesia during acute sensitization by repeated, noxious colorectal distension (CRD)?

MATERIALS AND METHODS

Animals. Adult male Wistar rats (250–275 g; Harlan, Indianapolis, IN) were maintained on a 12-h:12-h light/dark cycle (lights on at 0600). Animals were group housed (5 animals per cage) except when otherwise stated and maintained on a standard rodent food diet (Purina rat chow) with water ad libitum. The animals were allowed to acclimate to the animal facility for 1 wk before any surgical procedure.

For some experiments, adult female Sprague-Dawley rats (250–300 g; Harlan, Horst The Netherlands), maintained basically in the same standard conditions, were used. All protocols were approved by the Institutional Animal Care and Use Committee at the Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA (02007-05) or the Local Animal Ethics Review Committee in Göteborg, Sweden, as appropriate.

Surgery: implantation of electrodes for electromyography (EMG). Rats were deeply anesthetized with pentobarbital sodium (45 mg/kg ip, Nembutal; Abbott Laboratories, North Chicago, IL) and equipped with electrodes (Teflon-coated stainless steel wire; AstraZeneca, Mölndal, Sweden) implanted into the external oblique musculature, just superior to the inguinal ligament, as previously described (8, 46). Electrode leads were then tunneled subcutaneously and externalized laterally (left abdominal side) for future access through a plastic fistula (AstraZeneca). Following surgery, rats were allowed to recover for at least 7 days before any experimental procedure was started. Wounds were tested regularly for tenderness to ensure complete recovery from surgery before testing.

CRD. Two different procedures were used when assessing pain-related visceromotor responses (VMR) during CRD: EMG recordings in operated animals and colonic manometric recordings in intact animals.

CRD during EMG recordings. Briefly, animals were lightly anesthetized with halothane, and a flexible latex balloon (6 cm) lubricated with Surgilube (E. Fougera, Melville, NY) was inserted into the distal colon, 1 cm from the base of the balloon to the anus, and was secured in place by taping the balloon catheter to the base of the tail. Thereafter animals were placed in Bollmann cage-type restrainers (Plexiglas cylinders) and were allowed to recover for 30 min before the start of the CRD procedure. The CRD paradigm consisted in ascending graded intensities of phasic isobaric distensions (10, 20, 40, and 60 mmHg; 20-s duration; 4-min interstimulus interval). VMR to CRD was quantified by measuring EMG activity. The balloon pressure was continuously monitored online with a customized pressure control device (AstraZeneca R&D). The VMR to CRD was quantified by measuring the EMG activity of the external oblique musculature 20 s before (baseline), during, and 20 s after termination of every CRD pulse. The EMG activity was rectified, and the increase in the area under the curve of EMG amplitude (during each CRD pulse) over baseline (before CRD) was recorded as the response to distension. The same procedures have been previously used to assess pain-related responses to CRD in rats (8, 46).

CRD during colonic manometric recordings. These experiments were performed in female Sprague-Dawley rats following protocols described previously [42, 51]. A 3-cm polyethylene balloon (made in house) with connecting catheter (PE-50) was inserted in the distal colon 2 cm from the base of the balloon to the anus during light isoflurane anesthesia (Forene; Abbott Scandinavia, Solna, Sweden) and fixed to the tail with tape. At the same time, an intravenous catheter (Neolon; Becton Dickinson, Helsingborg, Sweden) was inserted in the tail vein for compound administration. The balloons were connected to pressure transducers (P-602, CFM-k33, 100 mmHg; Bronkhorst HI-TEC, Venendal, The Netherlands), and the animals were allowed to recover for at least 15 min before the start of experiments.

A customized barostat (AstraZeneca) was used to manage air inflation and balloon pressure control. A customized computer software (PharmLab on-line 5.0) running on a standard computer was used to control the barostat and to perform data collection. The CRD paradigm used consisted of repeated phasic distensions, 12 times at 80 mmHg, with a pulse duration of 30 s at 5-min intervals. The same software was used to quantify the magnitude of the balloon pressure signals both before the pulse (i.e., baseline response) and for the duration of the distension pulse. This CRD protocol has been shown to induce acute, transitory, mechanical sensitization, leading to VMR that increase over time along the experimental time (42, 51).

Water avoidance stress. Water avoidance stress (WAS) was performed as previously described (8, 27). Briefly, animals were placed on a pedestal (10 × 8 × 8 cm) affixed to the center of a Plexiglas tank (45 cm length × 25 cm width × 25 cm height) filled with fresh water (by 25°C) up to 1 cm from the top of the pedestal. Sham WAS consisted of placing the rats on the same platform in a waterless tank. Each WAS or sham WAS session lasted for 1 h and was repeated daily for 10 consecutive days.

Compounds. The selective CRF1 antagonist 4-(1,3-dimethoxyprop-2-ylamino)-2,7-dimethyl-(8,4,2-dichlorophenyl)-pyrazolo[1,5-a]1,3,5-triazine (DMP-696, AstraZeneca R&D) (20) was dissolved in 0.5% hydroxypropylmethylcellulose (Methocel) in sterile water. The selective V3 antagonist (28.4R)-1-(5-chloro-1-(2,4-dimethylphosphonyl)sulfonyl)-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1H-indol-3-y1-4-hydroxy-N,N-dimethyl-2-pyrrolidinecarboxamide (SSR149415, AstraZeneca R&D) (43) was dissolved in a solutol (Solutol HS 15):ethanol:saline solution [5:5:90 (vol:vol:vol)]. The corresponding vehicles were used as controls.

Experimental protocols. Rats were handled and habituated to the Plexiglas cylinders used for CRD for 30 min per day for 3 consecutive days before experiments to reduce motion artefacts and stress-related confounding effects attributable to the procedure. When necessary, according to the route of administration of the compound tested, habituation sessions were preceded and followed by oral dosing of water to habituate the rats to the dosing procedures. No habituation to the WAS environment (tank plus pedestal) was performed.
In WAS and sham WAS experiments, a baseline response to CRD (10–60 mmHg) was recorded before starting the stress protocol. Rats were then exposed to daily WAS or sham WAS for 1 h for 10 consecutive days. Twenty-four hours after the last session (day 11), rats were tested again for their response to CRD (10–60 mmHg). A schematic representation of the experimental protocols followed is included in Fig. 1.

Effects of repeated or single dosing with SSR149415 on chronic WAS-induced visceral hypersensitivity to CRD. SSR149415 (0.3, 1, or 3 mg/kg; equivalent to 0.5, 1.6, and 5 μmol/kg, respectively) or the corresponding vehicle (2 mL/kg) was administered intraperitoneally daily 30 min before WAS or sham WAS (days 1 to 10) and, on day 11, 30 min before the CRD procedure. A separate group of animals included in the same experiments underwent repetitive (10 days) WAS exposure but received a single dose of SSR149415 (1 mg/kg ip) on day 11 30 min before the CRD procedure.

Effects of DMP-696 on chronic WAS-induced visceral hypersensitivity to CRD. To further confirm the CRF/CRF1 dependence of the model, we also tested the effects of the selective CRF2 antagonist DMP-696 on repeated stress-induced visceral hyperalgesia. In two groups of animals subjected to chronic WAS for 10 days, DMP-696 (30 mg/kg, equivalent to 73 μmol/kg) or the corresponding vehicle (5 mL/kg) was administered orally on day 11 1 h before the CRD procedure. In an additional group of rats subjected to sham WAS for 10 consecutive days, the effects of DMP-696 (30 mg/kg orally) on CRD were also assessed.

Effects of SSR149415 on acute mechanical hyperalgesia induced by repetitive noxious CRD. SSR149415 (0.6 or 10 mg/kg, equivalent to ~1 and 15 μmol/kg, respectively) or vehicle (1 mL/kg) was administered intravenously through the venous catheter between distances 3 and 4 during the repetitive noxious (12 × 80 mmHg) CRD protocol. Female Sprague-Dawley rats were used for this procedure. Animals were tested without taking into consideration the phase of the estrous cycle. The same animals were used in these experiments, receiving vehicle in one occasion and compound in another, in a random order, and with at least a 4-day interval between experiments.

Statistical analysis. Data are expressed as means ± SE. For the sake of clarity, EMG data were normalized as percentages of the baseline (control) response to 60 mmHg (taken as 100%) and presented as normalized EMG for the different CRD pressures. Such normalization has generally been used to adjust for interindividual variations of the EMG signal. The overall effect of compounds in WAS or sham WAS groups was analyzed by repeated-measure two-way ANOVA followed, when appropriate, by a multiple comparison Bonferroni test. Thereafter, the effect of vehicle/compound or WAS/sham WAS was assessed by comparing the mean difference from baseline in each group by using a Student’s t-test. When using manometric recordings, differences over time in the response to CRD were assessed using one-way repeated measures. ANOVA was followed by, when necessary, a Student-Newman-Keuls multiple comparisons test. Differences between the two groups were assessed by paired or unpaired Student’s t-test as appropriate. Data were considered statistically significant when P < 0.05.

RESULTS

Repeated WA stress resulted in the robust development of visceral hyperalgesia, and this effect was abolished by the CRF1 receptor antagonist. Animals subjected to chronic WAS and receiving vehicle on day 11 1 h before the CRD procedure exhibited increased responses to CRD on day 11 compared with baseline (Fig. 2A). However, in animals subjected to chronic WAS and receiving a single oral dose of DMP-696 1 h before CRD (n = 12), the response to CRD at day 11 was identical to that observed during the basal CRD (Fig. 2B–C). In animals subjected to sham WAS for 10 days, pretreatment with DMP-696 on day 11 1 h before the CRD procedure did not affect pain-related responses to CRD (Fig. 2D).

Effect of repeated dosing with SSR149415 on the development of visceral hypersensitivity to CRD during chronic WAS. Rats exposed to chronic WAS and treated daily with vehicle (n = 9) 30 min before the WAS session exhibited an enhanced response to CRD at 40 and 60 mmHg at day 11 when compared with the basal response to CRD (Fig. 3). Consistent with stress-induced visceral hyperalgesia as previously shown (8, 46). Repetitive dosing of SSR149415 at 1 or 3 mg/kg 30 min before WAS (n = 18 and 12, respectively) completely prevented WAS-induced hypersensitivity leading to responses of similar magnitude to those observed at baseline for the four distension levels tested (Fig. 3). SSR149415, at 0.3 mg/kg (n = 11), did not affect WAS-induced visceral hypersensitivity. In these animals, responses to CRD at day 11 were of similar magnitude to those in the vehicle-treated group (Fig. 3). When comparing the mean difference of the CRD response poststress from baseline in vehicle and treatment conditions, we confirmed a significant antihyperalgesic effect of SSR149415 at the doses 1 and 3 mg/kg. For both doses, the posttreatment response was significantly different from the response observed after vehicle treatment at 40 and 60 mmHg (Fig. 4). In contrast, for the dose of 0.3 mg/kg, there was no significant difference in the effect of treatment compared with vehicle (Fig. 4).

In animals subjected to sham WAS for 10 days and receiving a daily dose of vehicle (n = 4), the response to CRD at day 11 was essentially identical to the basal response before sham WAS (Fig. 5). A similar response was observed in animals subjected to sham WAS and receiving daily doses of SSR149415 at 3 mg/kg (n = 7) (Fig. 5).

Effect of a single dose of SSR149415 on the expression of visceral hypersensitivity to CRD following chronic WAS. On the basis of the previous observations, we tested the effect of a single injection of SSR149415 at the dose 1 mg/kg on the established visceral hyperalgesia following chronic WAS. A single dose of SSR149415 (1 mg/kg, n = 7) administered 30 min before CRD on day 11 completely blocked the established visceral hyperalgesia, leading to responses to CRD of similar magnitude to those observed during basal CRD before WAS (Fig. 6).
Effects of SSR149415 on acute visceral hyperalgesia induced by repeated noxious CRD. Repeated CRD at 80 mmHg resulted in a viscerosomatic response that represented a three- to fourfold increase over the basal mechanical activity of the abdominal musculature (basal, 0.03 ± 0.001; distension, 0.11 ± 0.02; P < 0.05, Fig. 7). In the vehicle-treated group, repetitive distensions at 80 mmHg resulted in an increase in the viscerosomatic response to distension along the procedure [66 ± 43% increase from the 1st to the 12th distension; n = 6, F(11.5) = 26.98, P = 0.0051, Fig. 7], indicative of acute mechanical sensitization. Similar responses were observed when the animals received SSR149415 (10 mg/kg iv, n = 6) after the third CRD. In SSR149415-treated animals, the response to CRD increased by 60 ± 29% from the 1st to the 12th distension [F(11.5) = 22.08, P = 0.0037; Fig. 7]. The overall response to distensions 4 to 12 was similar in vehicle- and SSR149415-treated animals (Fig. 7).

DISCUSSION
Stress-related endocrine, autonomic, and behavioral responses in humans and animals are largely mediated through...
and, under chronic stress conditions, the involvement of AVP/V3 pathways become more prominent (1, 13, 15, 19). The present study demonstrates for the first time that V3 receptor-dependent signaling mechanisms are involved in the development and expression of chronic stress-induced visceral hyperalgesia during CRD in a rat model of visceral hypersensitivity with high-face and construct validity for IBS. The enhanced VMR to CRD observed after chronic WAS was completely prevented by chronic peripheral administration of a highly selective, centrally acting nonpeptide antagonist of the V3 receptor, namely SSR149415. Similarly, once expressed, a single dose of the antagonist was also able to abolish the hyperalgesic responses to CRD. These results demonstrate that, in the rat, the AVP/V3 signaling system is necessary for the development and expression of chronic psychological stress-induced visceral hyperalgesia.

Effect of repeated dosing with SSR149415 on the development of visceral hypersensitivity to CRD during chronic WAS. SSR149415 is a competitive, highly selective V3 antagonist with at least a 270- to 2,200-fold selectivity for rat V3 receptors compared with other rat AVP receptors or to rat oxytocin receptors (48). The fact that SSR149415 was effective at doses similar to those used in previous rodent studies showing efficacy-modulating ACTH secretion as well as behavioral responses to different stressors (see Refs. 47 and 48 for review) suggests a central antihyperalgesic action mediated by V3 receptors. SSR149415 and DMP-696 were equally effective at blocking chronic psychological stress-induced visceral hyperalgesia. This finding, together with earlier observations with different CRF1 antagonists (24, 28, 46), suggests that, in the chronic WAS model, CRF- and AVP-dependent pathways are activated sequentially and that, in contrast to acute stressors, chronic stress-dependent modulation of emotional and pain responses might depend on the sequential action of CRF- and AVP-signaling pathways. This double control might be similar to that regulating pituitary ACTH secretion and HPA axis activation during acute and chronic stress, which also depends on the interaction between CRF- and AVP-dependent mechanisms (11).

Effect of a single dose of SSR149415 on the expression of visceral hypersensitivity to CRD following chronic WAS. Interestingly, stress-induced visceral hyperalgesia was prevented to a similar extent with repeated treatment of SSR149415 before each stress session or with a single treatment on day 11 before the CRD procedure. Although the mechanisms underlying this effect on central pain amplification are not known, one may speculate that repeated dosing during the chronic stressor may prevent the upregulation of V3 receptors as

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**Fig. 4.** Effect of repetitive treatment with the selective V3 antagonist SSR149415 on chronic stress-induced visceral hyperalgesia at day 11. Data represent the change in EMG activity at day 11 after subtraction of the mean EMG activity as determined during baseline for the different experimental groups included in Fig. 1. Data are means ± SE of 9–18 animals per group.

*P < 0.05 vs. the response in the vehicle-treated group.

**Fig. 5.** Lack of effects of repetitive treatment with the selective V3 antagonist SSR149415 on responses to CRD in animals subjected to sham WAS. A: VMR to CRD in vehicle- and SSR149415-treated animals subjected to sham WAS for 10 days. Sham WAS did not affect the VMR to CRD compared with baseline. Daily treatment with SSR149415 did not affect the responses to CRD. B: change in EMG activity at day 11 after subtraction of the mean EMG activity as determined during baseline for the different experimental groups included in A. Data are means ± SE of 4–7 animals per group.
previously reported in a chronic restraint stress model (2) or prevent prolonged elevations of glucocorticoids and their secondary effects on the central nervous system. On the other hand, a single dose of the antagonist given after the chronic stressor has resulted in the development of chronic visceral hyperalgesia, which may exert primarily an antihyperalgesic effect via antagonism of an already upregulated AVP/V₃ signaling system.

V₃ receptor antagonism does not affect normal or acutely sensitized VMR to CRD. SSR149415 did not affect CRD-evoked pain responses in animals subjected to sham stress and did not result in hypalgesic responses to a noxious stimulus. Similarly, SSR149415 at a dose threefold higher than the maximal dose preventing stress-induced hypersensitivity was ineffective at reducing hyperalgesic responses to CRD induced by acute mechanical sensitization of the colon. Repeated noxious distension of the colon (3) or urinary bladder (12) has been shown to induce central sensitization in rodents and acute visceral hyperalgesia in male and female human patients (40). The greater sensitization of patients with IBS, compared with controls and patients with quiescent ulcerative colitis, has been taken as evidence for compromised engagement of endogenous pain inhibition systems in IBS (31). Viewed together, these findings suggest that, similar to CRF/CRF₁ signaling, AVP/V₃ signaling is not directly involved in the modulation of ascending visceral afferent pathways or in the acute spinal amplification of visceral pain but plays an important role in the affective modulation of pain responses following chronic stress. A potential limitation of our studies on acute sensitization is the fact that experiments were performed in female rats, whereas the chronic WA stress hyperalgesia model has only been validated in male rats. However, the fact that acute sensitization to repeated noxious distension in different rat strains and in humans develops both in males and females and that the molecular mechanisms underlying spinal sensitization are similar in both sexes makes it unlikely that our findings are confounded by sex-related differences in AVP/V₃ signaling.

Possible sites of the antihyperalgesic effects of SSR149415. From the present studies, the exact site(s) of action of AVP to modulate visceral pain responses cannot be inferred. Neuronal actions of AVP-modulating emotional processes associated with stress-related states are likely to be mediated through V₃ receptors located in hypothalamic and extrahypothalamic sites, including the amygdala (25, 52). These brain areas are acti-

Fig. 6. Effect of a single dose of SSR149415 before CRD on day 11 on chronic WAS-induced visceral hypersensitivity. A: a single dose of SSR149415 (1 mg/kg) blocked repetitive WAS-induced visceral hypersensitivity, leading to similar VMR to CRD as that obtained in baseline. B: change in EMG activity at day 11 after subtraction of the mean EMG activity as determined during baseline after a single treatment with SSR149415 or vehicle. Data are means ± SE of 7 animals per group.

Fig. 7. Effects of intravenous SSR149415 (10 mg/kg) on the viscerosomatic responses to repetitive noxious CRD (80 mmHg) in rats. A: viscerosomatic responses to CRD determined by colonic manometry assessing changes in the intracolonic balloon pressure (BalP). The graphs with open symbols and dashed lines represent the basal intracolonic balloon pressure between distensions. The arrow indicates the time of vehicle or SSR149415 administration (between distensions 3 and 4). Data are means ± SE of 6 animals per group. B: individual responses to SSR149415. Data represent the cumulative response for distensions 4 to 12 (area under the curve, AUC) for each individual animal after treatment with vehicle or SSR149415. The symbols with error bars represent the means ± SE for each treatment group.
vated during WAS and noxious visceral stimuli in rats (29, 37)
as demonstrated with the use of Fos expression as a marker or
neuronal activation, indicating that they are components of the
brain circuitry involved in stress-related pain modulation. Since
SSR149415 is a brain-penetrant compound, it is likely that the
effects observed in the present study are related to the
inhibition of stress- and/or CRD-activated neural circuits
within the central nervous system. The mechanisms and brain
circuits underlying stress-induced visceral hyperalgesia in the
rodent model used in the present study are incompletely un-
derstood. Upregulation of central CRF/CRF1 receptor (22), as
well as spinal neurokinin/neurokinin-1 receptor signaling (7),
has been demonstrated during stress, and recently a possible
role for glucocorticoid receptor-mediated upregulation of spi-
nal glia and visceral pain has been reported (9). Future studies
will need to address the relative importance of V3 receptor
antagonism of hypothalamic and extrahypothalamic AVP sig-
naling in the development and expression of chronic visceral
hyperalgesia.

Although V3 receptors are also expressed in the gastrointes-
tinal tract (38), AVP is released by CRD (21), and peripherally
administered AVP or AVP analogs exert significant effects on
colic secretomotor functions in animals and humans (44, 45,
46), a peripheral effect of SSR149415 on visceral afferent
pathways explaining the observed pattern of hyperalgesia is
unlikely. Similarly, even if the antagonist had exerted a mod-
ulatory effect on colonic tone (which was not evaluated in the
present study), the employed barostat technique would have
compensated for such a peripheral effect.

Possible translational implications of findings. The profile of
the V3 receptor antagonism on visceral nociceptive re-
sponses in a chronic rodent model of visceral hypersensitivity
with high-face and construct validity for IBS suggests that
AVP/V3 receptor signaling mechanisms in the central nervous
system may be a potential target for the symptomatic treatment
of chronic stress-related gastrointestinal disorders such as IBS.
In particular, the AVP/V3 pathway might represent an attrac-
tive alternative to the CRF/CRF1 mechanisms, largely explored for
the treatment of stress-related and anxiety/depression dis-
orders, but, so far, with limited clinical applications (see Ref.
28 for review of the topic). In addition, similar to the situation
with CRF1 antagonists, it remains to be determined whether
simultaneous antagonism of the HPA axis may limit the ther-
aputic window for such compounds.

GRANTS

This work was supported by AstraZeneca R&D (Mölnrad, Sweden).

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