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Forum Minireview

New Topics in Vasopressin Receptors and Approach to Novel Drugs: Involvement of Vasopressin V1a and V1b Receptors in Nociceptive Responses and Morphine-Induced Effects

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Abstract. Arginine vasopressin (AVP) receptors have been classified into V1a, V1b, and V2 subtypes. Recent studies have demonstrated the involvement of AVP in anti-nociception and in morphine-induced anti-nociception. However, the roles of individual AVP-receptor subtypes have not been fully elucidated. Here, we have summarized the role of V1-receptor subtypes in behavioral responses to noxious stimuli and to morphine. In this review, we focus on studies using mice lacking the V1a receptor ($V1a^{-/-}$ mice) and the V1b receptor ($V1b^{-/-}$ mice).

Keywords: arginine vasopressin, V1a receptor, V1b receptor, nociceptive response, morphine-induced response

Introduction

The neurohypophysial peptide arginine vasopressin (AVP) is known as an antidiuretic hormone derived from the posterior pituitary. AVP is widely distributed in the brain (1) and AVP has roles not only in the peripheral system, but also in the central nervous system, such as in learning and memory (2), social recognition (3), and anxiety-like behavior (3, 4). Several studies have also shown that AVP causes anti-nociception in both humans and animals (5 – 9). Moreover, it has been reported that the vasopressinergic pathway may contribute to several effects of morphine, such as the development of tolerance to its anti-nociceptive effects (10, 11). Both intracerebroventricular (i.c.v.) (12) and intravenous (13) injections of morphine have been shown to increase plasma AVP levels, leading us to hypothesize that AVP may mediate the responses to morphine.

The vasopressin receptors have been classified into three subtypes: V1a, V1b, and V2. V1a and V1b are mainly localized in the central nervous system, while the V2 receptor is predominantly expressed in the kidney and mediates the antidiuretic action of AVP. In the brain, the actions of AVP are mainly mediated by V1a receptors (14). However, the roles of AVP in the response to noxious stimuli and in the behavioral effects of morphine are not fully understood. In this review, we discuss the possibility of V1a and V1b receptor involvement in the responses to noxious thermal stimuli and typical acute morphine-induced effects (i.e. locomotor activity, body temperature, and anti-nociceptive effect). We used V1a receptor–knockout ($V1a^{-/-}$) mice, V1b-knockout ($V1b^{-/-}$) mice, and wild-type littermates to examine these behavioral responses.

$V1a^{-/-}$ and $V1b^{-/-}$ mice were derived as previously described (15, 16). All tests were performed in male adult mice. Animals were allowed free access to food and tap water and were kept under artificial light for 12 h each day in a room with controlled temperature and humidity. All behavioral tests were performed during the light portion of the circadian cycle. Nociceptive responses were assessed with the tail-flick test and the hot-plate test.

Role of the V1a and V1b receptors in nociceptive responses to noxious thermal stimuli

We examined nociceptive responses to noxious stimuli using the hot-plate and tail-flick methods. The hot-plate and tail-flick tests were performed as described pre-

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Table 1. Sensitivity to noxious thermal stumuli compared with wild mice

	Wild-type	$V1a^{-/-}$	$V1b^{-/-}$
Hot-plate test			
50°C	normal	normal	↓
55°C	normal	normal	↓
Tail-flick test			
Low intensity	normal	↑	↓
Hight intensity	normal	normal	↓

Male mice weighing 20 – 35 g were used. The $V1a^{-/-}$ and $V1b^{-/-}$ mice used were from F_3, F_4, and F_5 backcross generations and carried 129Sv and C57BL/6J genetic backgrounds. We tested nociceptive responses to noxious stimuli using the hot-plate and tail-flick methods (17). In the hot-plate test, the mice were placed on a commercial hot-plate at 50°C and 55°C surrounded by a clear plastic chamber. The latencies to lick one of the hind paws, flinching of the hind paws, or to jump off the plate were measured. ↑, Significant increase; ↓, Significant decrease.

viously (17). $V1a^{-/-}$ mice and wild-type mice showed the same nociceptive response in the hot-plate test. In the tail-flick test, however, with low intensity thermal stimulation, $V1a^{-/-}$ mice were hypersensitive compared with wild-type mice. When high intensity thermal stimulation was used, there were no differences between $V1a^{-/-}$ mice and wild-type mice (Table 1, manuscript in preparation). This result indicated a decrease in the threshold to thermal stimulation in $V1a^{-/-}$ mice. In contrast, $V1b^{-/-}$ mice were hyposensitive compared with $V1a^{-/-}$ mice and wild-type mice in the both the hot-plate and the tail-flick tests (Table 1, manuscript in preparation).

It is generally accepted that the hot-plate response involves supraspinal levels, whereas the tail-flick response mainly occurs at the level of the spinal cord (18). Furthermore, the descending pain control system in the supraspinal periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) also regulates nociceptive responses at the level of the spinal cord (19). AVP nerve fibers from the hypothalamic paraventricular and supraoptic nuclei project to other brain nuclei and spinal cord regions, including the PAG, the raphes magnus (RA), the raphes dorsalis nucleus, and dorsal horn of the spinal cord (20 – 22), which are all involved in anti-nociception. Many studies have suggested that intra-ventricular injection (i.c.v.) of AVP produced anti-nociception, and AVP antagonists weakened anti-nociception (23 – 25). Watkins et al. (26) and Thurston et al. (27, 28) also observed that intrathecal administration (i.t.) of AVP caused anti-nociception in rats. These findings suggest that AVP-induced anti-nociception occurs not only in the brain, but also in the spinal cord. Recent reports have shown that V2 rather than V1 in the PAG and RA were involved in AVP-induced anti-nociception (29, 30). AVP nerve fibers from hypothalamic paraventricular and supraoptic nuclei were also found to project to the spinal cord (22, 31). Lui et al. (32) reported that V1a binding sites were present in all laminae of the central gray in the spinal cord and that they seemed to facilitate glycinergic and GABAergic inhibitory transmission. It was reported that all these effects were mediated by V1a, but not by V1b, receptors.

In our study, no significant differences were observed among wild-type mice, $V1a^{-/-}$ mice, and $V1b^{-/-}$ mice in assays of motor function using open-field testing, the traction-meter test for muscle tone, and the rota-rod test for motor coordination. Thus, one possibility is that the V1a receptor may be play an inhibitory role on reflex circuits to input from sensory stimuli.

On the other hand, $V1b^{-/-}$ mice showed hypo-nociceptive responses in both the hot-plate and tail-flick tests. V1b receptors are located primarily in the pituitary and in several other discrete areas of the brain including the amygdala (33 – 35). In addition, AVP and corticotropin-releasing factor (CRF) are secreted into the portal circulation to synergistically stimulate pituitary adrenocorticotropic hormone (ACTH) secretion (36). Indeed, V1b receptors are present at a high density in the pituitary gland (14, 34).

Several studies have suggested that ACTH may play a physiological role similar to that of endogenous opioid antagonists (37 – 39). Indeed, the intravenous injection (i.v.) of ACTH produces hyperalgesia (38). Moreover, β-endorphin-induced analgesic effects were potentiated in hypophysectomized rats (39). Furthermore, systematic administration of the opioid receptor antagonist naloxone enhanced the nociceptive responses to the tail-flick (40) and hot plate tests (41 – 43). These findings suggest that endogenous opioids, such as β-endorphin, act to inhibit the response to noxious thermal stimuli. Taken together, pituitary ACTH may antagonize the action of endogenous opioids in response to noxious thermal stimuli. Tanoue et al. (15) have demonstrated that the basal plasma level of ACTH was decreased and that the ACTH response to stress stimulation in a forced swimming test was impaired in $V1b^{-/-}$ mice. These findings indicate that the V1b receptor plays a crucial role in the hypothalamo–pituitary–adrenal (HPA) axis activity under stress as well as under basal conditions, by regulating ACTH release (14). Therefore, $V1b^{-/-}$ mice with ACTH hypofunction may have hypo-nociceptive responses to noxious thermal stimuli in the tail-lick and hot-plate tests because they showed a decrease in the levels of the endogenous opioid antagonist ACTH.

Therefore, our data obtained in the hot-plate and tail flick tests suggest that V1b may facilitate noxious heat-

induced nociceptive responses at the supraspinal level via pituitary ACTH, while the V1a receptor may play an inhibitory role in noxious heat-induced nociceptive responses at the spinal level.

Role of V1 receptors in morphine-induced anti-nociception

Morphine-induced anti-nociception was assessed with the tail-flick test. The tail-flick test was performed as described previously (44). Wild-type, $V1a^{-/-}$, and $V1b^{-/-}$ mice showed significant analgesic responses to morphine. The dose–response curves of the morphine-induced analgesic responses were examined 30 min after the subcutaneous administration of morphine (0.5 – 10 mg /kg). The curve of $V1b^{-/-}$ mice was significantly shifted to the right compared to that for wild-type and $V1a^{-/-}$ mice (manuscript in preparation). These results indicate that $V1b^{-/-}$ mice have markedly enhanced sensitivity to morphine compared with wild-type and $V1a^{-/-}$ mice (Table 2). In contrast, no difference in the sensitivity to morphine was observed between wild-type and $V1a^{-/-}$ mice (Table 2).

The analgesic effects of opioids are thought to be due to inhibition of primary and secondary nociceptive afferent neurons, by presynaptic inhibition of excitatory neurotransmitter release in the dorsal horn of the spinal cord, and by activation of descending inhibitory systems. In addition, the activation of supraspinal opioid receptors in the central gray matter, the nucleus raphe magnus, and the locus coeruleus results in increased activity of descending inhibitory serotonergic and noradrenergic pathways that inhibit the processing of nociceptive information in the dorsal horn of the spinal cord (45).

However, V1b receptors have not been detected in the sites related to morphine-induced analgesia in the brain. Both i.c.v. (12) and i.v. (13) injections of morphine increase plasma AVP levels. Morphine is well known to cause an increase in plasma levels of ACTH leading to stimulation of the HPA axis (e.g., ref. 46). Interestingly, Brattleboro rats, in which the ability to synthesize AVP is impaired, exhibit a decrease in plasma ACTH levels induced by morphine (47). These results suggest that AVP, at least in part, is involved in the increase in plasma ACTH induced by morphine. As described above, AVP causes ACTH release through V1b receptors, and $V1b^{-/-}$ mice show ACTH hypofunction. Several papers have demonstrated that morphine administration in hypophysectomized rats reinforces the analgesic effect (48 – 50). In addition, the systemic administration of ACTH and its fragments inhibited morphine-induced analgesia (38, 51). The analgesic effect of β-endorphin, like morphine, following microinjection in the PAG was potentiated in hypophysectomized rats (39). The PAG has been reported to mediate the analgesic effects of morphine (52). In addition, ACTH acts as a partial agonist to opiate receptors (37). Thus, this region may be a possible neuroanatomical substrate for the observed interaction between ACTH and morphine. These reports support the same idea described in the section of "Role of the V1a and V1b receptors in nociceptive responses to noxious thermal stimuli" that ACTH may have a role as an endogenous opioid antagonist in morphine-induced analgesia.

Taken together, our data suggest that a morphine induced decrease in ACTH levels in $V1b^{-/-}$ mice may cause an increase of analgesic sensitivity to morphine in $V1b^{-/-}$ mice. Therefore, the results also suggest that V1b receptors may play an inhibitory role in the acute morphine-induced analgesic response via pituitary ACTH. However, further studies are required to demonstrate the exact mechanisms.

Table 2. Summary for morphine-induced behavior responses compared with wild mice

	Wild-type	$V1a^{-/-}$	$V1b^{-/-}$
Hyperlocomotion	normal	normal	↓
Analgesic effect	normal	normal	↑
Hypothermia	normal	normal	↑

Morphine-induced anti-nociception was assessed with the tail-flick method (44). To determine whether vasopressin plays a role in morphine-induced hyperlocomotor activity, we examined the acute effect of morphine administration on locomotor activity. Locomotor activity (ambulation) was measured in the open-field test (14). Immediately after morphine administration, locomotor activity was observed for 120 min. The effects of morphine on body temperature were evaluated by rectal temperature measurement. Rectal temperature was measured with a thermistor probe (Toshiba Electronics Co., Tokyo) inserted into the rectum. The temperatures were measured immediately after morphine administration and were observed for 120 min. ↑, Significant increase; ↓, Significant decrease.

Involvement of V1 receptors in morphine-induced locomotor activity

We determined whether vasopressin plays a role in morphine-induced hyperlocomotor activity. Both wild-type and $V1a^{-/-}$ mice showed a significant progressive increase in locomotor activity (hyperlocomotion) after the subcutaneous administration of morphine (10 mg /kg). The morphine-induced locomotor activity was similar between wild-type and $V1a^{-/-}$ mice. However, $V1b^{-/-}$ mice did not show a significant increase in locomotor activity due to morphine (Table 2, manuscript in preparation). On the other hand, spontaneous locomotor activity did not differ among the three genotypes.

The hyperlocomotor effect of acute and repeated

morphine treatments are thought to be mediated by activation of the mesolimbic dopamine system (53, 54). Microinjections of morphine into the ventral tegmental area induce hyperlocomotion (53). Morphine in the ventral tegmental area disinhibits the firing of dopaminergic neurons in this region by inhibiting GABAergic interneurons, leading to an increase of dopamine release in the nucleus accumbens (NAcc) resulting in locomotor-stimulating effects.

Vasopressin and the V1b receptor are present in both the ventral tegmental area and the NAcc (35, 55). The the reduction of morphine-induced hyperlocomotion in $V1b^{-/-}$ mice may be due to a decrease in the levels dopamine released into the NAcc. These findings suggest that V1b receptors in the limbic system may be involved in the control of morphine-induced locomotion activity.

Involvement of V1 receptors in morphine-induced hypothermia

The effects of morphine and of other narcotic analgesics on body temperature, which act primarily on the μ-opioid receptor, are biphasic in rats and mice, with low doses producing hyperthermia and higher doses resulting in hypothermia at thermoneutral ambient temperatures (56, 57). However, it is unclear whether vasopressin and it receptors are involved in morphine-induced hypothermia. Therefore, the effects of morphine on body temperature, by evaluating rectal temperature, was examined in $V1a^{-/-}$ and $V1b^{-/-}$ mice.

Morphine administrated subcutaneously (10 mg/kg) significantly and markedly decreased the rectal temperature in wild-type, $V1a^{-/-}$, and $V1b^{-/-}$ mice, but the morphine-induced hypothermia in $V1b^{-/-}$ mice was enhanced compared with those in wild-type and $V1a^{-/-}$ mice (Table 2, manuscript in preparation). The basal rectal temperature did not differ between the three genotypes. It has been demonstrated that morphine caused hypothermia through a dopaminergic mechanism(s) (58). However, $V1b^{-/-}$ mice seem to have inhibited morphine-induced dopaminergic neurotransmission in the mesolimbic system since morphine-induced locomotion activity was reduced in $V1b^{-/-}$ mice. ACTH has also been implicated in the thermoregulatory effect of morphine (58, 59). In fact, systemically and centrally administered ACTH-like peptides inhibit morphine-induced hypothermia (60). Thus, decreased ACTH levels in $V1b^{-/-}$ mice may cause an increase in the morphine-induced hypothermia. These findings suggest the possibility that V1b receptors are involved in the control of morphine-induced hypothermia and that ACTH is involved in the mechanism.

Conclusions

This mini-review described the following: 1) Supraspinal V1b receptors contribute to an increase in the perception for noxious thermal stimuli, whereas spinal V1a receptors may contribute to a decrease in the perception of noxious thermal stimuli; 2) V1b receptors are involved in inhibiting the morphine-induced analgesic response; 3) V1b receptors are likely to be involved in the neural network of the mesolimbic dopamine system, which plays a crucial role in the control of morphine-induced hyperlocomotion; and 4) V1b receptors play a role in the regulation of the hypothermic effect of morphine.

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