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Research article

Arginine vasopressin antagonizes the effects of prostaglandin E_2 on the spontaneous activity of warm-sensitive and temperature-insensitive neurons in the medial preoptic area in rats



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ABSTRACT

Arginine vasopressin (AVP) plays an important role in thermoregulation and antipyresis. We have demonstrated that AVP could change the spontaneous activity of thermosensitive and temperature insensitive neurons in the preoptic area. However, whether AVP influences the effects of prostaglandin E_2 (PGE₂) on the spontaneous activity of neurons in the medial preoptic area (MPO) remains unclear. Our experiment showed that PGE₂ decreased the spontaneous activity of warm-sensitive neurons, and increased that of low-slope temperature-insensitive neurons in the MPO. AVP attenuated the inhibitory effect of PGE₂ on warm-sensitive neurons, and reversed the excitatory effect of PGE₂ on low-slope temperature-insensitive neurons, demonstrating that AVP antagonized the effects of PGE₂ on the spontaneous activity of these neurons. The effect of AVP was suppressed by an AVP V_{1a} receptor antagonist, suggesting that V_{1a} receptor mediated the action of AVP. We also demonstrated that AVP attenuated the PGE₂-induced decrease in the prepotential's rate of rise in warm-sensitive neurons and the PGE₂-induced that AVP antagonized the PGE₂-induced change in the spontaneous activity of warm-sensitive neurons through the V_{1a} receptor. Together, these data indicated that AVP antagonized the PGE₂-induced change in the spontaneous activity of warm-sensitive neurons through the V_{1a} receptor. Together, these data indicated that AVP antagonized the PGE₂-induced change in the spontaneous activity of warm-sensitive neurons in the prepotential of these neurons in the MPO partly by reducing the PGE₂-induced change in the spontaneous activity of warm-sensitive neurons through the V_{1a} receptor.

1. Introduction

Various studies have found that arginine vasopressin (AVP) plays an important role in thermoregulation and antipyresis [1,2]. It is released peripherally as a hormone and within the brain as a neurotransmitter or neuromodulator. Both the central and peripheral administration of AVP could reduce febrile responses to bacterial lipopolysaccharide [1,3].

The medial preoptic area (MPO) is an important subregion in the preoptic area. In this area, neurons are mainly classified as warm-sensitive neurons (WSNs, 20–30%) and temperature-insensitive neurons (> 70%) according to their responses to changes in the local temperature [4]. On the other hand, the number of cold-sensitive neurons, located more caudally in the posterior hypothalamus, is lower in the MPO [5]. A number of studies have reported that these different neurons are involved in thermoregulation and production of fever [4,6]. Our previous studies indicated that AVP could excite WSNs and inhibit temperature-insensitive neurons in the preoptic area, thus providing a possible mechanism for the reduction effect of AVP on body

temperature [7,8]. Nevertheless, the precise mechanism underlying the antipyretic effect of AVP remains unclear. Prostaglandin E_2 (PGE₂) is a critical pyrogenic mediator during fever [6]. In vivo experiments have shown that the MPO is a locus where PGE₂ act to produce fever [9,10]. In addition, an electrophysiological study of brain slice indicated that PGE₂ inhibited WSNs and excited temperature-insensitive neurons in the ventromedial preoptic area [5].

Based on the above data, we hypothesized that AVP may influence the effects of PGE_2 on the spontaneous activity of WSNs and temperature-insensitive neurons in the MPO. To test this hypothesis, we investigated the effects of AVP on the PGE_2 -induced change in the spontaneous firing rate of MPO neurons by using whole-cell patchclamp method. Furthermore, we assessed the effects of AVP on the PGE_2 -induced change in the depolarizing potential (or pacemaker potential) of MPO neurons.

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Fig. 1. Effects of different drugs on the firing rate of warm-sensitive neurons (A) and low-slope temperature-insensitive neurons (B). Neuron's firing rate during perfusion with different drugs was plotted as a function of its firing rates before perfusion. The distance from the dash line indicates the degree of change. Data points that lie above or below this dashed line indicate neurons whose firing rate increased or decreased, respectively. Each drug was applied at the concentration of 1 μ M. V_{1a} ant, Vasopressin V_{1a} receptor antagonist.

2. Experimental procedures

2.1. Preparation of brain slices

Based on previous studies [8,11], horizontal hypothalamic slices were prepared from male Sprague-Dawley rats (150–200 g). Each rat was anesthetized with pentobarbital and sacrificed in line with procedures approved by the NIH and the Chengdu Medical College Laboratory Animal Care and Use Committee. After removing the brain, the tissue block containing the MPO was cut into 300 μ m sections. Two or three slices were then placed in a chamber that was aerated with 95% O₂ and 5%CO₂ for 1.5–2 h. Subsequently, tissue slices were transferred to a recording chamber, and were continuously perfused with artificial cerebrospinal fluid (aCSF) consisting of (in mM) 124 NaCl, 26 NaHCO₃, 5 KCl, 2.4 CaCl₂, 1.3 MgSO₄, 1.24 KH2PO₄, and 10 glucose (pH 7.2–7.4).

2.2. Electrophysiological recordings and experimental protocols

The spontaneous activity of MPO neurons was recorded in the current clamp mode with $1-2 \,\mu$ m tip glass borosilicate microelectrodes (5–7M Ω), which were filled with an internal solution consisting of (in mM) 130 potassium gluconate, 10 EGTA, 10 HEPES, 2 Mg–ATP, 2 Na₂GTP, and 1 CaCl₂ (295 mOsm/kgH₂O, pH = 7.2–7.4). Recordings were carried out using an EPC-10 patch clamp amplifier (HEKA Electronik, Lambrecht, Germany). No holding current was applied to the neurons when recording spontaneous activity. The program package Patch Master was used for data acquisition and analysis.

Most neurons were assessed at temperatures ranging from 32 °C to 40 °C. Neuronal thermosensitivity (imp./s⁻¹ °C⁻¹) was characterized by the plotting firing rate as a function of tissue temperature to determine the linear regression coefficient (thermal coefficient) or the slope (m) of the plot. According to previous studies [5,8,12], neurons can be classified as warm-sensitive with thermal coefficient at least

0.8 imp./s⁻¹ °C⁻¹ or cold-sensitive with thermal coefficient 0.6 imp./s⁻¹ °C⁻¹ or less. All other neurons were classified into two subtypes: moderate-slope temperature-insensitive neurons (M-TINs), whose thermal coefficient was < 0.8 imp./s⁻¹ °C⁻¹ but > 0.4 imp./s⁻¹ °C⁻¹, or low-slope temperature-insensitive neurons (L-TINs), whose thermal coefficient was ≤ 0.4 imp./s⁻¹ °C⁻¹. After the neuronal thermosensitivity were determined, the perfusate was switched to an experimental aCSF containing PGE₂ (Sigma Chemical Co., St. Louis, MO, USA), PGE₂ + AVP (Sigma Chemical Co., St. Louis, MO, USA), or a mixture of PGE₂, AVP, and an AVP V_{1a} receptor antagonist (Sigma Chemical Co., St. Louis, MO, USA). Subsequently, the experimental aCSF was switched back to the control aCSF to remove the effects of the drugs. Based on previous studies [8,13], each drug was applied at a concentration of 1 μ M.

2.3. Data analysis

All results are expressed as the means \pm SE. Mean firing rates (impulse/s) were determined over a 2 min period at 36–37 °C. The response of the firing rate of neurons must at least partly return to that under control conditions after washout. The prepotential's rate of rise was calculated from the slope of the membrane potential at 4–20 ms periods immediately preceding the action potential [14]. Statistical analysis was performed with Student's *t*-tests or one-way ANOVA. Differences in mean values were considered significant at p < 0.05. All statistical analysis was performed by IBM SPSS Statistics 19 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Effects of AVP on the PGE_2 -induced change in the spontaneous activity of WSNs and temperature-insensitive neurons

We recorded 81 neurons in the MPO. These neurons included 25

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Fig. 2. AVP attenuated the PGE₂-induced decrease in the spontaneous firing rate of warm-sensitive neurons via V1a receptor. (A) Top: experimental records of spontaneous firing rate and tissue temperature in a warm-sensitive neuron during different drugs. Each drug was applied at the concentration of 1 uM. (A) Bottom: spontaneous firings at different times indicated (1-4) at Top. (B) PGE2 decreased the mean firing rate of warm-sensitive neurons (p < 0.01). (C) Bars represent mean change in the firing rate of warm-sensitive neurons during different drugs. The percent change of firing rate = (firing rate during application of drugs-baseline firing rate)/baseline firing rate. All values are reported as mean ± SE. FR. firing rate. Temp, temperature; V1a ant, Vasopressin V_{1a} receptor antagonist. **p < 0.01; *p < 0.05.

WSNs, 15 M-TINs, and 38 L-TINs. During perfusion of drugs, 9 WSNs, 5 M-TINs, and 17 L-TINs lost their activity, so we did not use these neurons for analysis. The mean baseline firing rate of WSNs, M-TINs, and L-TINs were 7.3 ± 0.9 impulse/s, 6.1 ± 1.1 impulse/s, and 5.5 ± 0.5 impulse/s, respectively. The effects of different drugs on the spontaneous firing rate of WSNs and L-TINs were shown in Fig. 1. The typical responses of firing rates of these neurons to different drugs are shown in Figs. 2 A and 3 A.

The mean change in the spontaneous firing rate of WSNs in the three different treatment groups are shown in Fig. 2B and C. During PGE₂ treatment, the mean firing rate was decreased by 62.6 \pm 11.2% (from 7.3 \pm 0.9 to 2.4 \pm 0.8 impulse/s, n = 16, p < 0.01). In contrast, the mean firing rate during PGE₂ + AVP treatment was decreased less than that during PGE₂ treatment ($-0.8 \pm 12\%$ vs. $-62.6 \pm 11.2\%$, n = 16, p < 0.01), demonstrating that AVP attenuated the PGE₂-

induced decrease in the firing rate. Additionally, the mean change in firing rate with a mixture of PGE₂, AVP, and the V1a receptor antagonist was similar to that with PGE₂ ($-60.6 \pm 12.1\%$ vs. $-62.6 \pm 11.2\%$, n = 16, p > 0.05), and it was larger than that with AVP + PGE₂ ($-60.6 \pm 12.1\%$ vs. $-0.8 \pm 12\%$, n = 16, p < 0.01), indicating that the V_{1a} receptor antagonist suppressed the reduction effect of AVP on the PGE₂-induced decrease in firing rate. Taken together, these results suggest that AVP attenuated the inhibitory effect of PGE₂ on the spontaneous activity of WSNs through the V_{1a} receptor.

The mean changes in the spontaneous firing rate of L-TINs in three distinct treatment groups are shown in Fig. 3B and C. During PGE₂ treatment, the mean firing rate was increased by 57.9 \pm 17.5% (from 5.5 \pm 0.5 to 7.5 \pm 0.8 impulse/s, n = 21, p < 0.05). The mean change in firing rate during PGE₂ + AVP treatment was inverted compared with that during PGE₂ treatment (-9.8 \pm 9.2% vs.

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Fig. 3. AVP reversed the PGE2-induced increase in the spontaneous firing rate of low-slope temperatureinsensitive neurons via V1a receptor. (A) Top: experimental records of spontaneous firing rate and tissue temperature in a low-slope temperature-insensitive neuron during different drugs. Each drug was applied at the concentration of 1 µM. (A) Bottom: spontaneous firings at different times indicated (1-4) at Top. (B) PGE2 increased the mean firing rate of low-slope temperature-insensitive neurons (p < 0.05). (C) Bars represent mean change in the firing rate of low-slope temperature-insensitive neurons during different drugs. The percent change of firing rate = (firing rate during perfusion of drugs-baseline firing rate)/baseline firing rate. All values are reported as mean + SE, FR, firing rate. Temp, temperature; V1a ant, Vasopressin V1a receptor antagonist. **, p < 0.01; *, p < 0.05.

57.9 \pm 17.5%, n = 21, p < 0.05), indicating that AVP reversed the PGE₂-induced increase in firing rate. Furthermore, the mean change in firing rate with a mixture of PGE₂, AVP, and the V_{1a} receptor antagonist was similar to that with PGE₂ (53.4 \pm 18.5% vs. 57.9 \pm 17.5%, n = 21, p > 0.05), and it was different from that with PGE₂ + AVP (53.4 \pm 18.5% vs. -9.8 \pm 9.2%, n = 21, p < 0.01), indicating that the V_{1a} receptor antagonist blocked the reduction effect of AVP on the PGE₂-induced increase in firing rate. Taken together, these results suggest that AVP reversed the enhancement effect of PGE₂ on the spontaneous activity of L-TINs via the V_{1a} receptor.

However, PGE₂ did not significantly change the mean firing rate in the population of M-TINs (from 6.1 \pm 1.1 to 5.8 \pm 1.2 impulse/s, n = 10, $p^{>}$ 0.05). In addition, neither AVP nor the V_{1a} receptor antagonist influenced the action of PGE₂ on M-TINs (PGE₂: $-3.8 \pm 17.3\%$, PGE₂ + AVP: 11.9 \pm 21.0%, PGE₂ + AVP + V_{1a}

receptor antagonist: 3.9 \pm 10.8%, n = 10, p $^{>}$ 0.05).

3.2. Effects of AVP on the PGE₂-induced change in the depolarizing prepotential of WSNs and L-TINs

Most spontaneously firing neurons in the preoptic area displayed depolarizing prepotentials that reach a threshold to produce action potentials. Evidence has indicated that the prepotential is an important factor in determining the spontaneous firing rates of neurons in the preoptic area [14]. To determine whether the prepotential plays a role in the effect of AVP on the PGE₂-induced change in the firing rate of WSNs and L-TINs, we observed the effect of AVP on the PGE₂-induced change in the prepotential's rate of rise of these neurons. The representative responses of the prepotential to different drugs are shown in Fig. 4A and C.

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Fig. 4. AVP reduced the PGE₂-induced change in the depolarizing prepotential of warm-sensitive neurons (A, B) and low-slope temperature-insensitive neurons (C, D) through V_{1a} receptor. (A, C) Left: superimposed action potentials in response to different drugs. (A, C) Right: superimposed signal-averaged prepotentials. Each drug was applied at the concentration of 1 μ M. (B, D): Bars indicate the mean rate of rise of prepotential in warm-sensitive neurons (n = 16) and low-slope temperature-insensitive neurons (n = 21). All values are reported as mean \pm SE. V_{1a} ant, Vasopressin V_{1a} receptor antagonist. **, p < 0.01; *, p < 0.05.

Fig. 4B shows the mean rate of rise of prepotential after the application of different drugs in WSNs. PGE₂ treatment decreased the mean rate of rise of prepotential from $0.44 \pm 0.04 \text{ mV/ms}$ to $0.20 \pm 0.03 \text{ mV ms}^{-1}$ (p < 0.01, n = 16). In contrast, the mean rate of rise of prepotential during $PGE_2 + AVP$ treatment was similar to that during control aCSF treatment $(0.41 \pm 0.05 \text{ mV/ms})$ VS. 0.44 \pm 0.04 mV/ms, $p^{>}$ 0.05, n = 16) and was faster than that during PGE₂ treatment $(0.41 \pm 0.05 \text{ mV/ms} \text{ vs.} 0.20 \pm 0.03 \text{ mV/ms},$ p < 0.01, n = 16), indicating that AVP reduced the PGE₂-induced decrease in the prepotential's rate of rise. In addition, the mean rate of rise of prepotential with a mixture of PGE₂, AVP, and the V_{1a} receptor antagonist was similar to that with PGE₂ (0.25 \pm 0.03 mV/ms vs. $0.20 \pm 0.03 \text{ mV/ms}$, p > 0.05, n = 16) but slower than that with $PGE_2 + AVP$ $(0.25 \pm 0.03 \text{ mV/ms})$ vs. $0.41 \pm 0.05 \, \text{mV/ms}$ p < 0.01, n = 16), indicating that the V_{1a} receptor antagonist suppressed the reduction effect of AVP on the PGE2-induced decrease in the prepotential's rate of rise. Taken together, these results suggest that AVP attenuated the reduction effect of PGE₂ on the prepotential's rate of rise in WSNs via the V_{1a} receptor.

Fig. 4D shows the mean rate of rise of prepotential after the application of different drugs in L-TINs. PGE_2 increased the mean rate of rise of prepotential from 0.26 \pm 0.03 mV/ms to 0.39 \pm 0.04 mV/ms⁻¹ (p < 0.05, n = 21). In contrast, the mean rate of rise of prepotential during PGE₂ + AVP treatment was similar to that during control aCSF treatment (0.23 \pm 0.02 mV/ms vs. 0.26 \pm 0.03 mV/ms, $p^{>}$ 0.05, n = 21) but slower than that during PGE₂ treatment (0.23 \pm 0.02 mV/ms vs. 0.39 \pm 0.04 mV/ms⁻¹, p < 0.05, n = 21), indicating that AVP attenuated the PGE2-induced increase in the prepotential's rate of rise. Furthermore, the prepotential's rate of rise with a mixture of PGE₂, AVP, and the V_{1a} receptor antagonist was similar to that with PGE₂ (0.37 \pm 0.04 mV/ms vs. 0.39 \pm 0.04 mV/ms, p > 0.05, n = 21) and was faster than that with PGE₂ + AVP $(0.37 \pm 0.04 \text{ mV/ms vs.} 0.23 \pm 0.02 \text{ mV/ms, } p^{<} 0.05, n = 21)$, indicating that the V1a receptor antagonist abolished the reduction effect of AVP on the PGE₂-induced increase in the prepotential's rate of rise. Taken together, these results suggest that AVP reduced the enhancement effect of PGE₂ on the prepotential's rate of rise in L-TINs via the V1_a receptor.

4. Discussion

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The main finding of this study was that AVP reduced the inhibitory effect of PGE_2 on WSNs and reversed the excitatory effect of PGE_2 on L-TINs via the V_{1a} receptor in the MPO, thus indicating that AVP antagonized the effect of PGE_2 on the spontaneous activity of these neurons. These effects of AVP appeared to be associated with the V_{1a} receptordependent reduction effect of AVP on the PGE_2 -induced change in the depolarizing prepotential. These results demonstrate a possible mechanism underlying the antipyretic effect of AVP.

Our present study showed that PGE_2 decreased the spontaneous firing rate in WSNs and increased that in L-TINs in the MPO, this result is consistent with that of a previous study [5]. Studies have demonstrated that the microinjection of PGE_2 into the MPO can produce fever [9,10]. In addition, a number of studies have reported that either the inhibition of WSNs or stimulation of temperature-insensitive neurons in the preoptic area could result in an elevated core temperature [4,6,15–17]. These data indicated that PGE_2 could act on the WSNs and L-TINs in the MPO to produce fever. Accordingly, the antagonistic effect of AVP on the PGE_2 -induced change in the spontaneous activity of WSNs and L-TINs may contribute to the antipyretic effect of AVP.

AVP is mainly synthesized in the hypothalamic supraoptic and paraventricular nuclei (PVN). Previous studies indicated that an elevation of body temperature or intraperitoneal injection of LPS could activate the AVP neurons within the PVN to release AVP [18,19]. On the other hand, the preoptic area is marked by a rich innervation of medium-sized AVP-immunoreactive fibers, which are typical of projections deriving from the PVN [20]. These reports suggest that the AVP may be transmitted from the PVN to MPO to antagonize the actions of PGE₂ on the WSNs and L-TINs within the MPO during fever. In line with this theory, activating neurons within the PVN reversed the increases in thermogenesis of brown adipose tissue evoked by microinjection of PGE₂ in the medial preoptic area [21]. Hence, it is possible that the AVP play an important role in the endogenous antipyresis and the formation of an upper limit of fever.

AVP has three receptor subtypes: V_{1a} , V_{1b} , and V_2 . The V_{1a} receptor is abundantly expressed in the MPO [22,23]. Our previous study indicated that it participated in the regulation of the activity of MPO neurons [8]. Thus, in the present study, we hypothesized that AVP may influence the actions of PGE₂ on MPO neurons via the V_{1a} receptor. As expected, we found that the V_{1a} receptor antagonist almost completely blocked the antagonistic effect of AVP on the PGE₂-induced change in the spontaneous firing rate of WSNs and L-TINs, demonstrating that the effect of AVP was mediated via the V_{1a} receptor. In accordance with this finding, previous studies showed that V_{1a} receptor antagonist prevent antipyresis induced by central administration of AVP, suggesting that AVP induce antipyresis via V_{1a} receptor [24,25]. Therefore, it is possible that AVP evokes antipyresis by antagonizing the actions of PGE₂ on the WSNs and L-TINs within MPO after binding to V_{1a} receptor.

Our previous study has indicated that AVP could increase the prepotential's rate of rise in WSNs and decrease that in L-TINs in the preoptic area [8]. In contrast, PGE_2 seems to have an opposite effect on these neurons [13]. Accordingly, we believe that AVP may influence the effect of PGE₂ on the prepotential of WSNs and L-TINs. Consistent with this hypothesis, we demonstrated that AVP attenuated the PGE2-induced decrease in the mean rate of rise of prepotential in WSNs and the PGE₂-induced increase in that in L-TINs. Moreover, we found that the V_{1a} receptor antagonist abolished the reduction effect of AVP on the PGE2-induced change in the prepotential, suggesting that the effect of AVP was mediated by the V1a receptor. Several studies have indicated that an increase in the prepotential's rate of rise could shorten the interspike interval, which in turn would increase the firing rate of neurons in the preoptic area, whereas a decrease would have the opposite effect, thus demonstrating the positive correlation between the prepotential's rate of rise and the neuronal firing rate in the preoptic area [8,13,14,26]. Overall, these data suggest that after V_{1a} receptor binding, AVP antagonized the effect of PGE2 on the spontaneous activity of WSNs and L-TINs partly by attenuating the PGE2-induced change in the prepotential of these neurons.

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