The Mechanism of Noradrenergic α_1 Excitatory Modulation of Pontine Reticular Formation Neurons

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The α_1 adrenergic receptor occurs in all major divisions of the CNS and is thought to play a role in all behaviors influenced by norepinephrine (NE). In the medial pontine reticular formation (mPRF), the proposed site of adrenergic enhancement of startle responses (Davis, 1984), α_1 agonists excite most neurons (Gerber et al., 1990). We here report that α_1 excitation results from a reduction of a voltage- and calcium-dependent potassium current, not previously recognized as ligand-modulated. The calcium sensitivity is suggested by its antagonism with Mg^{2+} , Cd^{2+} , Ba^{2+} , low concentrations of tetraethylammonium, and charybdotoxin. The voltage sensitivity of this conductance falls within the membrane potential range critical to action potential generation. Based on this voltage sensitivity, the change in repetitive firing characteristics may be predicted according to a mathematical model of the mPRF neuronal electrophysiology. The predicted response to a 50% decrease in the phenylephrine (PE)-sensitive conductance is similar to the observed responses, with respect to both the current response under voltage-clamp conditions and alterations of the AHP and frequency/current curve. In contrast, modeling a reduction of a voltage-insensitive leak current predicts none of these changes. Thus, the noradrenergic reduction of this current depolarizes the membrane, increases the likelihood of an initial response to depolarizing input, and increases firing rate during sustained depolarization in a manner consistent with an NE role as an excitatory neuromodulator of the mPRF.

[Key words: phenylephrine, potassium channels, calcium dependence, startle response, neuronal simulation]

Norepinephrine (NE) is recognized as one of the most important neurotransmitters in the CNS. There are noradrenergic projections to almost every CNS region including spinal cord, cerebellum, brainstem, thalamus, striatum, and cerebral cortex (Dahlstrom and Fuxe, 1964). NE appears to play a key role in almost every behavioral system including sleep–waking, feeding, thermoregulation, sensory processing, and motor activity (see Foote et al., 1983; Steriade and McCarley, 1990).

In the pontine reticular formation, adrenergic neurotransmission is thought to enhance reflex activity, to modulate motor

activity, and to be involved in changes in behavioral state. This region contains neurons involved in the execution of head and neck movements, limb movements, and eye movements (Steriade and McCarley, 1990). Reticulospinal mPRF neurons are necessary for the execution of the acoustic startle response, which is enhanced by noradrenergic agonists (excluding the α_2 agonist clonidine) and inhibited by phentolamine, a nonspecific α -antagonist (Davis, 1984). These actions are consistent with α_1 excitatory modulation of mPRF neurons. However, the direct effects of NE on neurons of the mPRF have not been fully characterized.

Gerber et al. (1990) found that NE depolarized the majority of mPRF neurons, but did not determine the mechanism of this action, or the effects upon repetitive firing. A noradrenergic depolarization has been described in the hippocampus and, acting via β receptors with cAMP as a second messenger, reduced the long-duration AHP and the associated adaptation of firing frequency (Madison and Nicoll, 1986). Similar action of β agonists have been reported in thalamus (McCormick and Prince, 1988) and cortex (Foecking et al., 1989). A β receptor also mediates a depolarizing response due to an increase in hyperpolarization-activated current in the thalamus (Pape and McCormick, 1989). Depolarizing responses to NE associated with a decrease in potassium conductance have been described in the thalamus (McCormick and Prince, 1988) and brainstem (Fukuda et al., 1987) where they are mediated by α_1 receptors. In addition, α_2 receptor-mediated inhibitory responses have been reported in the spinal cord (North and Yoshimura, 1984) and the brainstem (Williams et al., 1985; Williams and Reiner, 1993).

Materials and Methods

Long-Evans hooded rats 9–15 d old were anesthetized and brain slices prepared as previously described (Stevens et al., 1992). Slices were superfused (medium in mM: NaCl, 124; KCl, 3.75; KH_2PO_4 , 1.25; $MgCl_2$, 1.3; $CaCl_2$, 2.5; $NaHCO_3$, 26.0; glucose, 10; bubbled with 95% O_2 , 5% CO_2 to maintain oxygenation and pH) and kept at $30 \pm 2^\circ C$. NE, phenylephrine (PE), isoproterenol, 8-bromoadenosine cyclic AMP, and tetrodotoxin (TTX) (Sigma, St. Louis) were applied in known concentrations as part of the superfusate. Intracellular recordings were obtained using microelectrodes with 2 M KCl or 2 M methylsulfate (resistance, 60–120 M Ω). Voltage and current recordings were made either in the bridge mode or in the single electrode voltage-clamp mode using an Axoclamp 2A amplifier.

Simulations of mPRF neurons were made employing a computer program developed by Huguenard and McCormick (1993) to model the electrophysiology of thalamic relay neurons. In the application of this model to mPRF neurons, the following currents were used: I_{Na} , I_{Ca} (high threshold), I_K , I_C , I_{leak} , and I_{CL} (the calcium- and ligand-sensitive current examined in the present study). The relative amplitude of the conductance for I_K was 5% of that for Na. For I_{CL} and I_C the conductances were 10% and 1.8%, respectively, of that for I_K . The selection of the

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Figure 1. The α_1 agonist phenylephrine (PE) increases excitability of mPRF neurons. *A*, PE evokes a depolarization and increases spontaneous activity (arrow indicates AHP associated with a single AP). Increased firing is reduced by repolarization of the membrane potential (asterisk indicates DC current injection). *B*, The firing rate during depolarizing current steps was increased in the presence of PE. *C*, Single APs in control and PE treatment are superimposed to demonstrate the similarity of AP amplitude and time course. *D*, Return to threshold following the AP occurred more quickly during PE treatment (arrow), resulting in a shortened interspike interval (DC current was applied to return the membrane potential to the original resting potential prior to the current step).

relative magnitudes of these currents was based on our observations under both current clamp (Greene et al., 1986; Gerber et al., 1989) and voltage-clamp (unpublished observations) conditions. The magnitude of I_K was estimated from the current remaining in the presence of Ca antagonists with depolarizations from -60 to -50 mV. I_C was distinguished from I_{CL} by its more rapid onset that resulted in restriction of action potential duration; however, in mPRF neurons this effect was small. The inactivating currents I_A and I_T were not considered as the membrane potentials examined in this study were in the range of maximum inactivation of these currents. The parameters used for the voltage sensitivity of I_{CL} were $V_{1/2} = -30$ mV and k (slope factor) = 12. I_{leak} was a mixture of Na and K conductance that gave a resting membrane potential of -62 mV with control I_{CL} present and an input resistance of 100 M Ω .

Results

Norepinephrine (NE) and/or the α_1 agonist phenylephrine (PE) depolarized 83% of medial pontine reticular formation (mPRF) neurons tested. Application of PE ($n = 10$, 5 μ M) resulted in depolarization and an increase in action potential frequency (Fig. 1*A*). There was no change in action potential shape (Fig. 1*C*); however, there was a decrease in the duration of the afterhyperpolarization (AHP; 50 – 80 msec duration) in the presence of PE (Fig. 1*D*; measured as a decrease in the third ISI in Fig. 5). The action of PE was not mimicked by the β agonist isoproterenol ($n = 4$) or by 8-bromo-cAMP ($n = 3$). Bath application of prazosin, an α_1 antagonist, on neurons depolarized by NE ($n = 4$) had no effect by itself, but prevented both the depolarization and the decreased AHP response to NE (Fig. 2).

Under voltage-clamp control, PE treatment resulted in an inward current (118 of 137 neurons tested; Fig. 3*A*). I – V relationships (from ramp protocols of 2.5 mV/sec from -100 to -40 mV, $n = 25$), recorded before and during treatment with PE show a decrease in the current required to complete ramp voltage commands in the latter condition (Fig. 3*B*). Tetrodotoxin (TTX; 0.3 μ M) was present throughout the experiments. Subtraction of the I – V relation recorded under control conditions from that during PE exposure yielded the PE-induced steady-state current. This was voltage dependent, with increasing negative slope conductance observable from -70 to -40 mV (Fig. 3*C*).

Depolarizing steps from -52 mV to -42 activated an outward current that did not inactivate (Fig. 3*D*). On return to the holding

Figure 2. The excitatory effects of NE are blocked in the presence of the α_1 receptor antagonist prazosin. *A*, Repetitive firing was evoked in a previously quiescent neuron with a depolarizing current step of 250 msec duration and 0.3 nA amplitude. *B*, Application of NE resulted in a depolarization of 7 mV, spontaneous firing, and increased firing rate (decreased AHP) in response to identical current injection. *C* and *D*, In the presence of prazosin, NE had no effect on the membrane potential, spontaneous firing, or response to depolarizing current.

potential, an outward tail current was observed (asterisk) that was due to the relaxation of the noninactivating currents elicited by the depolarizing step command. Treatment with PE resulted in a reduction of both the depolarization-evoked instantaneous (the result of a decrease in steady state conductance at the holding potential) and time-dependent outward currents as well as the tail current (Fig. 3*D*).

This reduction might have resulted from either fewer channels available to open, a decreased single-channel conductance, or, alternatively, from a more rapid closing, once the usual number of channels opened. Since the latter would result in a faster decay rate, this was examined by fitting the time course of the tail current decay by a single exponential ($\tau = 47 \pm 5$ msec, $n = 9$). PE treatments that reduced the tail current amplitude by greater than 50% did not change the time course ($n = 3$; Fig. 3*E*), most consistent with one of the former possibilities.

A reversal potential (-98 ± 4 mV; 5 mM $[K^+]_o$) of the PE current was demonstrated in only 5 of 53 neurons tested. In the remainder, I – V relationships did not intersect. When extracellular potassium was raised to 10 mM the polarity of the PE-induced current reversed at -67 ± 4 mV ($n = 3$; Fig. 4) consistent with a potassium dependence of this response. In 2.5 mM $[K^+]_o$ the reversal potential was estimated by extrapolation to be -123 mV.

A number of pharmacological manipulations reduce Ca^{2+} -dependent g_K values in neurons, including the addition to the perfusate of either tetraethylammonium (TEA; Brown and Griffith, 1983; Lancaster et al., 1991), charybdotoxin (Miller et al., 1985; Hermann and Exrleben, 1987; Lancaster and Nicoll, 1987), calcium antagonists, or Ba^{2+} (Heyer and Lux, 1976; Hotson and Prince, 1980; Halliwell and Adams, 1982; Akasu and Tokimasa, 1989). Exposure to each of these agents evoked a small inward current over baseline and, in addition, each of these treatments reduced the tail currents following a depolarizing step command. Treatment with TEA (10 mM) resulted in a reduction of both the PE-induced inward current ($64 \pm 21\%$, $n = 5$) and the PE-induced decrease in the conductance at all membrane potentials

Figure 3. *A*, Phenylephrine (PE) induces a voltage-sensitive inward current in mPRF neurons. Currents associated with ramp voltage commands are reduced, as are outward (upward) currents required to complete step commands (-65 to -40 mV) during PE treatment. *B*, I - V relations derived from ramp currents obtained prior to (○) and during (●) exposure to PE, indicate that PE decreases conductance. *C*, Subtraction of the two I - V curves gives the PE induced current that is voltage dependent with increased slope conductance at more depolarized membrane potentials. *D*, Currents recorded during depolarizing steps indicate that treatment with PE results in a decrease in both instantaneous current and in a slowly developing outward current. PE also decreases the amplitude of the outward tail current (*) observable upon return to the holding potential. *E*, The plot of the log of the relative tail current amplitude versus time indicates that the tail currents decayed with a single exponential time course that was not altered by PE treatment.

examined (Fig. 5*A,B*). No further reduction of the tail currents associated with PE in control conditions was observed with PE in the presence of TEA. The mPRF neurons responding to charybdotoxin with an increase of inward current and a reduction of tail currents (two of four), had a greater than 60% reduction of PE response (Fig. 6). The PE-induced current was reduced

by Mg^{2+} ($56 \pm 10\%$, $n = 5$; Fig. 5*C*), Cd^{2+} (not shown; $n = 3$), and Ba^{2+} ($81 \pm 12\%$, $n = 5$; Fig. 5*D*). As with TEA and charybdotoxin, no further PE effect on tail currents was observed in the presence of these divalent cations. The result of the Ba^{2+} experiment was particularly important in distinguishing between a decrease in outward current and an increase in inward

Figure 4. The reversal potential of the phenylephrine-induced inward current is dependent on extracellular potassium. The I - V relation is shown for phenylephrine-induced current in 10 mM extracellular potassium and demonstrates a reversal potential of -67 mV.

current. If the PE-induced inward current resulted from increased cation entry, Ba^{2+} would not be expected to reduce this action (Eckert and Lux, 1976; Hagiwara and Byerly, 1981).

Repetitive firing evoked by depolarizing current steps was increased during treatment with PE (Figs. 1*B*, 7). The effect on repetitive firing was more pronounced with low-amplitude excitatory current injection than with higher amplitudes. The frequency adaptation that occurs in association with a long duration AHP is often a target of neurotransmitters including NE (Madison and Nicoll, 1982, 1986; Haas and Konnerth, 1983; McCormick and Prince, 1988); however, this adaptation is not observed in mPRF neurons (Fig. 1*B*; Greene et al., 1986).

Discussion

Noradrenergic excitation of mPRF neurons results from activation of an α_1 -receptor that causes a decrease in conductance. This decrease is primarily a reduction of potassium conductance

based on the shift in the observed (or extrapolated, with 2.5 mM K^+) reversal potential of about 18 mV elicited by a doubling of the extracellular potassium concentration. The reversal potentials for 2.5 and 5 mM $[\text{K}^+]_o$ were more negative than would be expected based on previous experiments in mPRF neurons (Gerber et al., 1992; Stevens et al., 1992). In light of the difficulty of demonstrating a reversal potential, even in 5 mM $[\text{K}^+]_o$, it is probable that the receptors mediating the PE response are electrotonically remote. This condition would result in an overestimation of the reversal potential, particularly when voltage clamping at potentials much different from the resting potential. We cannot rule out a contribution by another conductance as responsible for the unexpectedly negative reversal potentials, but note that it would be a conductance antagonized by barium (Fig. 5*D*).

The current resulting from the ligand-antagonized potassium conductance, G_{CL} , was both voltage and calcium dependent. The I - V relationship of I_{CL} (the inverse image of the observed ligand-evoked current) is strongly outwardly rectifying and noninactivating. Its calcium dependence is supported by the observed blockade with calcium antagonists and with antagonists of calcium-dependent potassium current, TEA, charybdotoxin, and barium.

There are some contrasts between I_{CL} and other noninactivating delayed-rectifier currents, especially I_{C} , I_{m} , and I_{AHP} . Unlike the TEA-sensitive current designated I_{C} in hippocampal neurons (Brown and Griffith, 1983; Storm, 1987; Lancaster et al., 1991), the current reduced by NE in the mPRF does not contribute to action potential repolarization. This may be due at least in part, to the relatively slower activation kinetics (Fig. 3*D*). Although similar in voltage dependence to I_{m} (Brown and Adams, 1980), this current is distinct due to its calcium dependence and sensitivity to TEA and charybdotoxin. Like I_{m} , reduction of this current results in a greater increase in excitability than a similar reduction of a voltage-insensitive current (at resting potential). This current is unlike the ligand-sensitive I_{AHP} (Fowler et al., 1985; Pennefather et al., 1985) with respect to its voltage sensitivity and, accordingly, its lack of association with either a long-duration AHP or firing rate adaptation.

Figure 5. Ca^{2+} and K^+ channel blockers reduced the action of phenylephrine (PE) in mPRF neurons. *A*, The inward current and decrease in conductance elicited by PE were reduced in the presence of TEA (the large deflections in the records reflect the time period during which ramp protocols were being run). *B*, The current-voltage plot of the PE-induced currents shown in control and TEA treatment conditions. PE-induced current was generated by subtraction of I - V curves as described in Figure 3, *B* and *C*. TEA reduced the PE-induced current at all potentials tested. *C*, Mg^{2+} (7.5 mM; 0.3 μM TTX present) reduced the PE-induced current. *D*, Barium (2 mM) blocked the PE response. Ba^{2+} was the most effective blocker of membrane conductance.

Figure 6. Charybdotoxin evoked an inward current and reduced the inward current evoked by phenylephrine, consistent with an occlusive mechanism. *A*, The upper trace is a chart record of current under voltage-clamp control in the presence of TTX. Upward deflections reflect the current required to complete a 400 msec voltage step command from -65 mV to -40 mV. Bath application of PE ($5 \mu\text{M}$) caused an inward current with a decrease in conductance. In the presence of charybdotoxin (CTX; application begins at arrow) PE had little effect on either parameter. *B*, The voltage-sensitive effect of PE was reduced over the range of membrane potential examined (-90 to -35 mV) by about the same fraction ($>60\%$) as illustrated in the I - V curves.

In a simulation [see Materials and Methods for details of the modifications of the Huguenard and McCormick (1993) thalamic relay neuronal simulation], a 50% reduction of this current resulted in decreased instantaneous and time-dependent outward currents and in decreased outward tail currents (Fig. 8*B*). Under simulated current-clamp conditions, a 50% reduction of the PE-sensitive current resulted in a depolarization of the resting membrane potential and an increased firing rate during depolarizing inputs similar to the experimental results (Fig. 8*C*). A graph of the repetitive firing rate as a function of depolarizing injected current also closely matched the experimentally derived graph (Fig. 7). The simulated third ISI durations were all within 2% of the experimentally determined mean third ISIs (except that evoked by 0.6 nA of current, which was 18% less). However, a reduction of $I_{K, \text{leak}}$ of the same amplitude as that resulting from a 50% reduction of the PE-sensitive conductance at a resting membrane potential of -62 mV had less effect on repetitive firing rate (a 5.5% reduction compared to the experimentally determined 24% reduction or the simulated 26%).

The NE-evoked changes in the neuronal response to injected current and I - V relationship are consistent with a reduction of a single voltage-dependent conductance fit by the Boltzmann equation ($V_{1/2} = -30$ and a steepness factor of 12; Figs. 7, 8). The resulting current closely resembles that induced by PE treatment (Figs. 8*A,B*). The possibility of an additional NE-evoked reduction in a resting voltage-insensitive conductance cannot be excluded. However, a single voltage-sensitive current is sufficient to account for all the observed actions of NE on mPRF neurons.

These results indicate that adrenergic α_1 agonists depolarize mPRF neurons by reducing a calcium-dependent potassium conductance. While this action is similar to that of adrenergic β agonists on pyramidal neurons of the hippocampus (Madison and Nicoll, 1986) it is mediated, in contrast, by an α_1 receptor subtype acting upon a strongly voltage-sensitive current. This result is consistent with the findings that neither isoproterenol nor 8-bromo-cAMP mimics the action of phenylephrine, and prazosin blocks the depolarizing action of NE. The depolarizing action of NE on neurons of the spinal cord (North and Yoshimura, 1984) and trigeminal motor nucleus (Fukuda et al., 1987)

may occur through a similar mechanism. It is possible that the action of NE on mPRF neurons is secondary to a reduction of calcium current, but this would require a calcium current that was tonically active at resting potential, ruling out the high-

Figure 7. NE alters the relationship between depolarizing input and the repetitive firing rate. The duration of the third interspike interval (the mean $\pm$ SD; $n = 4$) is plotted relative to the amplitude of intracellularly injected current in the top graph. The bottom graph illustrates a computed simulation of the ISI/current curve (for details, see text). In the simulation, the PE-sensitive g_K was reduced by 50%. The leak g_K was reduced so that the current generated by its reduction was equal to the current generated by a 50% reduction of the PE-sensitive g_K at resting membrane potential = -62 mV.

Figure 8. Simulation of the NE evoked reduction in a calcium- and voltage-sensitive current. **A**, A Boltzmann relationship of voltage-sensitive fractional conductance to membrane potential (V_m), $G/G_{\max} = \{1 + \exp[(V_{1/2} - V_m)/k]\}^{-1}$, is shown with the parameters $V_{1/2} = -30$ mV and $k = 12$. The diamonds show the experimentally derived relationship from the currents illustrated in Figure 3C, using $G_{\max} = 8.8$ nS and $G_{\min} = 0.7$ nS so $G/G_{\max} = (G - G_{\min})/(G_{\max} - G_{\min})$. **B**, The current evoked by the reduction of this conductance is illustrated using the I - V relationship, $I = (V_{\text{rev}} - V_m)G$, with $V_{\text{rev}} = -105$ mV. The diamonds reflect the same currents as illustrated in Figure 3C. **C**, The computed current response to a voltage step command from -55 mV to -37 mV before and after reduction of the noninactivating current described above. The currents I_K , I_{Ca} , and I_{leak} are also present in this model. Compare with Figure 3D. **D**, Repetitive firing response of a simulated neuron to an injected current step of 150 msec duration before (1) and after (2) a 50% reduction of this current. Compare with Figure 1B.

threshold as well as the transient Ca^{2+} channels as candidates for such modulation (Tsien et al., 1988). Another possibility is that the rate of intracellular Ca^{2+} uptake is increased by PE. However, this would require an uptake rate more rapid than the channel closing rate as the tail current decay was unaffected by PE. The results are consistent with observations from a recent report of a muscarinic mechanism of action involving uncoupling of intracellular calcium from Ca^{2+} -dependent potassium current in hippocampal neurons (Müller and Connor, 1991).

The characteristics of the potassium current modulated by NE result in a specific type of increased excitability. Since this current contributes to the resting membrane potential, NE can facilitate initial responsiveness to excitatory neurotransmission by depolarization as well as by increasing input resistance. Long-duration excitatory input can be facilitated by a reduction of the AHP, increasing repetitive firing rates. The repetitive firing rate of mPRF neurons is relatively insensitive to injected depolarizing current as reflected by gradual slope of frequency/current curves (Gerber et al., 1989; Fig. 6); thus, the frequency response to excitatory input is determined to a large extent by the currents responsible for this AHP, including the current reduced during α_1 activation. In contrast to acetylcholine, which inhibits more than 20% of mPRF neurons (Gerber et al., 1991), NE inhibited less than 10% of cells examined (Gerber et al.,

1990; Stevens and Greene, unpublished observations). This inhibition may be an important factor affecting the elicitation of strikingly distinct behaviors from localized injection of these transmitters into the mPRF, that is, an REM sleep-like state from cholinergic agonists and a decrease of REM sleep with an increase in waking from noradrenergic agonists (Bier and McCarley, 1991). Facilitation of mPRF neurons by NE is consistent with a proposed role in behavioral state control. In particular, the increased excitability may facilitate waking behaviors, including the startle response that is mediated by mPRF neurons and, in *in vivo* is facilitated by NE agonists (Davis, 1984).

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