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THE ACTIONS OF NORADRENALINE ON NEURONES OF THE RAT SUBSTANTIA GELATINOSA *IN VITRO*

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SUMMARY

1. Intracellular recordings were made from substantia gelatinosa (s.g.) neurones in slices cut from adult rat spinal cord and maintained *in vitro*.

2. Noradrenaline applied by superfusion (1–50 μM), or by brief pressure ejection from a micropipette, reversibly hyperpolarized 80% of the s.g. cells.

3. The noradrenaline induced hyperpolarization was associated with an increase in conductance and it reversed in polarity at −88 mV. The reversal potential changed when the external potassium concentration was changed, as predicted by the Nernst equation.

4. The noradrenaline hyperpolarization was antagonized by phentolamine and yohimbine but not by propranolol and prazosin.

5. The hyperpolarization was probably a direct action on the impaled cell and not due to release or block of release of other transmitters, because the effects persisted during a perfusion with a low calcium/high magnesium solution or in a solution containing cobalt and high magnesium.

6. In 35 of 148 cells, noradrenaline caused a dose-related increase of spontaneous excitatory post-synaptic potentials (e.p.s.p.s). This effect was blocked by tetrodotoxin.

7. The noradrenaline induced increase in e.p.s.p.s was blocked by phentolamine and prazosin but not by the α_2-blockers yohimbine and RX 781094. A few cells were depolarized by noradrenaline, and this was blocked by prazosin but not by yohimbine.

8. It is suggested that noradrenaline may inhibit nociceptive input to the spinal cord by increasing the potassium conductance of s.g. neurones.

INTRODUCTION

Numerous noradrenaline containing fibres terminate in the dorsal horn of the spinal cord, particularly in the region of the substantia gelatinosa (s.g.) (lamina II of Rexed, 1952) (Dahlstrom & Fuxe, 1965; Satoh, Kashiba, Kimura & Maeda, 1982).

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Administration of noradrenaline into the s.g. causes a remarkably selective reduction of nociceptive responses of cat dorsal horn neurones, leaving spared the responses to non-nociceptive stimuli (Headley, Duggan & Griersmith, 1978). A similar selective block of nociceptive responses can be obtained by electrical stimulation of certain mid-brain sites (Duggan & Griersmith, 1979), and evidence exists that this results from activation of descending noradrenergic fibres (Hodge, Apkarian, Stevens, Vogelsang & Wisnicki, 1981; Proudfit & Sagen, 1982). The electrophysiological experiments (Headley *et al.* 1978) and recent ultrastructural studies (Satoh *et al.* 1982) seem to localize an important site of action of noradrenaline within the s.g. itself. However, it is unclear whether the selective blockade of noxious input arises from an action on terminals of small diameter afferents, as proposed by Headley *et al.* (1978), or a direct inhibition of s.g. cells which serve as interneurones in the noxious pathway to the deeper laminae.

A major impediment to electrophysiological studies in the dorsal horn has been the difficulty in making stable intracellular recordings from s.g. neurones (Bennett, Hayashi, Abdelmoumene & Dubner, 1979; Cervero, Iggo & Molony, 1979; Light, Trevino & Perl, 1979; see Brown, 1981). These difficulties have been largely overcome in the present experiments by first removing the spinal cord from the anaesthetized animal and recording from a thin transverse slice of spinal cord *in vitro*. This preparation has the advantages that the regions of the dorsal horn can be directly observed, and that noradrenaline and other drugs can be applied in controlled concentrations. Unfortunately, it has the disadvantage that the neurones studied can no longer be identified in respect of their physiological connexions. Preliminary reports of some part of this work have been published (Yoshimura & North, 1983*a*).

METHODS

Preparation of the slice. Slices were prepared in a manner similar to that described for the cat by Yoshimura & Nishi (1982). Adult male Sprague–Dawley rats (150–300 g) wee anaesthetized with urethane (1·5 g/kg, intraperitoneal). A lumbosacral laminectomy was performed and a 1·5–2 cm length of spinal cord was quickly excised. Pia and arachnoid were stripped from the isolated spinal cord while it was submerged in oxygenated physiological saline solution at 4–6 °C, and the block of tissue was then mounted on a Plexiglas slide using cyanoacrylate adhesive. Serial transverse slices were cut with a vibratome (Oxford) at a thickness of 400 μm, while the tissue was submerged in solution at 4–6 °C. A single slice was placed on a nylon mesh (Bridal veil) in the recording chamber (volume about 0·5 ml). A titanium electron microscope grid was placed on the top of the slice and held lightly in position by a platinum loop attached to a micromanipulator. The slice was completely submerged in a continuously flowing solution (5 ml/min) equilibrated with 95% O_2/5% CO_2 at 37 °C. The composition of the solution was (mM): NaCl, 117; KCl, 4·7; $CaCl_2$, 2·5; $MgSO_4 . 7H_2O$, 1·2; NaH_2PO_4, 1·2; $NaHCO_3$, 25; and glucose, 11. Neurones were viable for up to 24 h after removal from the animal and stable intracellular recordings were made from single s.g. cells for periods of up to 5 h.

Identification of s.g. neurones. The area of the s.g. (lamina II of Rexed, 1952) was easily identifiable in the transverse slice preparation. When viewed with transmitted light it appeared as a relatively translucent band across the dorsal horn. However, differentiation between lamina I and lamina II was usually difficult in the living slice. In order to decrease the possibility of recording from lamina I cells, the micro-electrode was inserted into the slice at a distance of between 50 and 200 μm from the border of the grey matter of the dorsal horn with the overlying white matter. Therefore, in the present study of the membrane actions of noradrenaline, we have not attempted to identify the neuronal elements from which the recordings were made other than by their position in the slice preparation. We are inclined to think that they are cell bodies of neurones intrinsic to the

s.g. rather than axons or dendrites of cells in other lamina because of their membrane properties (M. Yoshimura, in preparation).

Recording and focal stimulation. Micro-electrodes filled with 3 M-KCl having DC tip resistances of 60–140 MΩ were used to record from s.g. neurones, with a high-input impedance bridge amplifier (WP Instruments, M 707) which permitted current injection. Intracellular potentials were amplified and displayed by conventional methods. Values for resting potential were determined by sudden

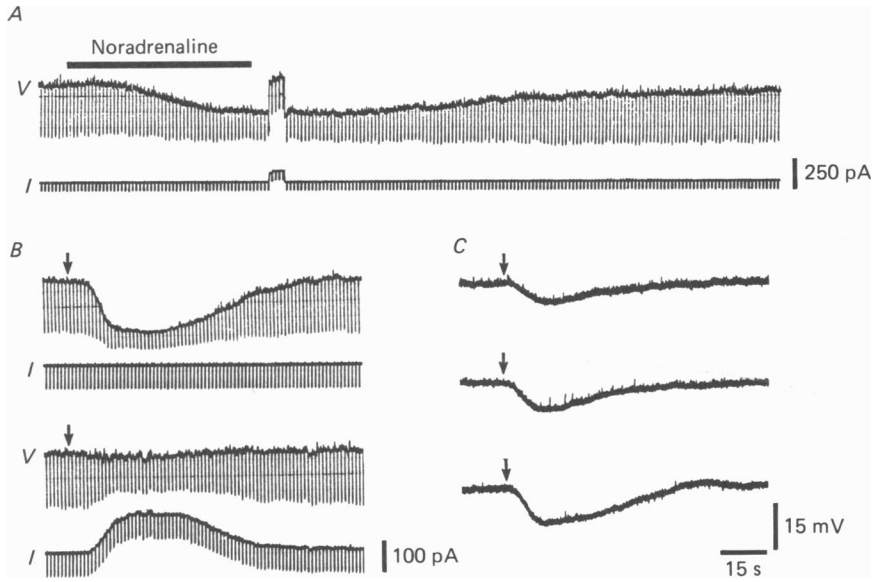

Fig. 1. Noradrenaline hyperpolarizes s.g. neurones. *A*, superfusion with noradrenaline (20 μM) during the period indicated by the bar caused a 10 mV hyperpolarization. In this and other Figures the apparent delay in the onset of the response when noradrenaline was applied by superfusion includes 15–25 s for passage through the pre-heating system prior to reaching the tissue. At the peak of the noradrenaline hyperpolarization the membrane potential was restored to its control level by passing depolarizing current. Note the fall in input resistance during the noradrenaline hyperpolarization. *B*, application of noradrenaline by pressure application (105 kPa for 50 ms). In the top pair of traces, the hyperpolarization was associated with a large fall in input resistance. The bottom traces show the effect of the same application of noradrenaline in which the potential change was annulled by passing an equal and opposite current. The noradrenaline induced conductance increase is apparent. *C*, pressure application of increasing numbers (1, 2 and 3) of 'puffs' of noradrenaline caused increasing responses. Each 'puff' was 105 kPa for 70 ms. Calibrations (mV, ms) in *C* refer also to *A* and *B*.

withdrawal of the micro-electrode; input resistance was estimated from the slope of the current–voltage relationship, and changes in input resistance were often measured from the amplitude of hyperpolarizing electrotonic potentials (e.g. Fig. 1). Synaptic potentials were evoked by applying rectangular voltage pulses (duration 500 μs) to a bipolar tungsten electrode insulated except at its tip. The tip of this electrode was positioned on the surface of the dorsal root entry zone, but not touching the slice.

Application of drugs and solutions of different ion content. Drugs and solutions of different ionic content were applied by changing the perfusion solution to one which contained known concentrations of drug(s) by means of three-way taps so that the perfusion rate did not change. The time required for the changed solution to flow from the tap to the bath was about 15 s. The volume of the recording chamber was 0·5 ml. Noradrenaline was also applied by pressure ejection

from a micropipette (tip diameter 10–15 μm) placed in the bathing solution above the slice. The solution in the pressure ejection pipette contained 1 mM-noradrenaline bitartrate dissolved in saline. Various amounts of noradrenaline were applied by changing the number of pressure pulses. [^{3}H]noradrenaline release from such pipettes is linearly related to the number of pulses applied (Williams, Henderson & North, 1983). To reduce the possibility that cells were exposed to noradrenaline leaking from the pipette, membrane potential and input resistance were continuously monitored as the pipette was positioned above the slice. Drugs used were (−)-noradrenaline bitartrate (norepinephrine, Sigma), (−)-isoprenaline hydrochloride (isoproterenol, Sigma), clonidine hydrochloride (Boehringer Ingelheim), phentolamine hydrochloride (Ciba-Geigy), propranolol hydrochloride (Ayerst), prazosin hydrochloride (Pfizer), yohimbine hydrochloride (Sigma), RX 781094 [2-(2-(1,4benzodioxanyl))2-imidazoline hydrochloride] (Reckitt & Colman) and tetrodotoxin (Sigma).

RESULTS

The results described in this paper were obtained from 148 neurones located in the s.g. S.g. cells had resting membrane potentials of $-66{\cdot}3 \pm 0{\cdot}7$ mV (mean ± S.E. of mean, $n = 89$) and apparent input resistances of $266{\cdot}5 \pm 15{\cdot}9$ MΩ ($n = 70$). Many cells had numerous spontaneous depolarizations ranging in frequency from 2 to 40 Hz and in amplitude from 2 to 10 mV. These depolarizations usually did not initiate action potentials. Focal stimulation with the bipolar stimulation electrode located near the slice surface above the dorsal root entry zone elicited depolarizations similar in time course to the spontaneous depolarizations. In some cells this depolarization was followed by a hyperpolarization. Both evoked responses were graded in amplitude according to the strength of stimulation and the depolarization readily initiated action potentials when the stimulus strength was increased. The amplitude of the depolarization increased as the membrane was hyperpolarized while the amplitude of the hyperpolarization decreased. Both evoked responses were reversibly abolished by a solution containing 0·25 mM-calcium and 5 mM-magnesium (low calcium/high magnesium). For this variety of reasons we conclude that the depolarizing response is an excitatory post-synaptic potential (e.p.s.p.) and the hyperpolarizing response is an inhibitory post-synaptic potential (i.p.s.p.).

Noradrenaline hyperpolarization

Superfusion with noradrenaline hyperpolarized the membrane of s.g. neurones in sixty-six of seventy-seven cells tested (Fig. 1). Effective concentrations of noradrenaline were 1–50 μM. The mean amplitudes of hyperpolarizations evoked by 5 μM, 10 μM and 20 μM were 6·7 mV ($n = 19$), 8·8 mV ($n = 25$) and 9·6 mV ($n = 9$), respectively. Brief application of noradrenaline by pressure ejection produced a similar hyperpolarization but with a relatively shorter time course. This was also dose-dependent in that it increased with the number of pressure pulses applied (Fig. 1*C*). The noradrenaline hyperpolarizations were always associated with an increase in conductance; this was not due to membrane rectification since it was observed when the potential was temporarily restored to its original level (Fig. 1*A* and *B*). The magnitude of the conductance increase was proportional to the amplitude of the noradrenaline hyperpolarization. If the hyperpolarization results from an increase in conductance to ions having a reversal potential $E_{\mathrm{rev},R}$, and if the increase in conductance is entirely responsible for the change in input resistance measured

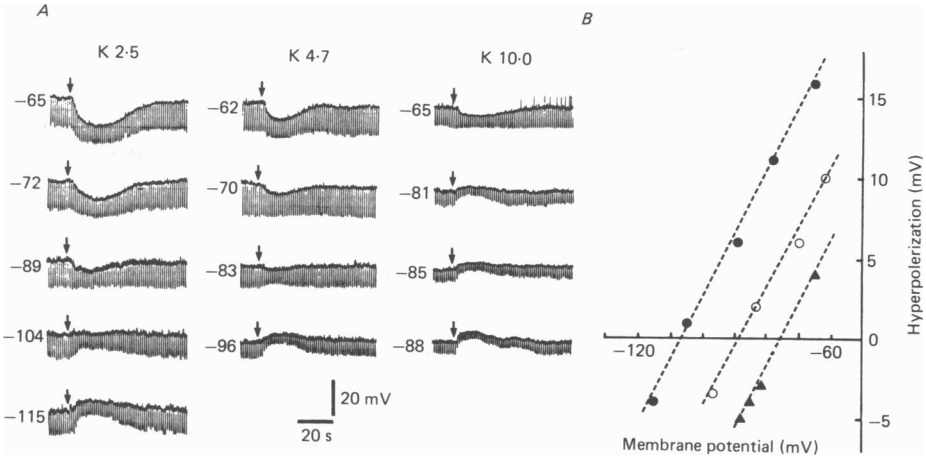

Fig. 2. Noradrenaline increases membrane potassium conductance. *A*, each trace shows the response to one pressure application of noradrenaline (125 kPa, 70 ms) at different membrane potentials, and in three different extracellular potassium concentrations (mM). *B*, the amplitudes of the noradrenaline hyperpolarization are plotted as a function of the membrane potential.

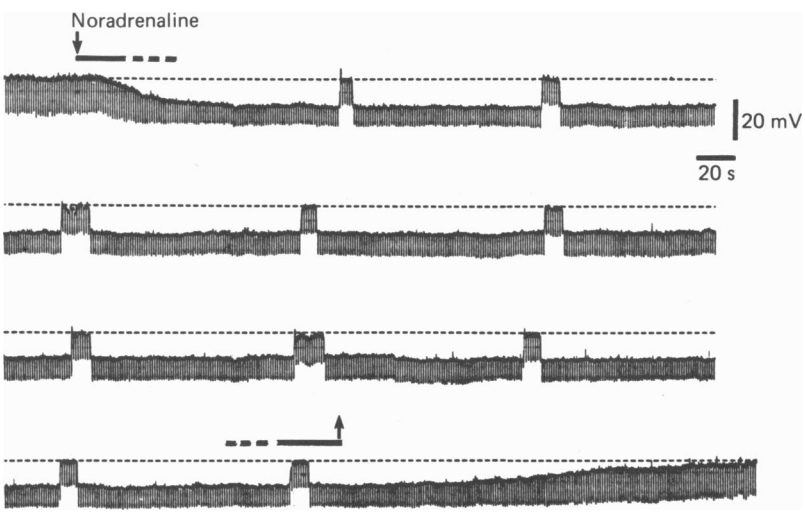

Fig. 3. Noradrenaline hyperpolarization showed no decline during applications up to 20 min. The four traces are continuous recordings, and the times of starting and ending the superfusion with noradrenaline (20 μM) are indicated. The dashed line indicates the resting potential (−67 mV). At intervals of approximately 2 min the potential was restored to this level to estimate input resistance. The noradrenaline conductance increase also showed no desensitization.

experimentally, then $\Delta V = (1 - R'/R)\ (E_m - E_{rev,R})$ where R' and R are the input resistances in noradrenaline and in control, E_m is the control (resting) membrane potential and ΔV is the amplitude of the hyperpolarization (Ginsborg, 1967; Morita, North & Tokimasa, 1982). In six experiments, the estimate of $E_{rev,R}$ was −90·8 mV.

When s.g. cells were hyperpolarized by passing current through the recording

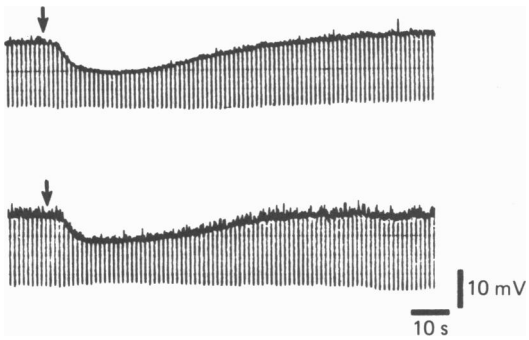

Fig. 4. Noradrenaline hyperpolarization was not blocked by cobalt/high magnesium solutions. Top trace, response to pressure application of noradrenaline (105 kPa, 60 ms) in normal superfusion solution (control). Bottom trace, response to the same application after 15 min superfusion with a solution containing 2 mM-cobalt and 20 mM-magnesium. All evoked synaptic potentials were blocked within 5 min of superfusing with cobalt and high magnesium solution (not shown).

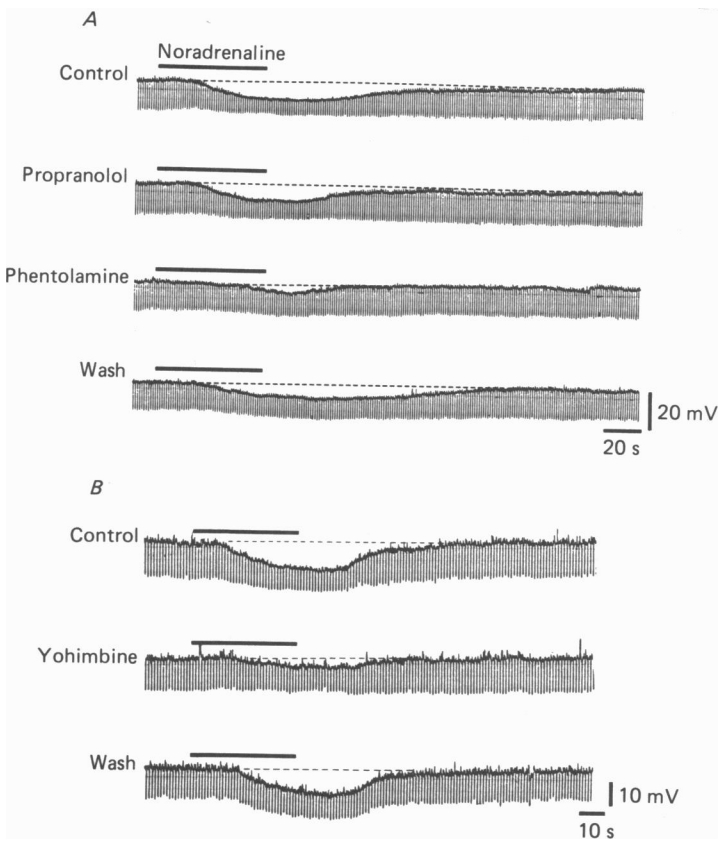

Fig. 5. Phentolamine and yohimbine antagonize noradrenaline hyperpolarizations. *A*, responses to noradrenaline superfusion (20 μM, bar) were unaffected by propranolol (1 μM, 8 min), reduced by phentolamine (1 μM, 11 min) and subsequently recovered (after 30 min wash). *B*, another cell. Responses to noradrenaline superfusion (5 μM, bar) were markedly depressed by yohimbine (500 nM, 10 min) and subsequently recovered (after 16 min wash).

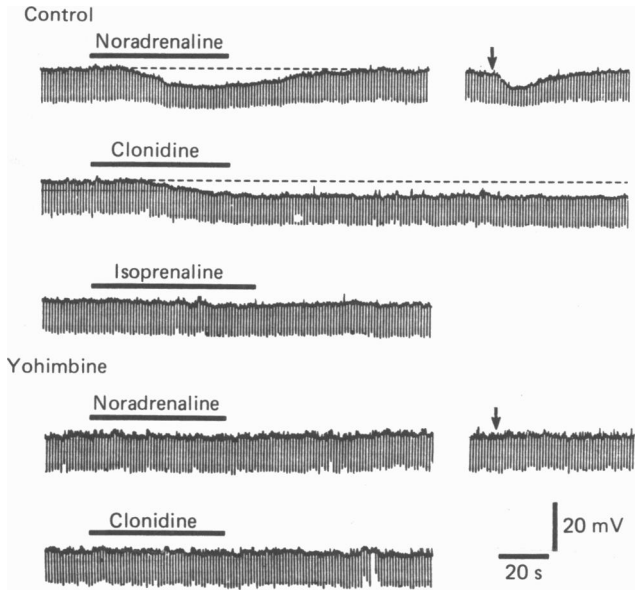

Fig. 6. Clonidine, but not isoprenaline, mimicked noradrenaline. All recordings are from the same s.g. neurone. Control, top trace shows responses to noradrenaline superfusion (5 μM, bar) and pressure application (105 kPa, 40 ms). Middle trace shows response to clonidine superfusion (500 nM, bar). The membrane potential eventually returned to its control level after 10 min washing. Bottom trace shows lack of effect of isoprenaline (10 μM, bar). After yohimbine, recordings made after 15 min superfusion with yohimbine (500 nM). Equal applications of noradrenaline and clonidine by superfusion, and noradrenaline by pressure, were now ineffective.

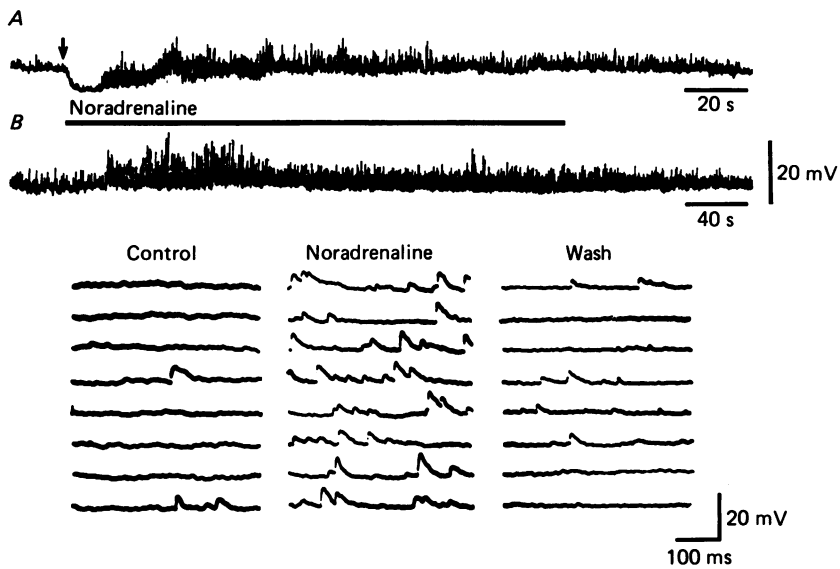

Fig. 7. Noradrenaline increases spontaneous e.p.s.p.s. *A*, top trace shows response to pressure application. The initial hyperpolarization is passing off when a marked increase in the occurrence of spontaneous e.p.s.p.s begins. *B*, another neurone held at -77 mV by passing hyperpolarizing current. Noradrenaline superfusion (10 μM, bar) caused an increase in the amplitude and frequency of spontaneous e.p.s.p.s. Note that latency to onset is longer than that typically observed for hyperpolarizing responses (Figs. 1, 3 and 5). Lower panels and photographs of oscilloscope recordings of membrane potential before, during and after the application of noradrenaline shown above.

electrode, the noradrenaline hyperpolarization became small and its polarity reversed at −88 mV (Fig. 2). This reversal potential ($E_{rev,E}$) shifted when the external potassium concentration ($[K]_o$) was changed according to $E_{rev,E} = 51 \log_{10} [K]_o/140$. It is not likely that chloride ions are involved in these responses, since long duration hyperpolarizing currents passed through the KCl-filled electrode appeared not to change the response amplitude.

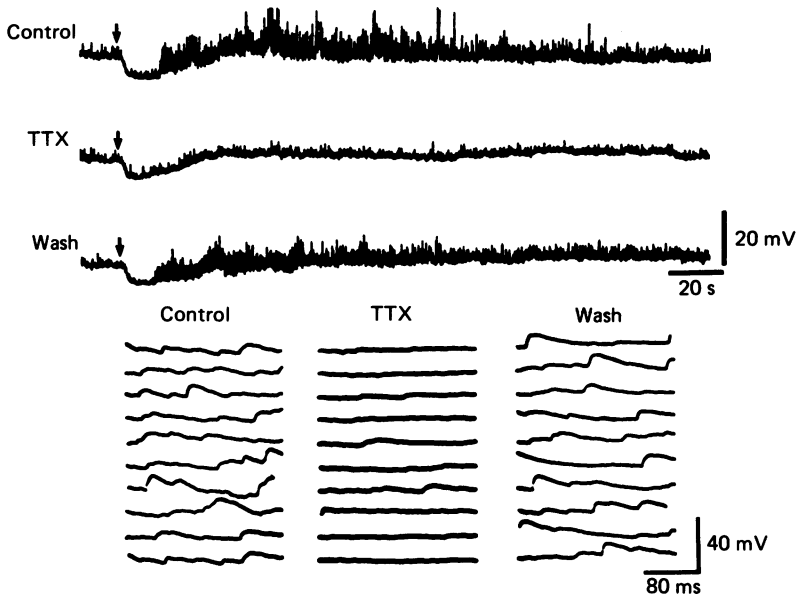

Fig. 8. Tetrodotoxin (TTX) prevents the increase in e.p.s.p.s evoked by noradrenaline. Top three traces show responses to noradrenaline applied by pressure (105 kPa, 20 ms) before (control), during and after (wash) superfusion with tetrodotoxin (700 nM, present for 7 min). Bottom panels are oscilloscope photographs of the spontaneous e.p.s.p.s before, during and after tetrodotoxin.

The noradrenaline hyperpolarizations showed no evidence of desensitization during applications of up to 20 min duration. This applied both to the potential change and the underlying conductance change (Fig. 3).

The noradrenaline hyperpolarization was a direct effect on the impaled cells and was not due to release or block of release of other transmitters. Superfusion of the slice with low calcium/high magnesium solution or solutions containing normal calcium but additional cobalt (2 mM) and magnesium (20 mM) for up to 20 min did not depress the noradrenaline hyperpolarization (Fig. 4). Both these solutions rapidly (within 3 min) abolished synaptic potentials. Longer exposure to low calcium or cobalt containing solutions did progressively depress the noradrenaline hyperpolarization.

The effect of noradrenaline was reversibly blocked by phentolamine (500 nM–1 μM) but unaffected by propranolol (1 μM) (Fig. 5). It was also reversibly blocked by the more selective α_2-adrenoceptor antagonist yohimbine (Fig. 5) but not by the α_1-adrenoceptor antagonist prazosin. Clonidine (500 nM) caused a hyperpolarization

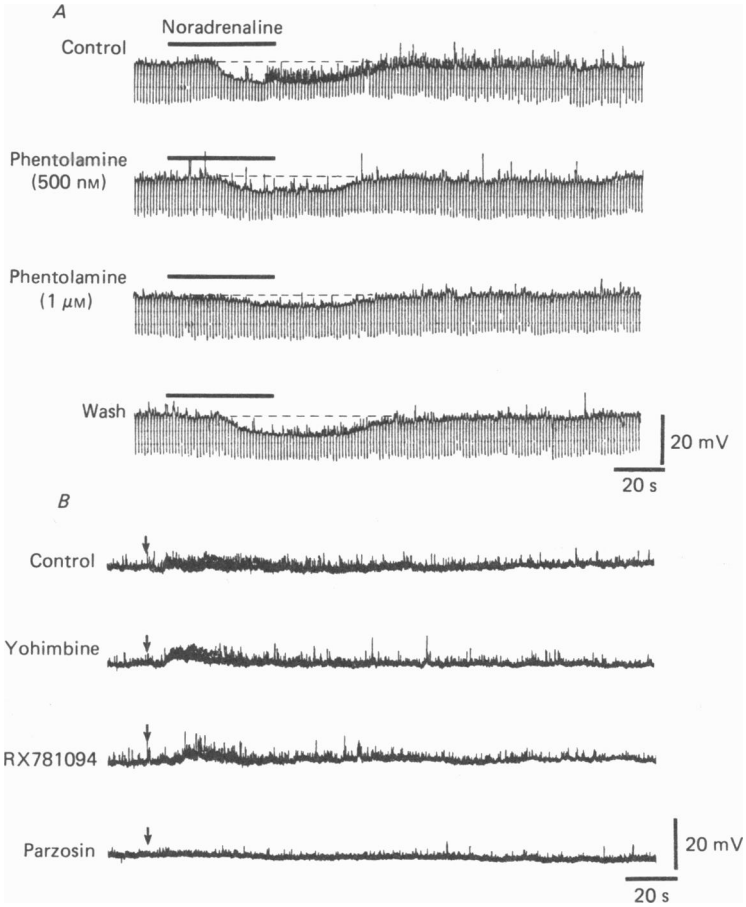

Fig. 9. Noradrenaline increase in e.p.s.p.s is reduced by phentolamine and prazosin, but not by yohimbine. *A*, the four traces show the effects of noradrenaline superfusion (5 μM, bar) before, during and after the presence of phentolamine (500 nM, later increased to 1 μM). Note the typical 'late' appearance of the e.p.s.p.s in the control recording. Phentolamine (1 μM) almost abolished both the hyperpolarization and the increase in e.p.s.p.s. *B*, a similar experiment in which noradrenaline was applied by pressure (105 kPa, 70 ms). This pressure application caused an 18 mV hyperpolarization from the resting level (not shown). Throughout the traces shown, the cell was hyperpolarized by 18 mV by passing constant current through the recording electrode. The noradrenaline induced potential change is therefore not observed. Top trace, control. Second trace, 10 min after superfusing with yohimbine (500 μM). Third trace, the α_2 antagonist RX 781094 (500 nM, 21 min later) had an effect similar to that of yohimbine. The small depolarizations which occurred during yohimbine and RX 781094 may result from blockade of the noradrenaline induced conductance increase. The spontaneous e.p.s.p.s were not blocked. Bottom trace, prazosin (500 nM, 6 min later) blocked the spontaneous e.p.s.p.s evoked by noradrenaline.

similar to that observed with noradrenaline, but which was very slow to reverse. This clonidine action was also blocked by yohimbine. Isoprenaline, even in high concentrations (50 μM), did not affect cells which were hyperpolarized by noradrenaline (Fig. 6). These observations establish that noradrenaline acts on an α_2-adrenoceptor of s.g. neurones to increase the membrane potassium conductance.

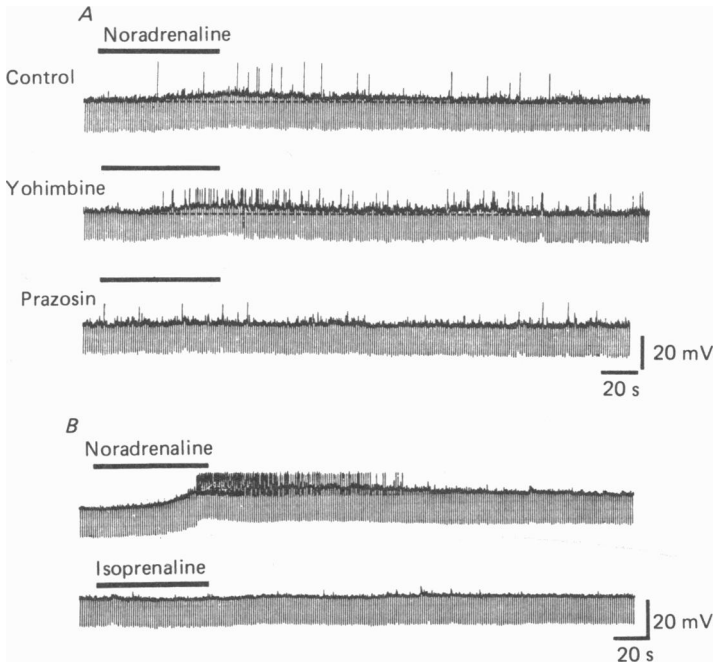

Fig. 10. *A*, depolarizing response to noradrenaline was blocked by prazosin but not by yohimbine. Control, superfusion of noradrenaline (20 μM, bar) caused a depolarization and increase in spontaneous e.p.s.p.s. This was still observed in yohimbine (500 nM) but was blocked by prazosin (75 nM). *B*, another cell which was depolarized by noradrenaline (20 μM, bar, top trace) and which discharged action potentials (full heights cut off by pen recorder response). Isoprenaline (40 μM, bar, bottom trace) had no effect on this neurone.

Noradrenaline increase in spontaneous e.p.s.p.s

In 35 of 125 cells, noradrenaline hyperpolarizations were accompanied by a marked increase in spontaneous e.p.s.p. amplitude and frequency. The e.p.s.p. time course was not markedly altered. Typical effects are shown in Figs. 7 and 8. This effect was observed even on the cells which were not hyperpolarized by noradrenaline (Fig. 7). However, when a hyperpolarization was observed it was apparent that the increase in e.p.s.p.s always occurred after a longer latency than the hyperpolarization. Moreover, the synaptic excitation usually considerably outlasted the hyperpolarization (Fig. 7). Tetrodotoxin (TTX) (700 nM) reversibly blocked this noradrenaline effect, suggesting that it resulted from direct excitation of other neurones in the slice, with an acceleration in their release of excitatory transmitter onto the impaled cell (Fig. 8). The spontaneously occurring e.p.s.p.s, in the absence of noradrenaline, were insensitive to TTX, indicating that these e.p.s.p.s resulted from spontaneous release of transmitter from the nerve terminals without sodium dependent action potentials. It appeared that the frequency and amplitude of the e.p.s.p.s evoked by noradrenaline depended on the concentration applied (5–40 μM), although careful quantification of the spontaneous e.p.s.p.s was not attempted. Both the noradrenaline hyperpolarization and e.p.s.p. increase were reversibly antagonized by phentolamine, but not by propranolol. Yohimbine and RX 781094 were without effect

on this e.p.s.p. increase. The α_1-adrenoceptor antagonist prazosin (500 nM) antagonized this effect of noradrenaline (Fig. 9).

Noradrenaline depolarization

The above observation led to the idea that some cells were excited by noradrenaline interacting with an α_1-adrenoceptor, brought to threshold for TTX-sensitive action potentials, and resulting in the increase of e.p.s.p.s. Thus, one might expect to find some neurones which were excited by noradrenaline. Indeed, in 4 of 148 cells, superfusion caused membrane depolarizations and sometimes initiated cell firing. This depolarization had a long latency to its onset and was long-lasting (Fig. 10). This time course is appropriate to the notion that such depolarizations underlie the increase in e.p.s.p. frequency observed in other cells. This depolarization was blocked by prazosin (75 nM), but not by yohimbine (500 nM). Isoprenaline did not depolarize cells which were depolarized by noradrenaline. It thus appears that some cells in the rat spinal cord are depolarized by noradrenaline acting on α_1-adrenoceptors, and that these cells release an excitatory neurotransmitter onto most cells of the s.g. The ionic mechanism of the α_1-adrenoceptor depolarization has not been characterized, due to the rarity of the response. The small number of cells affected implies that they show marked divergence to other s.g. neurones, or, perhaps more likely, that many of the cells excited by noradrenaline lie not in the s.g. but elsewhere in the slice.

DISCUSSION

Noradrenaline hyperpolarizes the majority of neurones in the s.g. by increasing their membrane potassium conductance. The action results from occupation of a receptor with the characteristics expected of an α_2-adrenoceptor. Noradrenaline hyperpolarizes a variety of mammalian neurones, and in some sites this has been shown to involve an α_2-adrenoceptor (locus coeruleus: Aghajanian & Van der Maalen, 1982; Egan, Henderson, North & Williams, 1983; superior cervical ganglion, Brown & Caulfield, 1979; myenteric neurones, Morita & North, 1981). In the locus coeruleus (Egan *et al.* 1983) and myenteric plexus (Morita & North, 1981) the α_2-adrenoceptor agonists were also shown to cause an increase in potassium conductance. It is therefore possible that α_2-adrenoceptor activation of potassium conductance might prove to be of fairly general significance in the nervous system.

The second action of noradrenaline, an increase in the occurrence of e.p.s.p.s, has the characteristics associated with α_1-adrenoceptor mediated events. Unfortunately the neurones directly excited by the α_1-adrenoceptor occupancy were sparse in the present experimental circumstances, perhaps because they really are few in number with a wide divergence onto s.g. neurones, because they are small and difficult to record from or because they are located outside the s.g. Although only four neurones were depolarized by noradrenaline, this action also appeared to be α_1-adrenoceptor mediated. The electrophysiological consequences of α_1-activation have not been reported previously in terms of ionic conductances. However, there is evidence to suggest that potassium inactivation may occur in facial motoneurones of the brain stem (Rogawski & Aghajanian, 1980; Van der Maalen & Aghajanian, 1980; Aghajanian & Rogawski, 1983). This would be compatible with our own observations (Fig. 10).

Our interpretation that the α_2-adrenoceptor hyperpolarization is a direct action on the membrane of s.g. neurones accords with the finding that α_2-binding sites determined autoradiographically are concentrated in this lamina (Young & Kuhar, 1980). By contrast, α_1 binding sites are more uniformly distributed throughout the spinal cord (Young & Kuhar, 1980). The absolute number of binding sites (defined with [^{3}H]para-aminoclonidine (α_2) and [^{3}H]WB4101 (α_1)) indicate that α_1 sites are at least as numerous as α_2 in homogenates of the entire rat spinal cord (Jones, Kendal & Enna, 1982). In other parts of the nervous system noradrenaline has significant action on β-adrenoceptors (Hoffer, Siggins, Oliver & Bloom, 1973; Madison & Nicoll, 1982). We have found no evidence for significant β-adrenoceptor mediated actions of noradrenaline in the rat s.g.

Assessment of the physiological significance of the two actions of noradrenaline awaits more information about the identity and connexions of the s.g. neurones. However, it seems likely that the α_2-adrenoceptor mediated hyperpolarization underlies the selective inhibition of nociceptive response of dorsal horn cells reported by Belcher, Ryall & Schaffner (1978) and Headley *et al.* (1978). There are two reasons for this assertion. The first is the evidence that noradrenaline and clonidine cause antinociception when applied locally onto the rat spinal cord (Reddy, Maderbrut & Yaksh, 1980). The second is the recent finding by Fleetwood-Walker, Hope, Iggo, Mitchell & Molony (1983) that ionophoretic application of clonidine inhibits noxious responses of identified cat spinocervical tract neurones; the α_1-agonist phenylephrine was much less effective. One might therefore conclude that α_2-agonists inhibit the transmission of noxious information by directly hyperpolarizing s.g. neurones which serve as interneurones relatively specific for the noxious modality. This action is identical to that recently described for opioids (Yoshimura & North, 1983*b*). The additional excitatory action mediated by α_1-adrenoceptors may represent the substrate for a more advanced form of signal processing in the dorsal horn, the physiological significance of which cannot be addressed by the present technique.

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