Br. J. Pharmac. (1974), **51**, 359-365

ON THE MECHANISM OF ACTION OF CLONIDINE: EFFECTS ON SINGLE CENTRAL NEURONES

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1 Noradrenaline and clonidine were applied by microiontophoresis to single neurones in the cerebral cortex and medullary reticular formation of anaesthetized rats.

2 Of a total of 247 neurones studied, 79% of medullary units and 60% of cortical units responded in the same manner to both noradrenaline and clonidine. The usual response was a depression of neuronal firing rate.

3 It proved possible to antagonize some responses to both substances by the microiontophoresis of bulbocapnine, whilst leaving unaffected similar responses to 5-hydroxytryptamine.

4 On 13% of the cells, clonidine produced an increase of firing rate. This effect could not be attributed to a post-synaptic antagonism of tonically released endogenous noradrenaline, but may indicate a presynaptic action of clonidine, reducing noradrenaline release.

5 These observations are thought to support the idea that clonidine may have an agonist action on noradrenaline receptors in the brain.

Introduction

The systemic administration of clonidine (Catapres; 2-(2,6-dichlorophenylamino)-2-imidazoline) produces an initial transient hypertension, followed by a fall of blood pressure (Schmitt, Schmitt, Boissier & Giudicelli, 1967). The initial hypertensive effect appears to be caused by a direct stimulation of α-adrenoceptors in the peripheral vasculature (Boissier, Giudicelli, Fichelle, Schmitt & Schmitt, 1968; Constantine & McShane, 1968). The subsequent relatively prolonged hypotensive phase appears to be mediated by an action of clonidine on the central nervous system since, for example, it has been shown to occur when clonidine is introduced directly into the central nervous system in individual animals or in cross-circulation experiments (Kobinger & Walland, 1967; Bentley & Li, 1968; Sherman, Grega, Woods & Buckley, 1968). Schmitt and his colleagues have demonstrated a marked fall of efferent sympathetic activity after clonidine administration and have proposed an action of clonidine on the vasomotor centres of the brain to account for this effect and the resulting hypotension (Schmitt *et al.*, 1967; Schmitt, Schmitt, Boissier, Giudicelli & Fichelle, 1968).

For several reasons it has been further suggested that this centrally-mediated hypotensive action of clonidine is due to an interaction with noradrenergic neurones in the central nervous system. Thus, clonidine no longer produces hypotension after the degeneration of such neurones as a result of 6-hydroxydopamine treatment (Dollery & Reid, 1973), and the hypotension normally produced may be reduced by the use of adrenoceptor blocking agents such as phentolamine and piperoxane (Schmitt, Schmitt & Fenard, 1971). The present experiments were therefore designed to investigate the effects of clonidine directly on the central nervous system by applying the drug in the vicinity of single neurones by microiontophoresis.

Spontaneously active cells in two areas of the brain were studied. Firstly, the parietal cerebral cortex was used, partly because the area is readily accessible without having to remove overlying tissue and partly because the responses to noradrenaline of cells in this area of the rat's brain have been characterized in previous experiments (Stone, 1973a).

Secondly, a number of cells in the medullary reticular formation have been examined since evidence has been provided that this area could be the main site of action of clonidine in producing hypotension (Shaw, Hunyor & Korner, 1971).

Some of these results have been communicated to the British Pharmacological Society (Anderson & Stone, 1973).

Methods

Male hooded Wistar rats weighing 250-300 g were anaesthetized with urethane, 5 ml/kg of a 25% solution in 0.9% w/v NaCl solution (saline) intraperitoneally.

Standard surgical procedures were employed to insert a tracheal cannula and to expose the somatosensory cortex of the left cerebral hemisphere (Stone, 1972a). For the experiments in the medulla, the skull overlying the cerebellum was removed and the cerebellum itself then removed either by surgical excision or by suction. The head was clamped in a stereotaxic frame to allow electrode penetrations within the limits of planes AP 12.5; Lat. 1-1.5; vert. 10.0-11.5 in the medullary reticular formation, according to the stereotaxic atlas of Fifková & Marsala (1967). Randomly encountered spontaneously active cells within this defined region were tested. The temperature of the rat was automatically maintained at 37-38°C by means of a rectal thermistor probe and a heating pad placed beneath the body (Krnjević & Mitchell, 1961). The conventional microiontophoretic techniques and recording equipment used have been described in detail elsewhere (Stone, 1972a, b; 1973a, b). Five-barrelled micropipettes were employed and the drug solutions used were clonidine hydrochloride (Boehringer Ingelheim Ltd) 200 mM at pH 5.5, (−)-noradrenaline bitartrate (Koch-Light) 200 mM at pH 4.5, 5-hydroxytryptamine creatinine sulphate (Koch-Light) 50 mM at pH 4.5 and bulbocapnine hydrochloride (K & K Rare Chemicals) 20 mM at pH 4.5. Each micropipette also contained a 200 mM solution of sodium chloride in one barrel so that current balancing (Stone, 1972a) was possible. A retaining current of 15 nA was used for all drugs. Apart from bulbocapnine, which was ejected with a current of 100 nA, the drugs were ejected with currents of 60-80 nA.

Unit activity was recorded via a single micropipette electrode containing potassium acetate (1 M), affixed alongside the multibarrel complex as described previously (Stone, 1973b). Neuronal spike activity was monitored continuously on D43 Telequipment oscilloscopes. The signal was then passed through a pulse-shaper unit and recordings of spike firing frequency were made via an Ekco Ratemeter onto a Servoscribe pen recorder.

Results

The responses of a total of 247 neurones were studied (Table 1), 185 in the cerebral cortex and 62 in the medulla. Of these cells, 65% and 68%, respectively, were responsive to the iontophoresis of noradrenaline with currents of 60-80 nA. This proportion is similar to that obtained in previous experiments (Stone, 1973a). Most of the cells in both regions were depressed by noradrenaline with few being excited. Typically, the depression of firing began some 10 s after the onset of iontophoretic ejection and the maximum effect was obtained some 30 s later (Figure 1).

A slightly smaller proportion of cells was responsive to the iontophoresis of clonidine with currents of 60-80 nA, 53% being affected in the cortex and 61% in the medulla. About half of the cells encountered were depressed (40% and 50% respectively) and a smaller number were excited by clonidine (13% and 11% respectively). However, a much smaller reduction of firing rate was produced by the ejection of clonidine than by noradrenaline ejected with a current of the same magnitude (Figure 1). The clonidine-induced depression also had a somewhat longer latency of

Table 1 Responses of neurones in rat cerebral cortex and medulla to clonidine or noradrenaline

		Numbers of cells			
Area studied	*Total studied*	*Unaffected*	*Excited*	*Depressed*	*Total responding*
Responses of neurones to clonidine					
Cerebral cortex	185	86 (46%)	24 (13%)	75 (40%)	99 (53%)
Medulla	62	24 (39%)	7 (11%)	31 (50%)	38 (61%)
Total	247	110 (45%)	31 (13%)	106 (43%)	137 (55%)
Responses of neurones to noradrenaline					
Cerebral cortex	185	65 (35%)	7 (4%)	113 (61%)	120 (65%)
Medulla	62	20 (32%)	3 (5%)	39 (63%)	42 (68%)
Total	247	85 (34%)	10 (4%)	152 (62%)	162 (66%)

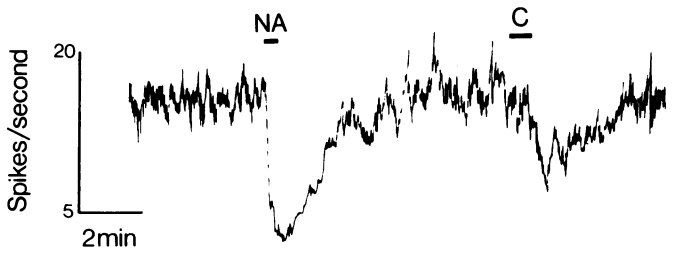

Fig. 1 Records of the firing rate of a neurone in the cerebral cortex in response to the application by microiontophoresis of noradrenaline 80 nA (NA) and clonidine 80 nA (C). Note the longer latency but smaller maximum size of the response to clonidine. Time: 2 minutes.

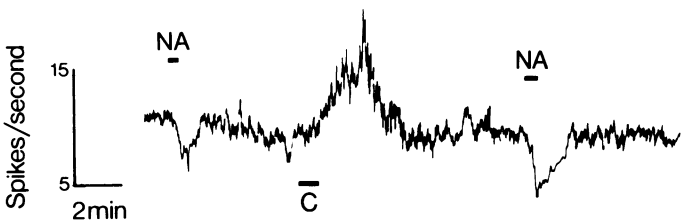

Fig. 2 Record of the firing rate of a neurone in the cerebral cortex in response to the application of noradrenaline 80 nA (NA) and clonidine 80 nA (C). This neurone was depressed by noradrenaline but excited by clonidine. Time: 2 minutes.

onset than that caused by noradrenaline, usually 30-60 seconds. This does not imply that clonidine is 'less potent' an agonist than noradrenaline, since the iontophoretic transport numbers of clonidine and noradrenaline may be substantially different. Excitatory responses to clonidine were seen on 24 cortical cells and 7 medullary cells. These responses had latencies of 30-60 s, but the firing rate was often increased by 100% (Figure 2). As shown in this figure, cells excited by clonidine were usually depressed by noradrenaline.

Comparison of the responses to noradrenaline and clonidine on the same neurone (Table 2) showed that cells unaffected by noradrenaline were usually unresponsive to clonidine, those responding to noradrenaline also responding to clonidine. In fact, 79% of the cells responding to noradrenaline in the medulla responded in the same manner to the ejection of clonidine. If cells unaffected by both drugs are included, then this similarity of behaviour occurred on 84% of medullary units. On cortical cells the corresponding figures are 60% and 69%.

On 68 cells it proved possible to apply noradrenaline both before and after the ejection of clonidine in an attempt to detect any change in the response to noradrenaline produced by clonidine. The responses of most of these cells to noradrenaline were unaffected by clonidine. However, on three cells a greatly reduced response to noradrenaline was obtained after clonidine, suggesting it has an antagonistic action, and on seven cells a potentiation of noradrenaline was produced by clonidine (Figure 3). Whilst these effects of clonidine are interesting, the number of occasions on which they were observed is small

Table 2 Comparison of the effects of noradrenaline and clonidine on central neurones

Response to noradrenaline	*Response to clonidine*	*Number of cells*	
		Cortex	*Medulla*
D	D	66	30
D	O	32	5
D	E	15	4
O	D	9	1
O	O	54	19
O	E	2	0
E	D	0	0
E	O	0	0
E	E	7	3
Total		185	62

E, Excitation; D, Depression; O, No effect.

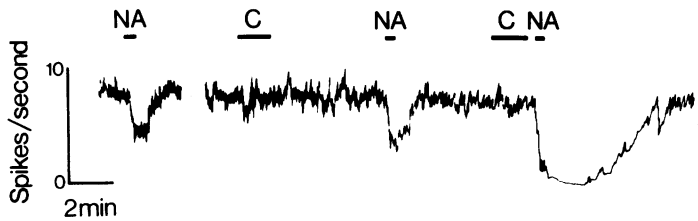

Fig. 3 Record of the firing rate of a cortical neurone in response to the iontophoresis of noradrenaline 65 nA (NA) and clonidine 65 nA (C). Clonidine ejected alone has no effect on the firing rate of the cell, which is depressed by subsequent application of noradrenaline. The noradrenaline response is clearly similar to the response obtained before any clonidine applications had been made. In this experiment, four such 'control' applications were made, including that illustrated. However, the iontophoresis of clonidine immediately prior to noradrenaline causes a large potentiation of that response. This effect was observed on seven cells. Time: 2 minutes.

and their significance is unclear. The clonidine was ejected for up to 2 min, but applications longer than this produced signs of non-specific depression involving a reduction of spike height.

Antagonism of noradrenaline and clonidine

Bulbocapnine has been shown by Gonzalez-Vegas & Wolstencroft (1971) to be an effective antagonist of the depressant responses to microiontophoretically applied catecholamines. In our experience, bulbocapnine can potentiate the effects of noradrenaline and dopamine on some cells but, nevertheless, does antagonize a high proportion of depressant responses to these amines. Figure 4 illustrates depressant responses to both noradrenaline and clonidine which were antagonized by iontophoretically applied bulbocapnine, whilst the depression produced by 5-hydroxytryptamine was left unaffected. Clonidine depressions were antagonized in this manner on all of ten medullary neurones in which depressant responses to noradrenaline were antagonized by bulbocapnine, and on 14 of 18 cortical cells in which noradrenaline responses were blocked.

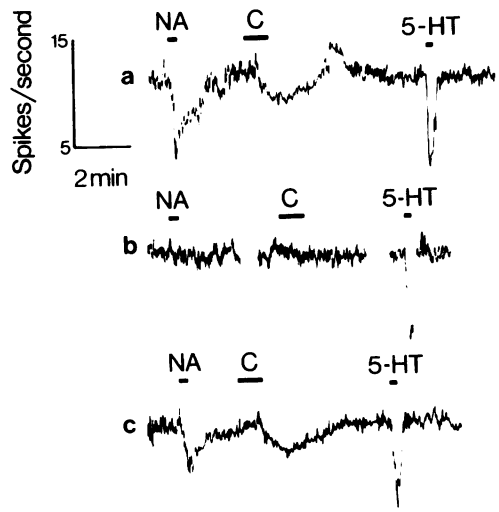

Fig. 4 Records of the firing rate of a cortical neurone in response to the iontophoresis of noradrenaline 60 nA (NA), clonidine 60 nA (C) and 5-hydroxytryptamine 60 nA (5-HT).

(a) shows initial responses to the three agents.

(b) each of the three traces in this series was begun immediately after the end of a 2 min application of bulbocapnine, 100 nA. The responses to noradrenaline and clonidine have been antagonized whereas the response to 5-hydroxytryptamine is unaffected.

(c) was begun 4 min after the 5-hydroxytryptamine ejection in (b), and shows the return of the noradrenaline and clonidine responses.

Current balancing was practised to rule out possible current artifacts. Time: 2 minutes.

Discussion

The finding that a majority of the cells studied in the present series of experiments responded in the same manner to the microiontophoresis of noradrenaline and clonidine, together with the antagonism of the depressant responses by bulbocapnine, suggests that, for the usually encountered depressions at least, they may be acting on the same neuronal receptors. The results, therefore, lend some support to the evidence of Schmitt, Schmitt & Fenard (1971b; 1972) that the hypotension produced by an action of clonidine on the central nervous system is due to an action of clonidine on noradrenaline receptors. It is particularly interesting that clonidine should depress most cells, as a depression of firing by

noradrenaline has been reported by several groups of workers both in cortex (Krnjević & Phillis, 1963; Lake, Jordan & Phillis, 1972; Nelson, Hoffer, Chu & Bloom, 1973; Stone, 1973a) and in the medulla of anaesthetized (Curtis & Koizumi, 1961) or unanaesthetized (Straschill & Perwein, 1971) preparations. The fact that some groups working on cortex (Johnson, Roberts, Sobieszek & Straughan, 1969) and medulla (Boakes, Bradley, Brooks, Candy & Wolstencroft, 1971) observed many excitatory responses has yet to be explained satisfactorily.

However, the pharmacological nature of the central noradrenaline receptors is uncertain. Many workers have successfully antagonized the hypotensive action of clonidine by means of α-adrenoceptor blocking agents such as phentolamine and piperoxane (Schmitt *et al.*, 1971b; 1972) but not by β-blockers (Schmitt, Fenard & Schmitt, 1971a). This is difficult to understand, since supposedly neuronal responses to microiontophoretically applied noradrenaline can be antagonized only occasionally by such 'conventional' antagonists (Johnson *et al.*, 1969; Boakes *et al.*, 1971; Stone, 1973a), and indeed β-blockers appear to be more successful in this respect than α-blockers (Stone, 1973a). However, it has been clearly shown that clonidine has a potent agonist action on α-adrenoceptors in the peripheral vasculature (Boissier *et al.*, 1968; Constantine & McShane, 1968) causing vasoconstriction, and the possibility needs to be investigated that peripherally administered clonidine may act partly by causing a vasoconstriction (via α-receptors) in the central nervous system, thereby altering neuronal activity. Zaimis (1970) has, in fact, demonstrated a reduction of cerebral blood flow during the administration of clonidine which occurs *before* the peripheral hypotension due to clonidine has developed.

It is certainly the case that the effects of clonidine were similar to those of noradrenaline more frequently in the reticular formation than in the cortex, and that the depressant responses to clonidine were antagonized more readily by bulbocapnine in the medulla. These facts may be a reflection of the apparently different pharmacologies of catecholamine depressant responses in the medulla and cerebral cortex (Boakes *et al.*, 1971; Stone, 1973a).

The number of occasions on which potentiation of noradrenaline by clonidine was observed was rather small and it is difficult to draw general conclusions, particularly because of the distorting effects of applications longer than two minutes. However, it may be noted that Salt (1972) has shown clonidine to be a potent inhibitor of the extraneuronal uptake process for noradrenaline in the periphery and the potentiation of noradrenaline might possibly be explicable on the basis of a similar action in the central nervous system.

The mechanism of the excitatory responses of neurones to clonidine is also uncertain. It is unlikely to be due to an antagonism by clonidine of tonically active noradrenergic inhibitory neurones, since clonidine very rarely antagonized noradrenaline in the present experiments and did not appear to do so on cells excited by clonidine. It is possible, however, that these excitations could be mediated by a presynaptic action of clonidine. Dollery & Reid (1973) have shown that 6-hydroxydopamine, which causes a degeneration of central catecholamine-containing neurones, greatly reduces the hypotensive response to clonidine. Since an interaction with possibly dopaminergic neurones has previously been shown to be unlikely by Bolme & Fuxe (1971), the observation of Dollery & Reid (1973) suggests that clonidine may interact at least in part with the noradrenaline-releasing neurones themselves rather than with the postsynaptic receptor. A reduction in the release of noradrenaline by sympathetic neurones in the presence of clonidine has been demonstrated by Starke, Wagner & Schümann (1972) and a reduced noradrenaline release from field-stimulated brain slices in the presence of clonidine by Farnebo & Hamberger (1971). Such a reduced release of noradrenaline from tonically active noradrenergic inhibitory neurones could explain the excitatory responses to clonidine on cells depressed by noradrenaline.

Briant & Reid (1972) have recently shown that desmethylimipramine, an inhibitor of noradrenaline re-uptake mechanisms, can antagonize the hypotensive effects of clonidine. This would support the idea that a reduction of noradrenaline release from central neurones could be part of the mechanism of action of clonidine.

A presynaptic action of clonidine could also explain the fact that peripherally administered clonidine seems to act on α-adrenoceptors in the central nervous system. The work of several groups (see Enero, Langer, Rothlin & Stefano, 1972; Starke, 1972) has implicated an α-adrenoceptor on the presynaptic membrane in a feed-back inhibition control of noradrenaline release. By stimulating those α-receptors clonidine could therefore inhibit noradrenaline release and this action would be antagonized by α-blockers (Starke & Altmann, 1973).

In conclusion, the present experiments support the suggestion that clonidine may have an agonist action on noradrenaline receptors in the central nervous system, causing an inhibition of neuronal activity. Shaw *et al.* (1971) have previously

provided evidence that clonidine acts at the medullary level to produce hypotension. The present experiments confirm that clonidine can affect unit activity in this area, but also show that other cells such as cortical units can be affected. It is possible that an action of clonidine on supramedullary areas such as cortex might account for the drowsiness and depression or euphoria which sometimes accompany its use in man (Connolly, 1970).

We wish to thank Boehringer Ingelheim Ltd for the gift of clonidine hydrochloride.

Please send reprint requests to Dr T.W. Stone.

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(Received January 10, 1974)