α -ADRENOCEPTOR BLOCKING DRUGS, PRESSOR RESPONSES TO NORADRENALINE, AND THE ANKLE JERK IN MAN

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1 Changes in pressor responses to infused noradrenaline and in triceps surae jerk amplitude have been measured after the i.v. administration of: chlorpromazine, thioridazine, prochlorperazine, dimethothiazine, indoramin, benzocetamine and clonidine.

2 Each of the drugs blocked pressor responses to noradrenaline and reduced triceps surae jerk amplitude, but little correlation was found between their potencies in the two systems.

3 The effects of the drugs on the triceps surae jerk are not incompatible with an action at a spinal α -adrenoceptor site, but other pharmacological factors may be involved, such as penetration of the drugs into the central nervous system, and differences in their uptake, blocking activity.

Introduction

The presence of noradrenergic bulbospinal pathways has been demonstrated in several species of animals (Dahlström & Fuxe, 1965) and suggested in man by the finding of suitable catecholamine-containing cell bodies in the medulla of the foetus (Nobin & Björklund, 1973). The role of those noradrenergic pathways which synapse with spinal motor cells in the control of muscle stretch reflexes is still controversial. Recent reports have suggested that they may have either facilitatory (Maxwell & Sumpter, 1974) or inhibitory (Commissiong & Sedgwick, 1974) activity.

Phillips, Richens & Shand (1973) showed that intravenously administered thymoxamine had a marked depressant effect on the triceps surae (ankle) jerk in normal human subjects, while propranolol produced no change in jerk size. Thymoxamine did not appear to affect maximal H reflex responses, and it was concluded that it could be acting by blockade of facilitatory pathways controlling fusimotor activity. Similar findings have been reported following administration of chlorpromazine (Brunia, 1973). Since thymoxamine has been reported to be a relatively selective α -adrenoceptor blocking agent (Birmingham & Szolcsanyi, 1965), it is possible that a noradrenergic spinal mechanism was involved.

The present study was designed firstly to determine whether, in man, drugs with α -adrenoceptor blocking activity consistently depress the triceps surae jerk, and secondly to explore the relationship between their α -adreno-

ceptor blocking potency in the cardiovascular system and their depressant effects on this monosynaptic stretch reflex.

Clonidine was included in the study because it has been reported to potentiate monosynaptic stretch reflexes in rats (Andén, Corrodi, Fuxe, Hökfelt, Hökfelt, Ryden & Svensson, 1970) although only with doses of 100 μ g/kg. It can also produce a transient hypertensive response after i.v. injection which is prevented by α -adrenoceptor blocking drugs (Kobinger, 1970). Some workers, however, have reported non-competitive α -adrenoceptor blocking activity by clonidine in human tissues at reasonably low concentrations (Coupar & Kirby, 1972).

Methods

The amplitude of the triceps surae jerk was measured isometrically using the method previously described by Phillips *et al.* (1973), modified to the extent that the subjects were lying instead of sitting. A standard tap was delivered to the Achilles tendon by a hammer dropped from a fixed height. The force produced by contraction of the triceps surae muscle was transmitted through the ball of the foot and a footplate to a Grass FT 10C strain gauge, and recorded on a Devices M2 recorder. The tendon jerk was elicited ten times at random intervals between 4-8 s, and the mean amplitude calculated for each set of readings.

The subjects were acclimatized by 15 min rest in position before two sets of control readings of tendon jerk amplitude, blood pressure and pulse rate were taken. Drug or placebo was given intravenously over 2 minutes. Further readings of jerk amplitude, resting blood pressure and pulse rate were taken at 5 and 10 min after the end of injection. The pressor responses to increasing doses of (–)-noradrenaline (Levophed, Winthrop) in 5% dextrose solution were then measured. Solutions of 8 or 12 µg/ml were delivered via an A23 oxytocin infusion set into an antecubital fossa vein, the rate controlled at 1.5 ml/min by a Watson-Marlow roller pump. Five minutes were allowed for blood pressure stabilization at each infusion rate before measurement using a standard sphygmomanometer. Mean blood pressure (diastolic + $\frac{1}{3}$ pulse pressure) was calculated and plotted against dose of noradrenaline. The shift in dose-response curves, expressed as a ratio of equieffective doses of noradrenaline after active drug and after placebo, was taken as a measure of α -adrenoceptor blockade.

The effects of the following seven drugs were measured: chlorpromazine hydrochloride (Largactil, May & Baker) 0.1 mg/kg, thioridazine hydrochloride (Melleril, Sandoz) 0.15 mg/kg, prochlorperazine mesylate (Stemetil, May & Baker) 0.1 mg/kg, dimethothiazine mesylate (Fusaban, May & Baker) 1.0 mg/kg, indoramin hydrochloride (John Wyeth & Bro.) 0.2 mg/kg,

benzocetamine hydrochloride (Tacitin, Ciba) 0.2 mg/kg, and clonidine hydrochloride (Catapres, Boeringer Ingelheim) 2 µg/kg.

All the drugs except clonidine ($n = 5$), benzocetamine ($n = 5$) and indoramin ($n = 11$) were given to six healthy volunteers on a randomized, balanced, double blind basis, using saline (0.9 w/v NaCl solution) as placebo. The same volunteers were not used to test all the drugs, so that a total of 18 subjects took part. Eleven were male, seven female. Their ages range from 20 to 35 years. Subjects gave a medical history, had their cardiovascular system examined and an ECG taken before experiments. Procedures were separated by at least 4 days.

The changes in triceps surae jerk amplitude after active drugs were expressed as a percentage change from control readings on that day, and changes at the same time after placebo subtracted. The significance of the mean differences in both triceps surae jerk amplitude and noradrenaline dose-responses was calculated using Student's paired t test.

Results

A reduction in the triceps surae jerk amplitude was seen after administration of each of the drugs, and this reached statistical significance with chlorpromazine, dimethothiazine, benzocetamine,

Table 1, % changes (mean $\pm$ s.e. mean) in triceps surae jerk amplitude, and mean dose ratios of noradrenaline $\pm$ s.e. mean of changes in dose, after injection of each of the drugs. Results at equivalent times after placebo have been subtracted. $n = 6$, except where stated. Previously published results after injection of thymoxamine (Phillips *et al.*, 1973) have been included for comparison.

Drug	Triceps surae jerk % changes			Noradrenaline dose ratios
	5 min	10 min	15 min	
Dimethothiazine (1.0 mg/kg)	–34 $\pm$ 13.4 NS	–39 $\pm$ 11.7 $P < 0.02$	–	1.40 $\pm$ 0.12 $P < 0.05$
Benzocetamine (0.2 mg/kg)	–22 $\pm$ 9.3 NS	–38 $\pm$ 7.2 $P < 0.01$	–	1.71 $\pm$ 0.22 $P < 0.05$
Chlorpromazine (0.1 mg/kg)	–29 $\pm$ 5.4 $P < 0.01$	–37 $\pm$ 3.7 $P < 0.01$	–	1.96 $\pm$ 0.32 $P < 0.05$
Clonidine (2.0 µg/kg)	–28 $\pm$ 12.5 NS	–23 $\pm$ 7.5 $P < 0.05$	–	see text
Indoramin (0.2 mg/kg)	–15 $\pm$ 6.4 NS ($n = 11$)	–22 $\pm$ 7.7 $P < 0.05$	–12 $\pm$ 6.1 NS ($n = 11$)	1.92 $\pm$ 0.18 $P < 0.01$
Prochlorperazine (0.1 mg/kg)	–40 $\pm$ 18.2 NS	–18 $\pm$ 8.2 NS	–	1.13 $\pm$ 0.16 NS
Thioridazine (0.15 mg/kg)	–3 $\pm$ 2.6 NS	–10 $\pm$ 4.9 NS	–	1.51 $\pm$ 0.14 $P < 0.02$
Thymoxamine (0.1 mg/kg)	–62 $\pm$ 5.0 $P < 0.005$			
Thymoxamine (0.2 mg/kg)	–71 $\pm$ 6.5 $P < 0.001$			

clonidine and indoramin. The mean percentage changes in jerk amplitudes are shown in Table 1.

Significant displacement to the right of noradrenaline pressor dose-response curves was found following injection of each of the drugs except prochlorperazine and clonidine (Table 1). The parallelism of the dose-response curves was felt to be satisfactory except on two occasions after clonidine. A plateau in response to increasing doses of noradrenaline was sometimes seen with relatively modest rises in mean blood pressure after active drugs. This was attributed to the unmasking of the β -agonist action of the larger doses of noradrenaline used during α -adrenoceptor blockade.

Injections of chlorpromazine (0.1 mg/kg), dimethothiazine (1.0 mg/kg) and benzocetamine (0.2 mg/kg) were followed by similar mean reductions in triceps surae jerk amplitude at 10 min after injection, while the mean displacement of noradrenaline dose-response curves after chlorpromazine was 2.40 times that after dimethothiazine and 1.35 times that following benzocetamine.

Assessment of the changes following prochlorperazine (0.1 mg/kg) was complicated by the development of marked and distressing restlessness, akathisia, in two of the six subjects. While reduction in jerk amplitude occurred in the other four subjects (mean $-26 \pm 9.8\%$, $n = 4$, NS), with diminished sensitivity to noradrenaline (mean dose ratio 1.39 ± 0.07 , $P < 0.05$), the two with akathisia had unchanged triceps surae jerks ($+1\%$ and -2% at 10 min after injection) and showed potentiation of the pressor responses to noradrenaline (dose ratios 0.56 and 0.74). Increases of $+29$ mmHg and $+22$ mmHg in the mean blood pressure of these two subjects occurred before infusion of noradrenaline.

Injection of clonidine ($2 \mu\text{g/kg}$) was followed by reduction of triceps surae jerk amplitude in all subjects. Changes in sensitivity to noradrenaline after this drug were variable, with individual dose ratios where calculable, of 1.52, 1.61, 5.12 and 0.61. In the other subject inhibition of pressor responses to noradrenaline occurred but the shape of the dose-response curves prevented quantitation.

Triceps surae jerk inhibition after indoramin (0.2 mg/kg) was less than that seen after all the drugs except thioridazine, but blockade of pressor responses to noradrenaline was marked and highly significant.

Changes in jerk amplitude after thioridazine were consistently small, although moderate reduction of pressor responses to noradrenaline occurred.

Sedation was seen after each of the drugs

except thioridazine, and it was particularly marked after chlorpromazine, dimethothiazine and indoramin. Some subjects slept through the experiment after receiving indoramin without change in triceps surae jerk size. Thioridazine produced no apparent central nervous effects.

Blood pressure and pulse rate

In the period after injection and before noradrenaline infusion, a significant mean change in resting pulse rate occurred only after chlorpromazine: $+16 \pm 5.5$ beats/min, $P < 0.05$, at 5 min, and $+16 \pm 5.0$ beats/min, $P < 0.05$, at 10 min after injection. No consistent changes occurred in resting blood pressure before noradrenaline infusion after any of the drugs.

Correlations

The results with clonidine were excluded from correlation analysis because two of the noradrenaline dose-response curves were unsatisfactory. Analysis of (a) group mean, and (b) all the individual, displacements of dose-response curves and reductions in tendon jerk amplitude after the remaining drugs using Pearson's correlation coefficient showed little correlation: $r = -0.21$, NS, and $r = 0.01$, NS, respectively.

Discussion

These experiments were designed to test the hypothesis that central noradrenergic pathways facilitate monosynaptic muscle stretch reflexes in man, by comparing the degree of depression of the triceps surae jerk produced by various drugs and their ability to block α -adrenoceptor mechanisms in the cardiovascular system.

Triceps surae jerk depression was seen after each of the drugs used, but little correlation was found between their potency as jerk depressants and their ability to block pressor responses to noradrenaline. The discrepancy was particularly marked when the effects of indoramin were compared with those of other drugs, since it had powerful cardiovascular α -adrenoceptor blocking activity but a relatively slight effect on the triceps surae jerk. The number of subjects receiving indoramin was increased to minimize possible bias due to between-subject variation of response.

Comparison with previously published results (Phillips *et al.*, 1973) suggests that thymoxamine was more potent than chlorpromazine in depressing the triceps surae jerk, and three times as potent as indoramin. Isolated tissue experiments have shown consistently that thymoxamine is a

weaker α -adrenoceptor blocker than chlorpromazine or indoramin (Birmingham & Szolcsanyi, 1965; Collis & Alps, 1973; Görlitz & Frey, 1973; Variava & Turner, 1973; Sugden, 1974).

Although the results do not appear to support the hypothesis that the spinal effects were mediated by blockade of a facilitatory noradrenergic pathway, two reservations in the interpretation of the results must be considered: (a) whether the drugs reached effective concentrations in the central nervous system, and (b) whether differences in the role of neuronal noradrenaline re-uptake (uptake₁; Iversen, 1967) at central and peripheral adrenergic synapses might account for the discrepancy between central and peripheral effects.

That all the drugs except thioridazine caused sedation within a few minutes of injection suggests that they were active at central nervous sites. It is possible that thioridazine did not so readily cross the blood-brain barrier since it caused no subjective effects. (The sedation caused by indoramin appeared to be as marked as that due to chlorpromazine. Degree of sedation did not correlate well with tendon jerk changes in the experiments.)

The suggestion that uptake₁ may be important depends on analogy with isolated tissue experiments, but does appear to be substantial. For reasons discussed below, it is likely that the effect of uptake₁ blockade on the vascular responses to noradrenaline will be relatively small in comparison with changes produced at central nervous synapses in noradrenaline concentrations. Since the vascular sympathetic plexus lies outside the tunica media of arteries and veins, and the vascular neuro-effector distances are generally much larger than the effective radius of the neuronal amine pump (Bevan & Su, 1973), the part played by uptake₁ in vascular noradrenaline clearance is probably small and usually not at all synapse-specific. De La Lande & Waterson (1967) demonstrated that in the rabbit ear artery the constrictor activity of intraluminally applied noradrenaline, which acts before reaching the neuronal plexus, is not changed by the blockade of uptake₁ mechanisms, while the activity of externally applied noradrenaline is much enhanced. In our experiments, noradrenaline was infused systemically at pharmacological concentrations. Under the same conditions in the dog the pressor effects of noradrenaline are somewhat potentiated by desmethylinipramine, but not through a simple local increase in vascular concentrations of the transmitter (Eble, Gowdey & Vane, 1970). In contrast, the noradrenaline concentrations at central nervous synapses in our experiments were in the physiological range, and

were presumably controlled by uptake₁ in the lower range of its activity.

Under those circumstances, the measured effects of each of the drugs at spinal noradrenergic synapses would represent α -adrenoceptor blockade counteracted by the degree of uptake₁ blockade due to the drug concerned, while the vascular effects would more nearly represent α -adrenoceptor blockade alone.

Information of the uptake₁ blocking activity of the drugs we have used is limited to chlorpromazine, indoramin, and thymoxamine (Sugden, 1974). It appears that the difference between effective α -adrenoceptor blocking and uptake₁ blocking concentrations of chlorpromazine and thymoxamine is large, whereas for indoramin it is relatively small.

The striking ineffectiveness of indoramin on the tendon jerk may therefore have resulted from its α -adrenoceptor blocking effect being counteracted by uptake₁ blockade, while in the vascular system it is as effective an α -blocker as isolated tissue experiments suggest it ought to be (Collis & Alps, 1973; Sugden, 1974).

Thus if uptake₁ blocking activity could be taken into account with all the drugs we have studied, the results could still be compatible with the hypothesis that they are acting on facilitatory noradrenergic pathways.

We cannot exclude the possibility that effects on neurotransmitters other than noradrenaline are involved. Bulbosplinal 5-hydroxytryptamine containing neurones may well have muscle stretch reflex augmenting activity (Andén, Jukes & Lundberg, 1964; Anderson & Shibuya, 1966; Anderson, Baker & Banna, 1967; Curzon, Ettlinger, Cole & Walsh, 1963; Oates & Sjoerdsma, 1960), although probably not by an action on the fusimotor system (Andén *et al.*, 1964; Ellaway, Pascoe & Trott, 1973). Recent studies on thymoxamine (Sugden, 1974) suggest that the difference between the noradrenaline and the 5-hydroxytryptamine blocking activity of this drug may not be as great as originally reported, and all the drugs we have used appear to have 5-hydroxytryptamine as well as α -adrenoceptor blocking activity. However, that both dimethothiazine (Julou, Ducrot, Bardone, Demaille, Feo, Guyonnet, Loiseau & Pasquet, 1966) and thioridazine (Haley, Flescher & Raymond, 1960) appear to possess greater 5-hydroxytryptamine than noradrenaline blocking activity in animal experiments, but produced relatively small changes in jerk amplitude in our studies, suggests that a 5-hydroxytryptamine mechanism might not be significantly involved.

The effects of clonidine in this study were: to depress the triceps surae jerk, and inhibit pressor

responses to noradrenaline in four subjects but potentiate them in one subject. There was no change in pulse rate or blood pressure prior to infusion of noradrenaline. It did have sedative activity. Clonidine has been reported not to affect pressor responses to noradrenaline in the anaesthetized rabbit (Hoefke & Kobinger, 1966). The mechanism whereby it reduced triceps surae

jerk amplitude at a dose of 2 μ g/kg is uncertain.

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