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COMMENTARY

ALPHA-ADRENERGIC DRUGS

PHARMACOLOGICAL TOOLS FOR THE STUDY OF THE CENTRAL VASOMOTOR CONTROL

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The role of the CNS in regulating arterial pressure has been known for more than a century. Alexander [1] using electrical stimulations managed to systemise vasopressive and depressive medullary areas (Fig. 1). He described a pressive zone in the rostral two-thirds of the medulla oblongata lying in the lateral reticular formation and a depressive zone in the caudal third of the medulla in the median position.

Since then, numerous works have more clearly identified the organization of the central regulation of arterial pressure. The nucleus of the solitari tract (NTS) was identified as the first relay of the afferent fibres of arterial baroreceptors [2]; then the anterior hypothalamic area was found to be the second relay in the baroreceptor reflex arc which, when stimulated electrically, provokes a fall in arterial pressure [3]. The locus coeruleus also affects the baroreceptor reflex, partly via projections into the posterior hypothalamus [4]. Electrical stimulation of both these regions results in an increase in arterial pressure.

A ventromedullary-located structure coinciding with the lateral reticular nucleus also acts as a baroreceptor relay, while the descending pathways seem to converge towards the intermedio-lateral nucleus of the spinal cord [5]. Palkovits and Zaborsky proposed a schema summing up present knowledge of

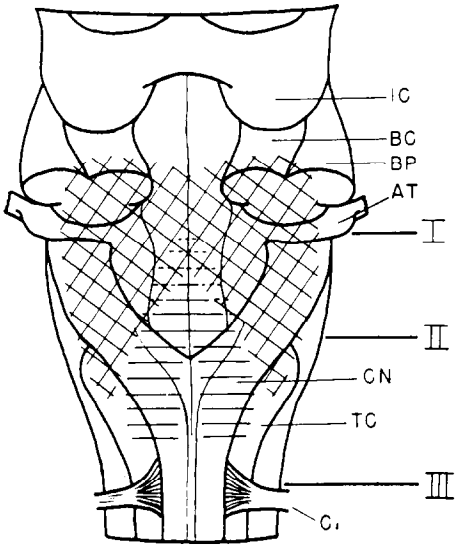

Fig. 1. Localization of pressor (cross-hatching) and depressor (horizontal ruling) centers in the brain stem of the cat. IC, inferior colliculus; BC, brachium conjunctiva; BP, brachium ponti; AT, auditory tubercle; CN, cuneate nucleus; TC, tuberculum cinereum; C_1, first cervical nerve (from Alexander [1]).

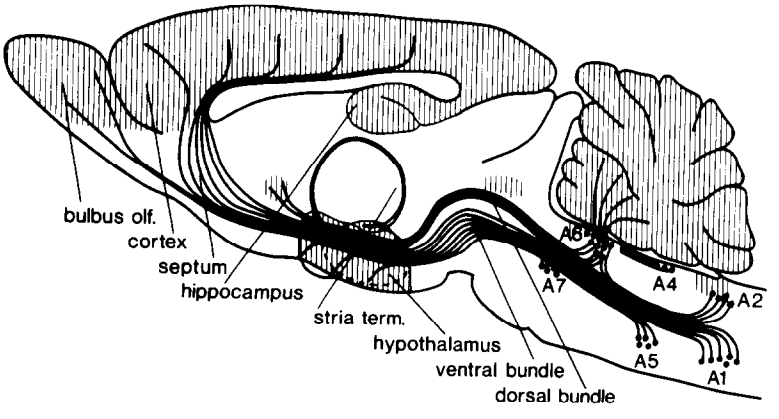

Fig. 2. Sagittal projections of the ascending noradrenergic pathways in the brain. The strips indicate the major nerve terminal areas (from Ungerstedt [7]).

the connections between these various structures [5].

At least three monoaminergic neurotransmitters have been directly implicated in the functioning of these structures.

Mapping of the catecholaminergic structures shows that in the rat, the NTS (area A_2), the locus coeruleus (area A_6), the posterior and anterior hypothalamus, and the lateral reticular nucleus (NRL) (area A_1) correspond to areas rich in noradrenaline (Fig. 2). These noradrenergic areas seem to be similarly disposed in the rat, the cat, the squirrel monkey and the rabbit [6–11]. Areas have also been reported which contain PNMT and which are therefore probably adrenergic adjoining structures involved in regulating arterial pressure: the NTS, the hypothalamus, the dorsal nucleus of the vagus (NDV) and the lateral column of the spinal cord [12] (Fig. 3). According to Palkovits *et al.* [13], serotonin also occurs in almost all of these structures, especially in the NTS and NRL.

Several authors have attempted to systematize the functional organisation of the central structures involved in cardiovascular regulation. The NTS and the anterior hypothalamus are generally considered as inhibitory structures: stimulating them electrically leads to a reduction in arterial pressure, whereas the NRL and posterior hypothalamus are considered as pressor zones. These observations led Korner [14], Chalmers [15], Spyer [16] and Palkovits and Zaborsky [5] among others to put forward schemas illustrating how this regulation works. That of Isaac [17] summarises what is generally accepted in this field (Fig. 4). However, the medullary pressor and depressor centres should perhaps not be too readily assimilated to histologically determined structures. Neumayr *et al.* [18], for example, revealed a pressor zone at the level of the NTS–NDV complex, whereas this is usually considered solely as inhibitory.

Centrally acting catecholaminergic molecules have proved highly active in treating arterial hypertension. This is so for clonidine and for alpha-methyldopa which is considered to act via its metabolite, alpha-methylnoradrenaline. These drugs have taken over from reserpine, long known to interfere with central catecholamines, at least as regards its neuroleptic activity.

Here, we shall describe and discuss the central action sites and mechanisms of alpha-adrenergic agents (with the exception of the reserpinic ones).

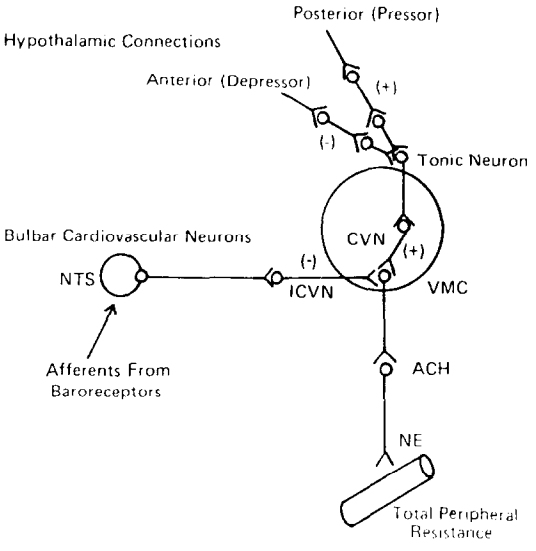

Fig. 4. Relationships between hypothalamic areas and bulbar cardiovascular neurons; stimulation of the anterior hypothalamus inhibits (−) activity of the excitatory cardiovascular neuron (CVN); stimulation of the posterior area enhances (+) activity of the DVN. VMC, vasomotor center; NTS, nucleus tractus solitari; ICVN, inhibitory cardiovascular neuron (from Isaac [17]).

Noradrenaline

It is generally accepted that noradrenaline, which is present in all the structures involved in the central regulation of arterial pressure, has a hypotensive action when injected directly into the brain, either intracerebroventricularly or intracisternally [19–21]. Its effects vary, however, according to the species, the anaesthesia techniques and the way of administration. For example, in the conscious monkey perfusing noradrenaline into the third ventricle regularly provokes hypertension; in the pentobarbital-anaesthetized monkey this hypertensive response is less marked [22]. When injected into the rat brain, noradrenaline is also hypertensive [23]. We have observed that intracisternally administered noradrenaline at cumulative doses from 1 to 100 μg/kg provokes hypotension in the pentobarbital-anaes-

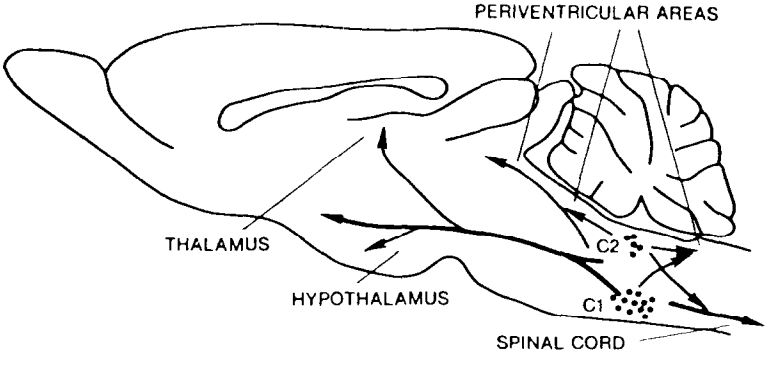

Fig. 3. Schematic illustration of the adrenaline pathways (from Hökfelt *et al.* [12]).

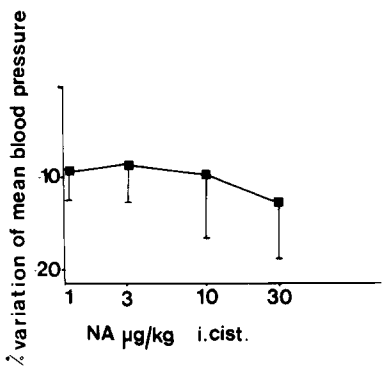

Fig. 5. Decrease in the mean blood pressure obtained with cumulative doses of noradrenaline intracisternally injected into the pentobarbital-anesthetized rabbit (data are the means ± S.E.M. of five experiments).

thetized rabbit, although this never exceeds 15% and is not dose-dependent (Fig. 5).

Philippu *et al.* [24] observed that electrical stimulation of the posterior hypothalamus results in an increase in noradrenaline release accompanying the hypertensive response and Zawoiski [25] reported a hypertensive response to injecting noradrenaline into the rat posterior hypothalamus. According to De Jong [26], and Kubo and Misu [27], noradrenaline injected directly into the NTS is hypotensive. We have never found any hypotension whatever the dose of noradrenaline applied to the NRL (Fig. 6). All in all, we have found the central pressure effects of noradrenaline to be very irregular. Opposite effects on different sites or the involvement of distinct pre- and post-synaptic $alpha_1$- and $alpha_2$-receptors may explain the variable effects of noradrenaline.

Alpha-methylnoradrenaline

This pharmacological tool was first of all considered as a false neurotransmitter because it is less active on the peripheral alpha-receptors than noradrenaline itself [28]. But now, it is clearly established that this substance has central cardiovascular actions. Nevertheless, its cardiovascular effects vary when it is injected intracerebroventricularly or intracisternally into an anaesthetized animal. Heise and Kroneberg [29, 30], however, reported a moderate hypotensive effect of the substance after long-term perfusion of cat brain cavities. Day and Roach [19] also reported hypotension when they injected alpha-methylnoradrenaline into the lateral ventricle of the conscious cat. Finch *et al.* [28] revealed a central hypertensive effect of alpha-methylnoradrenaline in the cat. We have also observed in the anaesthetized cat and rabbit that alpha-methylnoradrenaline injected intracerebroventricularly or intracisternally has a hypertensive effect (Fig. 7). Nevertheless, when injected directly into the nucleus of the solitari tract in low doses (2 µg/kg), it does provoke very marked hypotension in the anaesthetized rat [27, 31]. This is considered as the result of stimulating $alpha_2$-receptors in this region; yohimbine blocks the effect of alpha-methylnoradrenaline injected in the NTS which seems to be the essential site of its central action whereas prazosin does not antagonize this effect [27]. Moreover, in binding assays and in isolated organs alpha-methylnoradrenaline seems to be one of the most selective $alpha_2$-agonists known [32, 33].

Clonidine

Clonidine is an imidazolidine synthetized to develop a peripheral alpha-stimulant.

It does have an important vasoconstrictive effect by stimulating $alpha_1$- and $alpha_2$-receptors of the vascular wall [34]. Indeed, this peripheral hypertensive effect is blocked by $alpha_1$-blockers such as prazosin and by $alpha_2$-blockers such as yohimbine. It is also, however, the most powerful central hypotensive drug known to date. Its pharmacological profile poses numerous problems. It has the same type of selectivity as alpha-methylnoradrenaline. It has roughly 10 times more affinity for $alpha_2$- than for $alpha_1$-receptors, both in binding assays and in isolated organs [32]. Despite that, clonidine has practically no hypotensive action when injected in the NTS. Kubo and Misu [27] injecting clonidine directly into the NTS only obtained a hypotensive effect at

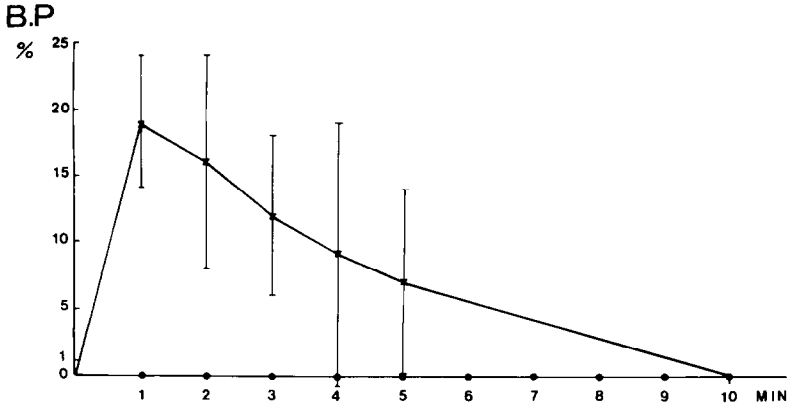

Fig. 6. Blood pressure effect of noradrenaline applied in the NRL region of the pentobarbital-anesthetized cat. A low dose (10 µg/kg) (●) does not change the mean blood pressure; a high dose (80 µg/kg) (×) increased the mean blood pressure (values are expressed as means ± S.E.M. of five experiments).

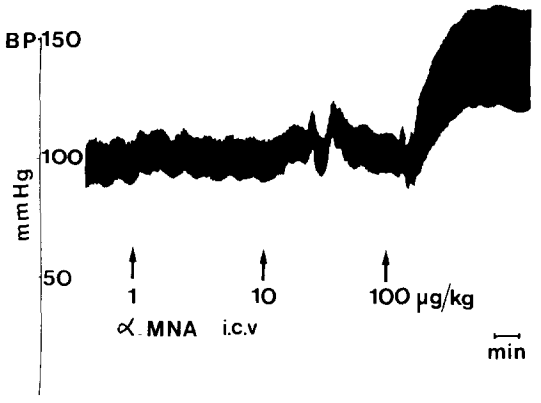

Fig. 7. Cat (3 kg). Alpha-methylnoradrenaline (α-MNA) injected intracerebroventricularly (i.c.v.) into a pentobarbital-anesthetized cat produces an increase in blood pressure at a dose of 100 µg/kg.

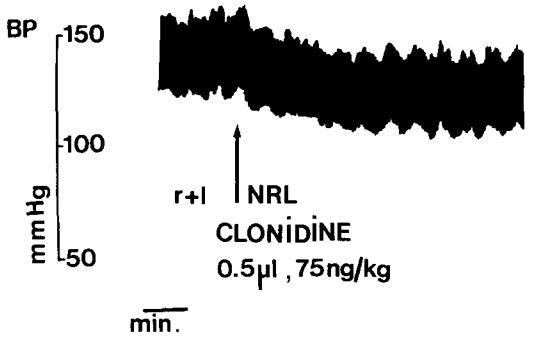

Fig. 8. Cat (2.9 kg) anesthetized with pentobarbital. Hypotensive effect of a bilateral microinjection of 75 ng/kg of clonidine in the nucleus reticularis lateralis (NRL). r, right; l, left (after Bousquet *et al.* [37]).

doses of 100 µg/kg. On the contrary, what may be the sole action site of clonidine lies in the ventral region of the medulla at the level of the NRL [35–39]. This region is characterised as a vasopressive centre having connections with the hypothalamus,

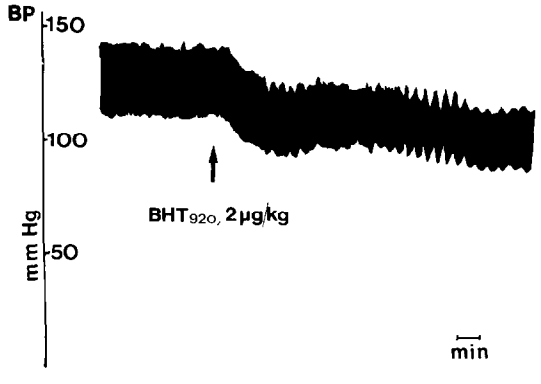

Fig. 9. Cat (3.2 kg) anesthetized with pentobarbital. Hypotensive effect of a bilateral microinjection of 2 µg/kg of BHT920 in the nucleus reticularis lateralis.

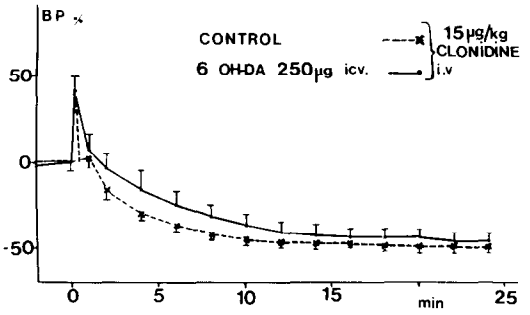

Fig. 10. Variation of the mean blood pressure obtained in the pentobarbital-anesthetized rat, with a standard dose of i.v. clonidine without and after 6-OH dopamine (6 OH-DA) pretreatment (N = 5 in each group).

the NTS and the intermedio-lateral nucleus of the spinal cord in particular [5, 40]. At this level, clonidine has a hypotensive effect at doses some 1000 times lower than those required in the NTS [37] (Fig. 8). Conversely, alpha-methylnoradrenaline (from 1 to 50 µg/kg) has no effect at the level of the NRL, whereas other alpha$_2$-selective agents such as BHT920 and BHT933 are hypotensive there (Fig. 9).

Of course, the cardiovascular effects of central origin of an alpha$_2$-stimulant might be due to pre- or post-synaptic actions within the brain. Certainly, the central hypotensive action of clonidine is known to be mediated only by post-synaptic receptors since treatment with 6-hydroxy dopamine, which destroys the noradrenergic nerve endings, does not affect the central effects of clonidine in the rat [41] (Fig. 10). Similar observations have been reported for prior treatment with reserpine or alpha-methyl-*para*-tyrosine which inhibit the functioning of the noradrenergic nerve endings [42]. So, we should follow Kobinger and others in recognising that central presynaptic alpha$_2$-receptors are not involved in the hypotensive effect of clonidine [43]. The latter is antagonized by alpha$_2$-blockers (yohimbine, piperoxan) [44]. However, despite the alpha$_2$-selectivity of clonidine, several authors showed that, under some circumstances, prazosin (a specific alpha$_1$-blocker) could also prevent the hypotensive effect of that drug [45–48].

In fact, stimulation of the alpha$_2$-receptor type does not account for all the pharmacological data on the hypotensive effect of clonidine.

The other alpha-agonists

Other reputedly specific alpha$_2$-agonists such as BHT920 and BHT933 are hypotensive when administered directly into the CNS of an anaesthetized animal [49, 50]. On the contrary, other alpha$_2$-agonists, such as naphazoline and oxymetazoline, are not hypotensive when injected intracisternally into the anaesthetized dog [51]. The situation is hardly any clearer for the alpha$_1$-agonists. Methoxamine has a hypertensive effect in the anaesthetized rabbit when injected intracerebroventricularly [52]. Phenylephrine is hypertensive in the rabbit according to some authors [52] and hypotensive for others [53]

when administered directly into the brain of the anaesthetized dog.

The alpha-blockers

The irregular pressure effects of noradrenaline injected centrally (intraventricularly or intracisternally), and the fact that it has no hypotensive effect when injected directly into the NRL, might be due to there being two functionally opposed alpha-receptor populations, the $alpha_1$-receptors being hypertensive and the $alpha_2$ hypotensive.

It is known from studies on binding and on isolated organs that noradrenaline has virtually equal affinity for $alpha_1$- and $alpha_2$-receptors [32]. The use of specific alpha-blockers should shed some light on this problem. In the anaesthetized rabbit, noradrenaline administered intracisternally has only a minor hypotensive effect which is not dose-dependent. But, after pretreatment with yohimbine, noradrenaline becomes very clearly hypertensive. Prazosin prevents this effect, since pretreatment with a mixture of yohimbine and prazosin prevents noradrenaline injected intracerebroventricularly from having any hypertensive effect on arterial pressure (Fig. 11). So, the two distinct effects of noradrenaline do indeed seem to be dissociated.

The central actions of the alpha-blockers seem fairly clear for the $alpha_2$-blockers since they are hypertensive when administered intracerebroventricularly for example. On the contrary, the actions of the $alpha_1$-blockers are less clear since for some in conscious rats they are also hypertensive [54] and for others they are rather weakly hypotensive [55, 56]. Here though, it should be pointed out that, for Cavero *et al.* [55], even part of the action observed after intracerebral injection of prazosin can be attributed to a leakage of the drug into the systemic circulation.

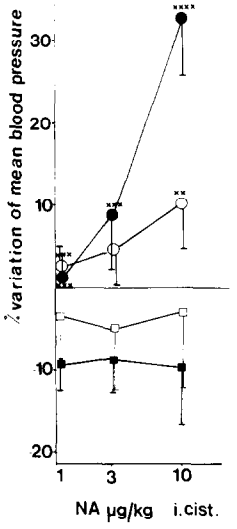

Fig. 11. Variation of the mean blood pressure of normotensive rabbits anesthetized with pentobarbital after intracisternal (i.cist.) injection of cumulative doses of noradrenaline. Measurements of the maximal effect of each dose of noradrenaline were made 10 min after the drug injection. In control animals (■) noradrenaline produced hypotension (N = 5). In animals pretreated with yohimbine [(○) 10 µg/kg (N = 5); (●) 100 µg/kg (N = 5)] injected i.cist. 30 min before noradrenaline, it provoked a dose-related hypertension. In animals pretreated with yohimbine (100 µg/kg) + prazosin 10 µg/kg (□), noradrenaline did not provoke any hypertension (N = 5).

Concluding remarks

Several central structures are known to be involved in the baroreceptor reflex arc.

Although they may have opposite functions, most of these neuronal structures contain catecholamines (anterior and posterior hypothalamus, locus coeruleus, NRL, NTS etc.). Several neurotransmitters are known to play a role in the central regulation of blood pressure: serotonin, GABA, histamine, glutamic acid, endorphin, substance P. Nevertheless, noradrenergic mechanisms appear to predominate. The importance of the catecholaminergic mechanisms is supported by the fact that all the central acting drugs used in the antihypertensive therapy interfere with catecholaminergic receptors.

The present review of the actions of central origin of alpha-adrenergic substances on arterial pressure brings out the disparity in experimental data in this domain.

Indeed, while substances such as clonidine have qualitatively reproducible cardiovascular actions according to the species and the conditions of anaesthesia, this is not so for other substances with a similar pharmacological profile, such as alpha-methylnoradrenaline. Noradrenaline, itself, an endogenous alpha-adrenergic substance, has variable central cardiovascular effects. Subclassifying the alpha-receptors into distinct groups might have enabled a better understanding of the action mechanism of the central hypotensive alpha-adrenergic agents: pre and post-synaptic receptors, $alpha_1$- and $alpha_2$-receptors according to the affinities of adrenergic drugs.

In fact, there is a large body of evidence for alpha-methylnoradrenaline and clonidine having a post-synaptic action site. Moreover, it is generally accepted that the hypotensive effect of noradrenaline and alpha-methylnoradrenaline injected into the NTS is linked with the stimulation of $alpha_2$-receptors.

On the other hand, clonidine, reputedly a specific agonist of the $alpha_2$-receptors, has practically no effect at the level of the NTS but acts rather in a structure both topographically and functionally opposed to the NTS, namely the NRL. At this level, clonidine is clearly hypotensive, whereas alpha-methylnoradrenaline is not, while the BHT series of substances (other specific $alpha_2$-agonists) are.

The concepts drawn from this subclassification do not, therefore, entirely account for the action mechanism of these central hypotensive drugs, least of all for clonidine. It should be added that the concept of specificity in this domain is very relative. Whereas for several years clonidine was the reference $alpha_2$-agonist, even the choice ligand for labelling and characterising or even defining receptors, we know today that at the periphery, in any case, its vasoconstrictive effect may well be linked with the

stimulation of two receptor populations: alpha$_1$- and alpha$_2$-receptors [34].

Yohimbine, rauwolscine and piperoxan which are used as alpha$_2$-antagonists have enabled the characterisation of numerous pharmacological effects, among them, the hypotensive effect of clonidine as resulting from the stimulation of alpha$_2$-receptors. These drugs however have a relative alpha$_2$-specificity, *in vivo* and *in vitro*, over a very limited range of concns [57–59].

In vitro, phenylephrine, reputedly a specific alpha$_1$-agonist, exhibits presynaptic alpha-adrenoceptor agonism and beta-stimulating properties at the concns at which it has its alpha$_1$-stimulating effects [60].

Nevertheless, alpha-methylnoradrenaline remains the most alpha$_2$-selective drug and prazozin the most alpha$_1$-selective drug.

In other words, incorrect interpretations or oversimplified interpretations of experimental data may be due to the use of scarcely selective pharmacological tools.

The lack of selectivity seems even more important at the doses used in the *in vivo* experiments. Moreover, some adrenergic substances in the imidazoline series may be partial agonists. According to Ruffolo *et al.* [61], clonidine for instance has barely 30% of the intrinsic activity of phenylephrine in the rat aorta. Thus, in *in vivo* experiments, substances like clonidine might even be both agonists and antagonists.

A certain measure of prudence would then have been advisable in interpreting the results of pharmacological experiments on alpha-adrenergic substances with a central hypotensive action.

Since prazosin is the alpha-blocker with the highest specificity for a given type of receptor, McGrath for example suggested adopting as a criterion the resistance to antagonism by prazosin rather than that of antagonism by yohimbine to characterize an alpha$_2$-mechanism [57]. If this criterion were to be applied to what is known of the hypotensive action of clonidine, one could only conclude that it lacked alpha$_2$-specificity. Indeed, according to several authors [45–48] prazosin can, under some circumstances at least, antagonize the central hypotensive action of clonidine.

One can thus see better why, after a period when most authors concluded unequivocally that the hypotensive action of clonidine was due to an alpha$_2$-type of mechanism, we are today entering a period when interpretations show more nuance. Most authors recognize that, if clonidine acts at the level of cerebral noradrenergic synapses, it is probably at the post-junctional level that it induces vasomotor effects [43]. Some however now believe that its hypotensive action is perhaps not so specific as regards the subtype of alpha-receptors involved as was first thought.

Tsoucaris-Kupfer *et al.* pointed out as early as 1980 that experiments intended to antagonize the hypotensive effect of clonidine gave variable results according to the species [62]. Those authors therefore suggested that characterising antagonists of the effects of clonidine was in no way sufficient to determine the receptors involved.

Quite recently, Beckett and Finch suggested that, in the hypertensive cat, the central hypotensive effect of clonidine might involve both alpha$_1$- and alpha$_2$-receptors [48].

On the other hand, it is accepted that the action mechanism of alpha-methylnoradrenaline involves the alpha$_2$-receptors at the level of the NTS, but we still do not know the reasons for the disparity in its cardiovascular effects when administered into the brain cavities. In other words, the mere notions of affinity or specificity for the alpha$_2$-receptors are not enough to explain the action mechanisms of these drugs. The notion of selectivity might offer a better explanation of the facts in this domain, as our results with noradrenaline seem to indicate. Noradrenaline has a central hypotensive effect apparently linked with the stimulation of alpha$_2$-receptors; after these alpha$_2$-receptors have been blocked with yohimbine, it has a hypertensive effect antagonised by prazosin. There is, therefore, some justification for suggesting that two populations of alpha-receptors may exist in the brain: the alpha$_2$-receptors being depressors and the alpha$_1$-receptors pressors. In this case, an alpha-adrenergic drug would be all the more centrally hypotensive as it would have both the greatest affinity for the alpha$_2$-receptors and the lowest affinity for the alpha$_1$-receptors, i.e. it would have the greatest alpha$_2$-selectivity. This argument does not however seem applicable to clonidine itself since part of its hypotensive effect is antagonized by prazosin, whereas it would apply to alpha-methylnoradrenaline. Like someone before us [57], we can only suggest in conclusion that the hypotensive effect of clonidine might involve alpha$_3$- or gamma-receptors.

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