Central sympathetic transmitters and hypertension

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Summary

1. The aim of this presentation has been to review the current status of some central neurotransmitter mechanisms in the control of arterial blood pressure and in experimental hypertension. In addition, anti-hypertensive drugs with centrally mediated actions have been considered.

2. There is ample evidence for a role of central noradrenaline mechanisms in central cardiovascular regulation. The catecholamine precursor, L-3,4-dihydroxyphenylalanine, lowers blood pressure by activating sympatho-inhibitory noradrenergic mechanisms in the lower brain stem. The receptors mediating this effect conform to the α-adrenergic type in peripheral tissues. Central noradrenaline receptors also appear to influence blood pressure at suprabulbar levels in the brain. Evidence is accumulating that central adrenergic receptors of the β type are also implicated in cardiovascular control. Central dopamine, 5-hydroxytryptamine and acetylcholine neurons are possibly involved in circulatory regulation but their precise role is less clear at present.

3. Considerable work has been done attempting to relate alterations in central neurotransmitter function to arterial hypertension. Central noradrenaline neurons appear to participate in the origin and maintenance of neurogenic hypertension. This may also be the case for other types of experimental hypertension but the results are less conclusive.

4. Anti-hypertensive drugs may act by interfering with central neurotransmitter function. The action of L-α-methyl-3,4-dihydroxyphenylalanine (methyl dopa) is largely mediated through an activation by its metabolite, methylnoradrenaline, of noradrenalineline mechanisms in the lower brain stem. The central noradrenaline agonist, clonidine, probably acts in an analogous way although some evidence indicates that this drug may influence blood pressure at several levels of central cardiovascular control.

Key words: dihydroxyphenylalanine, hypertension, methylnoradrenaline, neurotransmitters.

Introduction

The sympathetic nervous system holds a key position with regard to the control of arterial blood pressure. The significance of the peripheral division of the sympathetic system and its neural transmission mechanisms in circulatory homeostasis is by now fairly well recognized but the neurochemical processes underlying central sympathetic control are poorly understood. This is also true of the relations, if any, of such mechanisms to arterial hypertension. In view of the uncertainty thus implied it may seem premature to introduce the term central sympathetic transmitters and, even more so, to implicate mechanisms of this kind in the pathogenesis of hypertension. The aim of this presentation will be to review the current status of central neurotransmitter mechanisms in the control of blood pressure with a bias towards the author's own research in the field. Secondly, some interrelations of central neurotransmitter function and arterial hypertension will be considered and additional regard will be paid to anti-hypertensive drugs with centrally mediated hypotensive actions.

Among central transmitters involved in sympathetic control the catecholamines, dopamine and, in particular, noradrenaline seem to be of significance, while the role of 5-hydroxytryptamine mechanisms...
appears somewhat more difficult to evaluate at present. The same is true of other central neurotransmitters, e.g. acetylcholine. The evidence relating catecholamines and 5-hydroxytryptamine to a function as central neurotransmitters is beyond the scope of this review (see e.g. Bloom & Giarman, 1968; Andén, Carlsson & Häggendal, 1969). However, a brief consideration of the general morphology of central neurons containing catecholamines or 5-hydroxytryptamine is of interest (cf. reviews by Hillarp, Fuxe & Dahlström, 1966; Anden et al., 1969; Fuxe, Hökfelt & Ungerstedt, 1970). The cell bodies of these neurons are almost entirely confined to the lower brain stem, i.e. medulla oblongata, pons and mesencephalon. Their terminals are with varying density distributed in nearly all parts of the brain and the spinal cord. Several discrete monoamine neuron pathways have been mapped out, e.g. descending noradrenaline and 5-hydroxytryptamine pathways from the medulla oblongata innervating the grey matter of the spinal cord, notably the sympathetic lateral column. Another system of noradrenaline neurons forms ascending pathways which also originate in the brain stem, innervating not only cortical structures (neocortex, hippocampal formation and cerebellar cortex) but in addition subcortical brain parts involved in the regulation of autonomic and neuro-endocrine functions (e.g. the hypothalamus and the preoptic area). Within the brain stem are found short noradrenaline and 5-hydroxytryptamine neurons which seem to innervate, inter alia, brain-stem autonomic nuclei. It is evident from this survey that there exists at least an anatomical background for a central mediation of autonomic function through catecholamine- and 5-hydroxytryptamine-containing neurons.

Neurotransmitter mechanisms

Central neurotransmitters and sympathetic control

A number of early studies suggested that central catecholamine mechanisms might be involved in cardiovascular control but firm evidence was provided by the use of amino acid precursors of catecholamines in combination with selective inhibitors of various steps in their biosynthesis and correlating drug-induced changes in tissue monoamine concentrations with blood pressure recordings in conscious animals (review by Henning, 1973). The use of so-called peripheral decarboxylase inhibitors has been of particular importance since they inhibit the enzyme activity only outside the central monoamine neurons.

When the enzyme dopa decarboxylase in peripheral tissues is inhibited, L-3,4-dihydroxyphenylalanine (L-dopa) produces a hypotensive response, accompanied by an accumulation of dopamine in the brain. This is diminished and the hypotensive effect is abolished when dopa decarboxylase is inhibited both peripherally and centrally by other compounds entering the central nervous system, demonstrating that the lowering of blood pressure is mediated by an action of dopamine or noradrenaline (or both) formed from L-dopa in the central nervous system (Henning & Rubenson, 1970a, b). This has since been amply verified in a number of animal species (see Watanabe, Judy & Cardon, 1974) and probably serves to explain the occurrence of hypotension as a side-effect in the treatment of Parkinson's disease with L-dopa. Selective inhibition of the enzyme catalysing the synthesis of noradrenaline from dopamine, dopamine β-hydroxylase, was found to prevent the hypotensive response to L-dopa after peripheral decarboxylase inhibition in the rat (Henning & Rubenson, 1970b). Thus central noradrenaline mechanisms are most likely implicated, as also indicated by the finding that agents which block central dopamine receptors do not prevent the hypotensive action of L-dopa.

These observations permit the conclusion that activation of central noradrenaline receptor mechanisms mediates a decrease in arterial blood pressure. The characteristics of this noradrenaline receptor stimulation have been studied in experiments involving a depletion of endogenous noradrenaline stores by pretreatment with large doses of α-methyl-m-tyrosine in combination with inhibition of noradrenaline synthesis through α-methyl-p-tyrosine. Exhaustion of central catecholamine stores in this manner does not influence the basal blood pressure initially, but the administration of L-dopa is not followed by hypotension (Rubenson, 1971). Furthermore, the lowering of blood pressure cannot be reproduced after repeated injections of L-dopa (tachyphylaxis). These findings suggest that the effect of L-dopa is mainly indirectly mediated via a displacement of noradrenaline by the dopa formed from L-dopa (Rubenson, 1971). Inhibition of monoamine oxidase greatly enhances the hypotensive action of L-dopa and also appears to abolish the phenomenon of tachyphylaxis (M. Henning & G. Trolin, unpublished work).
There are also results available, which, to a certain extent, permit a localization within the central nervous system of the hypotensive effect of L-dopa after peripheral decarboxylase inhibition. This action persists after transection of the brain stem at mid-collicular level, thus excluding the diencephalon and cortical structures as possible sites of action and suggesting that brain-stem or spinal structures are responsible (Henning, Rubenson & Trolin, 1972). The possible contribution of spinal noradrenaline mechanisms is of interest in view of the dense innervation of the spinal sympathetic centre. This has been evaluated by local treatment with 6-hydroxydopamine, which causes a degeneration of catecholamine neurons, among others. In a 6-hydroxydopamine treatment schedule which reduced spinal noradrenaline levels to about 10% of control values, the hypotensive response to L-dopa was somewhat attenuated, suggesting a contribution of spinal noradrenaline mechanisms (Henning, Pernevi & Trolin, 1974). However, a major part of the effect is apparently located cranial to the sympathetic outflow from the spinal cord, most probably residing in brain-stem structures. Histochemical studies have demonstrated the existence of cell bodies (Dahlström & Fuxe, 1964) as well as a high density of catecholamine terminals (Fuxe, 1965) in, for example, the nucleus of the tractus solitarius and in the dorsal nucleus of the vagus; these brain loci are well known to participate in the central mediation of baroreceptor reflexes (see Chalmers & Wurtman, 1971). Bilateral lesions of these structures result in a severe arterial hypertension in which central catecholamine mechanisms are involved (Reis, Doba & Amer, 1973).

The mechanism by which L-dopa lowers blood pressure appears to be by diminishing the activity of the sympathetic system. The possible role of alterations in vagal activity is difficult to assess; however, the hypotensive response to L-dopa is usually accompanied by a bradycardia. No studies of the various influences on blood pressure (i.e. cardiac output and peripheral vascular resistance) seem to have been performed. L-Dopa causes a reduction of the directly recorded efferent preganglionic sympathetic discharge which parallels the fall in blood pressure (Watanabe & Cardon, 1971; Watanabe et al., 1974; Schmitt, Schmitt & Fénard, 1973). The nature of the central noradrenaline receptors mediating the hypotensive response to L-dopa has not been established but there is indirect evidence to suggest that they conform to the α-adrenergic type in peripheral tissues; the hypotensive action of L-dopa is antagonized by e.g. piperoxan and yohimbine (Schmitt, Schmitt & Fénard, 1972). Further evidence for an α-adrenergic nature of these receptors comes from studies with clonidine, which will be discussed below. An increasing body of evidence points to central components being implicated in the anti-hypertensive action of β-adrenergic-receptor-blocking agents (see e.g. Kellihier & Buckley, 1970; Stern, Hofman & Braun, 1971; Dollery, Lewis, Myers & Reid, 1973). However, the issue is far from clear at present and must await further research. No studies seem to have been performed with regard to central β-adrenergic receptor mechanisms and the hypotensive action of l-dopa.

It should be emphasized that the discussion so far has been focused on the central noradrenaline mechanisms mediating the hypotensive response to L-dopa. There is evidence that noradrenaline may subserve blood pressure-regulating functions at other levels in the brain than in the lower brain stem. As shown by A. Philippu and associates, noradrenaline mechanisms are perhaps involved in the pressor response to stimulation of the posterior hypothalamus (Przuntek, Guimarães & Philippu, 1971). This may have relations to, for example, the mechanisms of actions of some anti-hypertensive drugs and will be discussed below.

Little is known about the role of central dopamine transmission mechanisms in blood pressure regulation. Central dopamine receptor-blocking drugs seem to have little effect on blood pressure and heart rate but this does not necessarily exclude dopamine receptors from being involved in central cardiovascular control. Apomorphine, which stimulates such receptors in the brain (Andén, Corrodi, Fuxe, Hökfelt, Hökfelt, Rydin & Svensson, 1970), has been claimed to lower blood pressure by a central action (Barnett & Fiore, 1971; Finch & Haeusler, 1973). The possibility of dopamine mechanisms interacting with the previously discussed noradrenaline mechanisms does not seem to have been evaluated.

By means of the histochemical fluorescence method, 5-hydroxytryptamine-containing cell bodies have been demonstrated in the lower brain stem and 5-hydroxytryptamine terminals are abundant in this region as well as in others, notably in the sympathetic lateral column in the spinal cord (Fuxe, 1965). Attempts have been made to evaluate the role of central 5-hydroxytryptamine mechanisms in the
regulation of blood pressure by the same approach as used for catecholamine mechanisms, i.e. by selective inhibition of the peripheral decarboxylase and administration of the amino acid precursor to 5-hydroxytryptamine, 5-hydroxytryptophan. In these experiments, performed in conscious rats, only a slight hypotensive action was observed. Furthermore, increasing the accumulation of 5-hydroxytryptamine in the central nervous system by pretreatment with an inhibitor of monoamine oxidase (in addition to the peripheral decarboxylase inhibitor) did not result in any effects on blood pressure which could be attributed to central nervous actions of 5-hydroxytryptamine (Henning & Rubenson, 1971a). However, as mentioned with regard to central noradrenaline mechanisms in blood pressure regulation, there are indications of qualitatively different actions on blood pressure at different levels in the brain. This circumstance points to an obvious disadvantage of using systemically administered transmitters as tools in studies of this kind: the effects observed may be the net result of opposite actions neutralizing each other. A number of investigations have been performed with various experimental procedures in different animal species and aiming at defining the role of central 5-hydroxytryptamine neurons in controlling sympathetic activity and blood pressure; most of them are consistent with a centrally mediated decrease in sympathetic activity and blood pressure (Ito & Schanberg, 1972; Antonaccio & Robson, 1973; Chalmers, Reid & Wing, 1974; Florez & Armijo, 1974; Neumayr, Hare & Franz, 1974). Without discussing these studies in detail it should be pointed out that considerable caution should be exercised when interpreting data obtained with drugs claimed to affect specifically 5-hydroxytryptamine mechanisms. Thus the inhibitor of 5-hydroxytryptamine biosynthesis, p-chlorophenylalanine, also influences central noradrenaline metabolism (see, e.g. Miller, Cox, Snodgrass & Maickel, 1970) and 5,6-dihydroxytryptamine causes degeneration not only of 5-hydroxytryptamine neurons but also of catecholamine neurons when applied locally in the central nervous system (Baumgarten, Björklund, Lachenmayer, Nobin & Stenevi, 1971). In addition, interactions of 5-hydroxytryptophan with catecholamine neurons must be taken into account (see e.g. Butcher, Engel & Fuxe, 1970). It would appear that central 5-hydroxytryptamine mechanisms probably take part in blood pressure regulation but their precise role requires further investigation, in particular with regard to possible multiple sites of action.

Although the central neurotransmitter function of acetylcholine by now seems well documented (see Symposium, 1970), its role in central cardiovascular regulation is almost unknown. Indirectly, such functions are suggested by the observation that systemic administration of cholinesterase inhibitors penetrating into the brain (notably physostigmine) produce a hypertensive response in the rat, which can probably be attributed to central nervous actions (see Varagić & Krsić, 1966). These seem to involve activation of a central adrenergic mechanism as reflected by among other actions, an increased synthesis, turnover and release of noradrenaline in the central nervous system (Kažić, 1973), again emphasizing the significance of central noradrenaline mechanisms in the control of blood pressure. The effects of choline and its esters applied locally in the central nervous system are reviewed in a study by Lang & Rush (1973). Although clearly suggesting centrally mediated cardiovascular responses of cholinergic nature, such studies do not allow a close interpretation; in particular, interactions with central catecholamine mechanisms deserve consideration. There is also evidence for the existence of cholinergic mechanisms regulating blood pressure at the hypothalamic level (Brezenoff, 1972; Philippu, Demmeler & Roensberg, 1974).

**Central neurotransmitters and hypertension**

This intriguing topic has several important aspects. Of these, two will be discussed in some detail: (1) the possible relationship between various types of experimental hypertension and central monoamine transmitter turnover; (2) mediation of anti-hypertensive drug action by interference with central neurotransmitter function.

**Experimental hypertension.** Numerous attempts have been made to relate metabolism of catecholamines in the peripheral sympathetic nervous system to arterial hypertension, but the possibility of involvement of central catecholamines has received less attention so far. For methodological reasons such studies have been restricted to various animal models of experimental hypertension. Of these, the neurogenic type resulting from denervation of the carotid sinus and aortic arch baroreceptors provides the most convincing evidence that central noradrenaline neurons may participate in the origin and mainten-
ance of the hypertensive state. Thus sino-aortic denervation results in a pronounced increase in turnover of noradrenaline in the thoracolumbar region of the spinal cord (Chalmers & Wurtman, 1971). This suggests an increased activity in bulbospinal noradrenaline neurons innervating the sympathetic centres in the lateral horns, which is then responsible for the elevation of blood pressure via an increased activity in the peripheral sympathetic nervous system (Chalmers & Wurtman, 1971). In addition, treatment with 6-hydroxydopamine causes a great reduction in brain-stem and spinal noradrenaline concentrations and completely prevents the increase in blood pressure after sino-aortic denervation (Chalmers & Reid, 1972). These findings, and also electrophysiological studies after L-dopa (Neumayr et al., 1974), might suggest that noradrenaline is acting as a facilitatory transmitter in bulbospinal nerves, but this seems less likely in view of the fact that L-dopa in combination with a peripheral decarboxylase inhibitor does not elevate blood pressure. The possibility of the effects observed in neurogenic hypertension being secondary to the rise of blood pressure cannot be excluded.

The role of alterations in central neurotransmitter metabolism in other types of experimental hypertension is not clear. The genetically determined hypertension occurring in a number of rat strains, which probably offers the best animal model of human essential hypertension, has been extensively studied in this respect. Early results suggested a most interesting inverse relationship between arterial blood pressure and brain-stem metabolism of noradrenaline (Yamori, Lovenberg & Sjoerdsma, 1970). However, carefully controlled studies have failed to reveal any consistent relationships of metabolism of catecholamines to the pathogenesis of hypertension in these rats (Yamabe, de Jong & Lovenberg, 1973; Lovenberg, Yamabe, de Jong & Hansen, 1973). It should be emphasized, however, that currently available methods for studying metabolism of catecholamines may be insufficient for detecting subtle changes and it is likely that only a minor percentage of central noradrenaline neurons is associated with cardiovascular control. Small changes in these neurons may then be obscured when relatively large parts of the brain are analysed.

There are also indications of a decrease in the activity of central noradrenaline neurons in rats made hypertensive by treatment with deoxycortico-terone and salt after unilateral renal encapsulation (Nakamura, Gerold & Thoenen, 1971). Again, the possibility exists that such alterations are secondary to the increase in blood pressure. Further, in experiments of this kind the renin–angiotensin system may come into play and, by way of central actions of angiotensin (see review by Sever & Daniels-Severs, 1973), may affect central metabolism of catecholamines. This aspect of central transmitter function and hypertension would seem to deserve further attention.

Anti-hypertensive drug action. Significant evidence relating anti-hypertensive drug action to alterations in central neurotransmitter function has emerged from studies on the mode of action of methyldopa (L-α-methyl-3,4-dihydroxyphenylalanine) and, in fact, formed the background for the concept of central catecholamine receptor regulation of blood pressure (reviews by Henning, 1969a, b, 1973). The earlier view that mechanisms of false transmission in the peripheral sympathetic nervous system could account for the anti-hypertensive effect of methyldopa had to be abandoned when it was found that pretreatment with a peripheral decarboxylase inhibitor (i.e. preventing the synthesis of false transmitters peripherally) does not alter the hypotensive effect of methyldopa. On the other hand, this action is abolished after decarboxylase inhibition in both the peripheral and the central nervous system (Henning, 1968, 1969a; Day, Roach & Whiting, 1973; Nijkamp & de Jong, 1974). Thus central actions of methyldopa amine metabolites mediate the anti-hypertensive effect of the drug. Since this effect is counteracted by inhibition of dopamine β-hydroxylase, a-methyl noradrenaline is probably implicated (Henning & Rubenson, 1971; Day et al., 1973), apparently acting by direct stimulation of central noradrenaline receptors (Henning & Rubenson, 1971b; Rubenson, 1971; Haeusler & Finch, 1972; Heise & Kroneberg, 1972). These are probably located mainly in the brain stem (Henning & van Zwieten, 1968; Nijkamp & de Jong, 1974).

Clonidine [2-(2,6-dichlorophenylamino)-2-imidazolyl] lowers blood pressure and heart rate by an action in the central nervous system (Hoefke & Kobinger, 1966; Kobinger, 1967; Sherman, Grega, Woods & Buckley, 1968); part of the hypotensive response seems to involve a facilitation of vagally mediated cardiodepressor reflexes through a central action (Walland, Kobinger & Csongrady, 1974). Clonidine is also an effective agonist at central noradrenaline receptors (Andén et al., 1970; re-
viewed by Andén, 1973). Since the cardiovascular effects of clonidine are prevented by agents known to act as central noradrenaline receptor antagonists (Kobinger & Walland, 1967; Bock, Merquet, Brandt & Murata, 1970; Schmitt, Schmitt & Fénard, 1971; Haeusler & Finch, 1972), it is conceivable that the hypotensive action results from an activation of central noradrenaline receptors. Incidentally, the clinical implications of these observations with respect to possible interactions between clonidine and those phenothiazine neuroleptics blocking central noradrenaline receptors do not seem to have been evaluated. As with L-dopa and methyldopa the central noradrenaline receptors mediating the hypotensive response to clonidine seem to be at least in part located in the lower brain stem (Schmitt, Schmitt, Boissier, Giudicelli & Fichelle, 1968; Shaw, Hunyor & Korner, 1971). They may be classified as α-adrenergic since clonidine stimulates peripheral α-adrenergic receptors (Hoefke & Kobinger, 1966) and since the noradrenaline receptor antagonists which prevent the central actions of clonidine in addition are peripheral α-adrenergic receptor-blocking agents. Like L-dopa and methyldopa, clonidine reduces the activity in the peripheral sympathetic system through its central action; this is manifested, for example, in a diminution of the directly recorded sympathetic nerve activity (Schmitt et al., 1968).

There is evidence that receptor mechanisms are involved in the control of several presynaptic processes, e.g. synthesis and release of the transmitter, in central monoamine neurons. The possibility that presynaptic receptor effects may be exerted by clonidine must be considered (see e.g. Starke & Montel, 1973). The seemingly puzzling observation that desmethylimipramine abolishes the hypotensive action of clonidine (Reid, Briant & Dollery, 1973) may be interpreted in terms of an interference with presynaptic receptors. It should be mentioned that these results could not be reproduced in a recent study in anaesthetized animals (Hoefke & Warnke-Sachs, 1974). On the other hand, Kobinger & Pichler (1974) have shown that the facilitation by clonidine of the vagally mediated cardiodepressor reflex is independent of release of noradrenaline from central neurons, clearly demonstrating a direct stimulation of postsynaptic noradrenaline receptors.

Another interesting feature of clonidine is that it appears to influence blood pressure also through suprabulbar structures. Thus local administration of clonidine into the far posterior hypothalamus of the rat has been reported to reduce arterial blood pressure and heart rate (Struyker Boudier & van Rossum, 1972). As previously mentioned, the rise in blood pressure evoked by stimulation of the posterior nucleus of the hypothalamus in the cat seems to be mediated by adrenergic neurons (Przuntek et al., 1971). Clonidine enhances the same pressor response by activating hypothalamic noradrenaline receptors, which may be of α-adrenergic type (Philippu et al., 1974). Although caution must be exercised when interpreting data obtained with local administration of drugs into the central nervous system due to the possibilities of, for example, wide-spread diffusion, the push–pull cannula technique employed by A. Philippu and associates seems less fraught with problems of the kind mentioned than, for example, intraventricular injections (see Myers, 1972). At present, it does not seem possible to arrive at a definite conclusion on the precise mechanisms underlying the hypotensive action of clonidine; this also applies to an increasing number of anti-hypertensive compounds structurally related to clonidine (review by Zimmerman, 1972).

Conclusions
In this review attempts have been made to summarize a large number of observations which provide evidence for a role of central monoamine mechanisms in the control of arterial blood pressure. The picture emerging from the results presented is far from clear but the following conclusions appear justified. Central noradrenaline receptor mechanisms mediate hypotensive effects at the level of the lower brain stem but may influence blood pressure in other regions in the central nervous system as well, possibly subserving qualitatively different actions. The role of central dopamine mechanisms in circulatory control is sparsely documented. It seems likely that central 5-hydroxytryptamine neurons take part in blood pressure regulation, possibly with dissimilar functions at several levels of control and partly by interacting with catecholamine mechanisms. Such interactions may also partly explain some results obtained with respect to acetylcholine.

Central monoamine mechanisms may be implicated in the pathogenesis of certain types of experimental hypertension but it may be difficult to separate primary effects from those secondary to the elevation of blood pressure. Considerably more is known of drugs mediating their anti-hypertensive
effect by interference with central neurotransmitter mechanisms. This seems to be the case for methyl-dopa and clonidine. A centrally mediated hypotensive effect of L-dopa is also evident.

A large part of the information discussed here has been obtained in animal experiments, in many instances referring to acute effects of drugs or regimens. With few exceptions the relevance of such results to the clinical situation has not been established. It remains for clinical pharmacologists to carry the research on to studies in human beings. Such work could at least partly utilize principles laid down in animal work. For instance, decarboxylase inhibitors are currently available for use in combination with L-dopa in the treatment of Parkinson's disease. Several neuroleptic drugs interfere with the function of central noradrenaline receptors. The interactions of such drugs with the hypertensive effects in man, e.g. of methyl-dopa and clonidine, would provide valuable information with regard to the central mechanisms mediating their anti-hypertensive properties in man, and, in addition would be useful for the prediction of possible clinical interaction mechanisms. It should finally be recalled that an early clue to the pathogenesis of Parkinson's disease came from the demonstration of a marked reduction of dopamine concentrations in the basal ganglia of patients dying from this disease. Although grossly speculative, the possibility of similar local deficiencies in central monoamine transmission mechanisms as an aetiological factor in human essential hypertension might be considered.

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References


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Discussion after Dr Henning's paper

LOUIS: Dr Henning, one thing worries me in your interpretation of the work with the dopamine betahydroxylase inhibitors. When you administered dopa, you found it difficult to produce significant elevation of noradrenaline in the brain. Moreover, in the treatment of Parkinson's disease in man, there is no real evidence of an increase of noradrenaline production. I do not want to go into the reasons for this, but the main substance that seems to be produced is dopamine. I wonder why there is this discrepancy between the biochemical data and the biological data that you are showing here?

HENNING: The fact that we do not get much increase in central noradrenaline is not necessarily contradictory. There could be a significant displacement of central noradrenaline by the large amount of dopamine formed. The studies with inhibition of synthesis that I mentioned, where one can block the action of L-dopa after depletion of the endogenous stores, indicate that there might be an indirect component of action, but that does not exclude direct actions. After monoamine oxidase inhibition, the hypotensive effect of dopa is enormously potentiated and the dose of dopa can be reduced by almost 100 times. This may indicate that the effect is direct on noradrenaline receptors, so perhaps as you suggest the picture is mixed, even normally.

WELLENS: Recently, French investigators applied clonidine to the ventral medulla and observed hypotension. Also dopamine applied to the ventral medulla induced hypotension, whereas noradrenaline increased blood pressure. This central hypotensive activity of clonidine and dopamine is antagonized by pimozide, also a benzimidazole derivative. Do you have any comment on this?

HENNING: I did not comment on clonidine because in the first place we have not yet done much work with it and in the second place I think we are going to hear much more about it later. I am always rather uneasy about the local application of drugs to the brain stem since the whole brain stem is exposed to the drug and the specificity of such an application is open to question. Also, I believe that the concentrations of dopamine, for instance, in the experiments you mentioned were rather high.

SCHWARTZ: I would like to say that in our experiments the application of clonidine to the ventral medulla was done in such a way that the drug acted on a surface of less than 1 mm² and excitation was therefore restricted to a very small area of the brain stem.