EXCITATORY EFFECTS OF CATECHOLAMINES IN THE C.N.S.

(DISCUSSION OF PAPERS BY G. K. AGHAJANIAN AND B. J. HOFFER)

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I SHOULD like to discuss some excitatory actions of catecholamines in the central nervous system, particularly since the two previous presentations may give the impression that these substances produce only depression of neuronal activity in the brain. In fact, Dr. Hoffer goes as far as to suggest that excitatory effects of microiontophoretically applied noradrenaline 'may be at least partly artefactual'. Whilst this may be true for some effects of noradrenaline, we think that it is unlikely to be true for all; furthermore we consider that some excitatory effects may be of physiological significance.

In 1958, Mollica and I (BRADLEY and MOLLICA, 1958) showed that adrenaline and noradrenaline could modify the activity of single neurones in the brain stem reticular formation in decerebrate cats and that both excitation and inhibition of neuronal activity could be observed. However, these effects were obtained with systemic injections of the amines and could have been indirect. Subsequently (BRADLEY and WOLSTENCROFT, 1962) it was found that similar effects could be obtained with microiontophoretic applications of noradrenaline to spontaneously active single neurones in the brain stem of unanaesthetised decerebrate animals. Thus, the firing rate of some neurones was depressed, whilst others were excited, and there was a third group of neurones which were unaffected by iontophoretically applied noradrenaline.

In a further study in which the effects of the (+)- and (−)-isomers of noradrenaline, together with various agonists and antagonists were examined, it was found that there were four distinct types of response of brain stem neurones to iontophoretically applied noradrenaline (BOAKES, BRADLEY, BROOKES, CANDY and WOLSTENCROFT, 1971). These consisted of an excitatory response, as had been observed previously (Fig. 1D), two types of inhibitory response, one of which was short-lasting and with a rapid onset (Fig. 1A), whilst the other was long-lasting and often delayed in onset (Fig. 1C), and a biphasic response consisting of excitation preceded by inhibition (Fig. 1B). The excitatory response showed a tendency to desensitisation with repeated applications and it also demonstrated stereochemical specificity in that the (−)-isomer was more potent than the (+)-isomer (Fig. 2). This was less marked with the inhibitory responses. Other sympathomimetic amines tested showed agonistic effects but with varying potency (Fig. 2), and it was found that dopamine, for example, had no independent actions, i.e. it did not affect the activity of neurones which did not respond to noradrenaline. Many of the classical noradrenaline antagonists of the α- and β-type were found to be ineffective but α-methyl-noradrenaline (BOAKES, CANDY and WOLSTENCROFT, 1968) and chlorpromazine (BRADLEY, WOLSTENCROFT, HÖSLI and AVANZINO, 1966), consistently antagonised noradrenaline excitation. We therefore concluded (BOAKES *et al.*, 1971) that the excitatory actions of (−)-noradrenaline in the

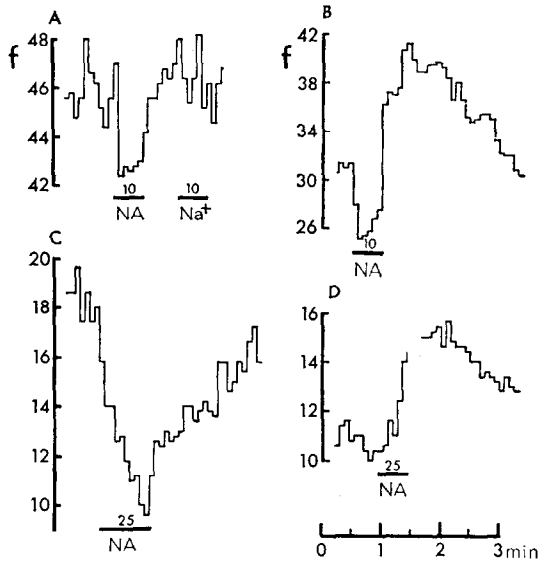
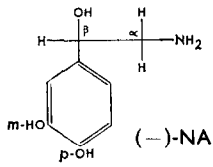


FIG. 1.—Effects of (−)-noradrenaline, applied iontophoretically, on the spontaneous activity of four neurones in the brain stem reticular formation of an unanaesthetised decerebrate cat. The mean firing rate of each neurone, in impulses/sec (f) in successive 5 sec epochs, is plotted against the time in minutes. Iontophoretic applications of (−)-noradrenaline (NA), or of a current control (Na^+) are shown by horizontal bars. Short-lasting and long-lasting inhibitory responses are shown in *A* and *C*. An excitatory response is shown in *D* and a biphasic response in *B*. The iontophoretic currents used were 10–25nA. (From: BOAKES *et al.*, 1971.)

brain stem are probably mediated by a specific mechanism and also that the receptors for noradrenaline in this region of the brain do not correspond to peripheral receptors of the classical α- and β-types. Further studies are in progress in order to characterise, both physiologically and morphologically, the neurones which show these different responses to noradrenaline.

Excitatory effects of noradrenaline have also been observed in other regions of the brain. For example, JOHNSON, ROBERTS, SOBIESCEK and STRAUGHAN (1969) reported excitation of neurones in the cerebral cortex with iontophoretic applications of noradrenaline and found that this response was especially sensitive to anaesthetic agents. Excitatory effects by noradrenaline on cortical neurones have also been reported by other workers (GIARDINA, PEDEMONTE and SABELLI, 1973). It is necessary to use acid solutions in order to expel noradrenaline by microiontophoresis and pH has been implicated as a possible factor in the effects observed since it has been found that hydrogen ions alone can cause excitation of single neurones in the cerebral cortex (KRNJEVIĆ and PHILLIS, 1963). Whilst pH may be a factor affecting the proportions of neurones in the cerebral cortex showing excitatory responses to iontophoretically applied noradrenaline (FREDERICKSON, JORDAN and PHILLIS, 1971), it is unlikely to account for all excitations observed, since KRNJEVIĆ and PHILLIS (1963) found that 'excitation by hydrogen ions is very unlikely if the internal pH exceeds 2·5', and most workers have used pH's of 3·5–4·0. Our own experiments were carried out with noradrenaline solutions at pH 4·0 (BRADLEY and WOLSTENCROFT, 1962) or pH 5·0–6·0 (BOAKES *et al.*, 1971). Since excitation of brain stem neurones was consistently



AGONIST	MOLECULAR CHANGE		EFFECT	
	RING	SIDE-CHAIN	EXCITATION	INHIBITION
(−)Noradrenaline			+++++	−−−−−
(−)Adrenaline		N-CH_3	++++	−−−−−
(−) Isoprenaline		N-C_3H_7	o	−
(−)α-MethylNA		α-CH_3	++	−−−−−
(+)Noradrenaline		Stereoisomer	++	−−−−−
Dopamine		no β-OH	+++	−−−
(−)Phenylephrine	no p-OH	N-CH_3	++	−−−
(−)Metaraminol	no p-OH	α-CH_3	+	−−−
(±)p-Sympatol	no m-OH	N-CH_3	o	−−−
Tyramine	no m-OH	no β-OH	++	−−−
(+)Amphetamine	no p-, m-OH	no β-OH, α-CH_3	++++	−−−−−
(−)Ephedrine	no p-, m-OH	N-CH_3, α-CH_3	++++	−−−
2-Aminoheptane			+++	−−

FIG. 2.—The potencies of various sympathomimetic amines as agonists of (−)-noradrenaline. The number of symbols (+ for excitation and − for inhibition) allotted to each compound is based on a comparison of the effects of the compound with those of (−)-noradrenaline on the same neurone. N.B. Inhibitory actions includes both short- and long-lasting effects. (From: BOAKES *et al.*, 1971.)

observed with these solutions, we do not consider pH effects to be an important factor in our experiments.

Another possible 'artefactual' explanation for excitatory responses by central neurones to iontophoretically applied noradrenaline is related to the suggestion that these effects may be due to an indirect action by noradrenaline on blood vessels (STONE, 1971). The main support for this is the parallel time course of constriction of arterioles as a result of noradrenaline application and the time course of excitatory effects on neurones in the central nervous system. However, interesting as this suggestion is, the comparison has so far only been made with arterioles in intestine and mesentary and there is no evidence that small cerebral vessels respond in the same way, or that if they do, their indirect influence on neighbouring neurones is likely to be excitatory.

The interpretation of the effects of microiontophoretically applied putative neurotransmitters and centrally active drugs, to single neurones in the central nervous system is certainly very difficult and we must not assume that the effects of a substance, released iontophoretically in the vicinity of a neurone, are necessarily the same as those of the endogenous transmitters. Some effects, which have been observed and reported in the literature, may well be due to artefacts. On the other hand, it must not be assumed that, because certain effects can be mimicked by hydrogen ions, or because there are similarities between the responses of peripheral arterioles and central neurones, that *all* noradrenaline excitations are necessarily artefacts. As far as neurones in the brain stem reticular formation are concerned it is our view that the excitatory

responses to noradrenaline we have observed are unlikely to be due to artefacts since they show stereochemical specificity and can be specifically antagonised. Furthermore, the actions of noradrenaline on brain stem neurones are closely mimicked by (+)-amphetamine whose actions appear to be dependent upon the presence of noradrenaline in presynaptic nerve terminals (BOAKES, BRADLEY and CANDY, 1972).

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