IMPLICATIONS OF FEEDBACK CONTROL IN CATECHOLAMINE NEURONAL SYSTEMS

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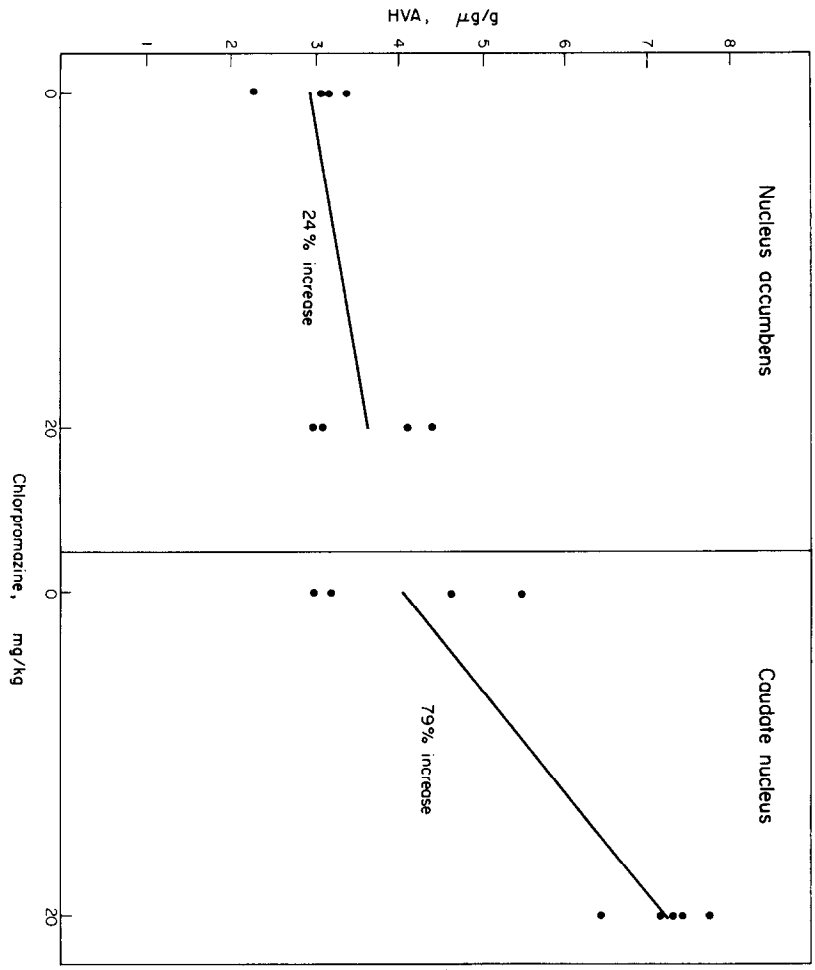
THE THEORY of feedback control of catecholamine neuronal systems leads one to expect certain peculiarities in their response to drugs which block or potentiate transmission at catecholamine synapses, peculiarities which may be relevant both to the interpretation of experiments with the drugs and to their use in therapy. These ideas were first suggested, I believe, by the neurologist Dr. Janice Stevens, and Dr. Kety made use of them in his talk at the conference on 'Catecholamines and their Enzymes in the Neuropathology of Schizophrenia'. This presentation adds only a slightly more complete theoretical development.

It is very well documented that the level of activity in the nigrostriatal dopamine tract is under negative feedback control; agents which block transmission, such as neuroleptics, increase the rate of neuronal activity in the substantia nigra and also the release of dopamine, as measured by its metabolite homovanillic acid. Conversely, as was reported by Dr. Aghajanian at this Symposium, amphetamine decreases the rate of firing in the substantia nigra. From the data obtained by his group, there is reason to think that feedback control is also present in the noradrenaline system emanating from the locus coeruleus, since amphetamine decreases activity in the locus coeruleus and this decrease is blocked by chlorpromazine.

If the feedback loop characteristic of these systems is a one-to-one inverse projection, that is, if the cell innervated by a given catecholamine neuron projects downward, without branching, directly to the cell of origin, the consequence of negative feedback will simply be to attenuate responses to blocking and potentiating drugs. On the other hand, it may be important to consider the case where the identity of the ascending neuron is lost through branching, so that the cell of origin may receive its feedback innervation from quite another neuron than the one to which it sends its ascending signals. There may even be such thorough mixing that the feedback compensation becomes only a statistical average applied diffusely to the cells of origin. Let us call this the 'mixing hypothesis'. When the mixing hypothesis is valid, the application of drugs may give rise to some unexpected effects.

Suppose, for example, that some neurons arising in the locus coeruleus make alpha-adrenergic connections in the cortex, while others are of the beta type. Just for discussion, let us suppose that most neurons originating in the locus coeruleus are alpha, and only a few are beta. Now imagine treatment with an alpha blocker. Because of the loss of negative feedback from the principal alpha pathway, the level of activity in the nucleus goes up substantially. Since by the mixing hypothesis the feedback is applied diffusely, the beta neurons will increase in firing rate as well as the alpha. They, however, are not synaptically affected by the alpha blocker, so the net effect is potentiation of the beta-adrenergic pathway to the cortex, along with inhibition of the alpha-adrenergic pathway. It is easily seen that the mixing condition



always amplifies the divergence between the magnitude of a drug's action on different classes of synapses. Mixing will be of no consequence if a particular drug has no differential effect on efferent branches from a nucleus. On the other hand, differential effects should be a relatively common occurrence. In addition to the alpha- and beta-receptor case just mentioned, Bradley observed that chlorpromazine blocked excitatory noradrenaline synapses in the brain stem, but did not block inhibitory noradrenaline responses. The magnitude of the amplification of differential drug effects will depend on the level of feedback control and the degree of asymmetry of the fibre bundles emanating from the nucleus in which mixing takes place. If feedback control were complete, blocking drugs would have no effect at all on major pathways, and effects exactly opposite to what is expected on minor pathways where they are less effective. With less complete feedback control, the major pathway would be blocked to some degree, and the minor pathway would either be facilitated or inhibited, depending on the quantitative relationships. The greater the discrepancy in size between the major and minor fibre bundles, the greater the paradoxical effects to be expected in the minor pathway.

There are several ways in which the validity of the mixing hypothesis for a particular catecholamine cell group can be tested; one of them is suggested by the experiments of Mr. Allen Nineberg in our laboratory, which are illustrated in the accompanying figure. Cats are injected with chlorpromazine or saline and sacrificed after four hours. The caudate and nucleus accumbens septi are dissected separately in the frozen tissue, and assayed for homovanillic acid. Because of the small size of the nucleus accumbens, it is necessary to pool tissue from two animals for each data point. The rise in homovanillic acid after chlorpromazine is much larger in the caudate than in the nucleus accumbens. If the mixing hypothesis were true for the system whose terminals are represented by these two structures, the percent rise should have been the same in both regions. According to data obtained by Andén and by Lloyd, after haloperidol the percentage rise in homovanillic acid in caudate and limbic system is approximately the same. The mixing hypothesis requires, however, that the percent rise be the same in all regions innervated by the cell group in which mixing takes place, not merely for some, but for all drugs, at least insofar as they act by blockade or potentiation of catecholamine synapses. The most likely explanation of the difference between chlorpromazine and haloperidol is that haloperidol blocks caudate and accumbens dopamine synapses equally, whereas chlorpromazine is less effective in the nucleus accumbens; but this inequality of effect would not manifest itself in differential homovanillic acid rise if the mixing hypothesis were valid for the cell group of origin. Of course it is no surprise that it is invalid, since the A9 region which innervates the caudate, and the A10 region which innervates the accumbens, are morphologically distinct cell groups. I think it is nevertheless reasonable to conjecture that within each of the catecholamine cell clusters, the mixing hypothesis applies. A diffuse downward projection is likely in view of the highly branched and ramified terminal plexi of the neurons of these groups.

The possibility of feedback mixing introduces some complexities in the interpretation of experiments. The most obvious is uncertainty whether a behavioural effect results from activation of a major pathway or inhibition of a minor pathway (or vice-versa). Furthermore, we should not be suprised to discover paradoxical effects of intraventricular drug administration. For example, endogenous norepinephrine may be involved in behavioural alerting through its effects on the cerebral cortex, but when introduced intraventricularly it could cause sedation by feedback inhibition of noradrenaline neurons, resulting from activation of cells postsynaptic to noradrenergic fibres in the periventricular zone of the hypothalamus. We might also expect qualitative rather than merely quantitative changes in drug effects as dose increases, that is, the emergence of new phenomena at high doses. At low doses, when the level of feedback control is high, a drug effect on a minor branch may not be observed because of feedback mixing from a more strongly affected pathway. In the case of synaptic blocking agents, the system may partially escape from feedback control at high doses, because facilitation of firing in the nucleus of origin can never exceed the maximum rate of which the neurons are capable. In the case of synaptic facilitating agents, the more strongly affected pathway will eventually reach a point of maximum potentiation, after which the degree of asymmetry in drug effect on the major and minor branch will decrease steadily as dose increases, permitting the minor branch effect to emerge. Examples of emergence of new phenomena at high doses include amphetamine stereotypy, which is not continuous with the behavioural

activation observed at low doses, and neuroleptic-induced catalepsy, which is unlike the sedative effects observed with lower doses of the drug.

Certain behavioural antagonisms may also find explanation through the mixing hypothesis. One is tempted to apply the principle to Dr. Leibowitz's finding that alpha receptors stimulate feeding and inhibit drinking, while beta receptors do the reverse. The mutual antagonism of these two behaviours may be caused by reciprocal inhibitory innervation of the hypothalamic receptors, but it could also be accounted for by the mixing hypothesis. If the feeding and drinking centers receive their adrenergic innervation from the same norepinephrine cell group, an alpha blocker might potentiate the beta branch through feedback facilitation, and vice versa. Similar reasoning could be applied to other behavioural antagonisms. Dr. Randrup has pointed out that during apomorphine or amphetamine-induced stereotypy there is not only facilitation of the compulsive activities, but also inhibition of ordinary goal-seeking motivated behaviour. Conceivably this antagonism could be caused by differential effects of the drugs on different branches of the A10 system.

There may be some potential applications of the mixing hypothesis to paradoxical drug responses in man. Why does pimozide, a dopamine blocker, increase arousal and motivation in chronic, withdrawn schizophrenics? Why do acute dystonic reactions which resemble dopamine-induced hyperkinesias sometimes occur during treatment with drugs expected to block dopamine synapses? Why does amphetamine have a quieting effect on hyperactive children? The application of feedback facilitation to the first of these phenomena was suggested by Dr. Kety; similar reasoning might apply to the others. The existence of mixing in the catecholamine feedback control systems, and its significance for behaviour in response to drugs, remain to be demonstrated; but I do not think they lie outside the range of experimentation.