(100 μmol/kg). The cerebral hemispheres were removed by freeze-blowing 2 min later and cerebral cyclic AMP measurements were performed by a protein binding assay. The increase in cyclic AMP in response to isoprenaline in reserpinized chicks (475%) or in chicks pretreated with 6-hydroxydopamine (441%) was significantly greater than that produced in control birds (266%), indicating an increased sensitivity to isoprenaline following the chronic depletion of cerebral catecholamines. Experiments were performed therefore to determine whether the chronic administration of isoprenaline would conversely reduce the sensitivity of the cyclic AMP response. (−)-Isoprenaline was suspended in glycerol trioleate and administered subcutaneously (150 μmol/kg) in two doses at 12 h intervals to effect a slow release of catecholamine. Six hours after the second injection the cerebral cyclic AMP response to intravenous isoprenaline was almost completely suppressed. The increase in cyclic AMP induced by histamine *in vivo* was not influenced by any of the drug treatments.

More detailed studies were performed *in vitro* using slices of chick cerebral hemispheres. Dose-response curves for isoprenaline indicated that the maximal increase in cyclic AMP produced by the catecholamines was significantly enhanced in slices prepared from reserpinized chicks but severely suppressed in the chronic isoprenaline group. However, although the supersensitive response was still observed in the presence of the potent phosphodiesterase inhibitor, Ro 20-1724 (4-(3-butoxy-4-methoxy benzyl)-2-imidazolidinone) (200 μM) the subsensitive response was almost restored to that of the controls.

The data suggest that the sensitivity of cerebral β-adrenoceptors mediating cyclic AMP formation may be regulated by the functional amount of transmitter at the receptor. The subsensitive condition may, in part, be due to a selective increase in phosphodiesterase activity but several alternative mechanisms need to be examined.

This work was supported by a grant from the Wellcome Trust.

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Comparison of the effects of DOPA and noradrenaline on single cortical neurones

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L-3, 4-dihydroxyphenylalanine (DOPA) is widely used in the treatment of Parkinson's disease. DOPA is a metabolic precursor of dopamine, and it is generally believed that DOPA exerts its therapeutic effect via the release of dopamine in the caudate nucleus (Hornykiewicz, 1974). However, DOPA is also known to be a precursor of noradrenaline (NA), and it has been suggested that in structures receiving a NA innervation, exogenously administered DOPA may cause the release of NA from pre-synaptic terminals and thus mimic the actions of NA on post-synaptic cells (Andén, Carlsson & Häggendal, 1969). We have used the technique of microelectrophoresis to compare the action of DOPA and NA on single neurones in the cerebral cortex, a structure rich in NA-containing terminals (Fuxe, 1965).

Single spontaneously-active cortical neurones were studied in cats and rats anaesthetized with halothane. Drugs were applied from six-barrelled micropipettes by microelectrophoresis. Our techniques and methods of study have been described elsewhere (Bevan, Bradshaw, Roberts & Szabadi, 1974).

The effect of DOPA (released from 0.05 M DOPA methyl ester HCl solution) was examined on 51 neurones in the rat; 44 were excited and 7 depressed by the drug. Eleven cortical neurones were studied in the cat; of these 10 were excited and one depressed by DOPA. When the effects of DOPA were compared with those of NA on the same cells it was found that neurones invariably responded in the same direction to the two drugs (40 cells). In the case of both excitatory and depressant effects DOPA appeared to be less potent than NA, both in terms of the intensity of

the ejecting current required to evoke equivalent responses, and in terms of the magnitude of the responses evoked by identical ejecting pulses. However, this apparent difference in potency might be due to a difference between the physical mobilities of the two drugs.

Excitatory responses to both DOPA and NA could be reversibly antagonized by phentolamine (12 cells). Excitatory responses to DOPA and NA could also be antagonized by propranolol (6 cells); responses to acetylcholine were not affected. On the other hand, excitatory and depressant responses to DOPA were not affected by atropine applied with ejecting currents sufficient to antagonize excitatory responses to acetylcholine (6 cells).

These results show that cortical neurones are sensitive to locally administered DOPA, and suggest that DOPA may activate receptors similar to those activated by NA. However, it is not clear from the present results whether DOPA acts directly on post-synaptic receptors, or indirectly via the release of NA from pre-synaptic terminals.

This work was supported by the Mental Health Trust and Research Fund.

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Induced receptors for noradrenaline and serotonin in guinea-pig vas deferens?

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We have previously reported recovery of responsiveness to noradrenaline during exposure to methacholine in tissues whose α-adrenoceptors were completely blocked by phenoxybenzamine (Iijima & Reiffenstein, 1972). Methacholine could also induce serotonin receptors. Further investigation of these induced receptors is reported here. Stripped guinea-pig vas deferens was mounted in Krebs solution at 37°C and isotonic contractions obtained under 0.5 g tension. Agonist concentrations used throughout were maximal. Induced serotonin receptors were investigated in normal tissues, while induced α-adrenoceptors were studied in tissues pretreated with phenoxybenzamine until response to noradrenaline was eliminated. Contractions were then obtained to serotonin, or noradrenaline, in the presence of a receptor-inducing agent (methacholine and others). To investigate whether noradrenaline and serotonin might be reacting with the same receptor, comparative blocking studies were done by cumulative additions of antagonists during responses to combined inducer (methacholine) and agonist. The induced α-adrenoceptors were as susceptible to phentolamine ($ID_{50} = 1.2 \times 10^{-5}$ M *vs.* noradrenaline) as were normal α-adrenoceptors ($ID_{50} = 2 \times 10^{-5}$ M). Methysergide (up to 10^{-3} M) failed to inhibit induced responses to noradrenaline. The induced response to serotonin could be blocked by phentolamine ($ID_{50} = 1.8 \times 10^{-4}$ M) but lower concentrations of methysergide were effective ($ID_{50} = 3 \times 10^{-5}$ M). Thus it is likely that two distinct receptors were involved. Agents other than methacholine also proved capable of reviving responsiveness to noradrenaline: KCl (1×10^{-2} M), $BaCl_2$ (2×10^{-8} M), or propranolol (2×10^{-4} M). The latter has been observed to have a similar effect in vasculature (Yamamura & Horita, 1968; Janis & Triggle, 1974). By themselves, these agents produced widely different contractions (or none at all) so that contraction does not seem to be a requirement. Should the substances, such as methacholine or propranolol, producing this effect depolarize the smooth muscle and thereby reduce the threshold for spike generation, then previously subthreshold receptor activation could then produce contraction and there would be no need to postulate the induction of new receptors. The revived responses to noradrenaline were also potentiated by cocaine, but cocaine had no effect in the absence of the receptor-inducing agent (when noradrenaline itself produced no effect). This supports the contention of Nakatsu & Reiffenstein (1968) that cocaine increases maximal responses to noradrenaline by increasing the efficacy of unblocked receptors rather than uncovering phenoxybenzamine-inhibited receptors. We also confirmed our original