Measurement of 5-HT was made 1 h following injection of saline (controls) or the monoamine oxidase inhibitors.

From previous data on the quantitative relationship between increased synthesis of brain 5-HT and hyperactivity produced by L-tryptophan and MAO inhibition (Grahame-Smith, 1971), the degree of increase of 5-HT synthesis after lithium and MAO inhibition did not account completely for the hyperactivity. In addition, one dose of LiCl (3 mEq/kg), 5 h before tranylcypromine, followed 30 min later by L-tryptophan (50 mg/kg), potentiated the hyperactivity. This dose of LiCl did not effect brain 5-HT synthesis.

Lithium pretreatment did not potentiate the hyperactivity produced by 5-methoxy-*N,N*-dimethyltryptamine, which is thought to stimulate post-synaptic 5-HT receptor sites (Grahame-Smith, 1971b), indicating that lithium does not alter the post-synaptic response to 5-HT.

It seems likely that chronic lithium treatment not only causes an increase in 5-HT synthesis but may also increase that proportion of the 5-HT synthesized which is available for functional activity. The precise mechanisms by which lithium produces these effects is not yet known.

References

GRAHAME-SMITH, D.G. (1971a). Studies *in vivo* on the relationship between brain tryptophan, brain 5-HT synthesis and hyperactivity in rats treated with a monoamine oxidase inhibitor and L-tryptophan. *J. Neurochem.*, **18**, 1053-1066.

GRAHAME-SMITH, D.G. (1971b). Inhibitory effect of chlorpromazine on the syndrome of hyperactivity produced by L-tryptophan or 5-methoxy-*N,N*-dimethyltryptamine in rats treated with a monoamine oxidase inhibitor. *Br. J. Pharmac.*, **43**, 856-864.

PEREZ-CRUET, J., TAGLIAMONTE, A., TAGLIAMONTE, P. & GESSA, G.L. (1971). Stimulation of serotonin synthesis by lithium. *J. Pharmac. exp. Ther.*, **178**, 325-330.

Mechanism of the early pressor effect of centrally administered propranolol in the conscious rabbit

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In a previous communication (Dollery, Lewis, Myers & Reid, 1973) we reported that the intracerebroventricular (ICV) propranolol in the conscious rabbit produced a transient rise in mean arterial pressure (MAP) followed by a prolonged fall. Destruction of central noradrenergic (NA) neurones with intracisternal 6-hydroxydopamine (6-OHDA) diminished the early rise and abolished the fall. The hypotensive effect was thought to be due to adrenoceptor blockade since it was shown only by the (−)-isomer. The early rise in MAP, however, followed ICV injection of both isomers. In the following experiments we have further investigated the mechanism of this early pressor effect in the conscious rabbit.

ICV (+)-propranolol (500 μg) produced a maximum rise in MAP of 76.2 ± 8.7 mmHg and increase in heart rate (HR) of 103 ± 36 b/min at 5 minutes. Pretreatment with ICV desmethylimipramine (DMI−1.25 mg), a tricyclic compound which inhibits the uptake of noradrenaline into NA neurones (Uptake$_1$) reduced the early rise in MAP following ICV (+)-propranolol to 8.6 ± 9.4 mmHg at 5 minutes. The central injection of DMI (1.25 mg) caused an increase in MAP (35.9 ± 8.3 mmHg) and HR (50 ± 14 b/min) at 5 min with a return to near baseline at 30 minutes. These observations are consistent with those of Lewis, Rawlins & Reid (1972) that ICV NA and 6-OHDA both raise MAP in this preparation, supporting the hypothesis that central NA neurones are concerned with the maintenance of arterial pressure. The possibility that ICV (+)-propranolol causes a rise in MAP and HR by releasing endogenous stores of NA was therefore studied.

ICV pre-treatment with the alpha-adrenoceptor blocking agent yohimbine (150 μg) 30 min before the central administration of (+)-propranolol resulted in a significantly diminished pressor response (increase in MAP 14.0 ± 6.8 mmHg and HR 38 ± 15 b/min) at 5 minutes. Depletion of central NA by the ICV injection of reserpine (100 μg) 24 h previously, reduced the rise in MAP and HR following ICV (+)-propranolol to 17.1 ± 8.0 mmHg and 0 ± 10 b/min respectively, at 5 minutes.

These results are consistent with the hypothesis that propranolol is taken up into NA neurones via Uptake$_1$ and causes the release of endogenous NA which has a central pressor effect. It appears therefore that central NA neurones participate in both the early pressor and late hypotensive actions of ICV propranolol.

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References

DOLLERY, C.T., LEWIS, P.J., MYERS, M.G. & REID, J.L. (1973). Central hypotensive effect of propranolol in the rabbit. *Br. J. Pharmac.*, **48**, 343P.

LEWIS, P.J., RAWLINS, M.D. & REID, J.L. (1972). Acute thermoregulatory and cardiovascular effects of 6-hydroxydopamine administered centrally in rabbits and cats. *Br. J. Pharmac.*, **46**, 559P.

Potentiation and antagonism of neuronal responses to monoamines by methysergide and sotalol

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It has been reported that methysergide can antagonize responses of single cortical neurones to 5-hydroxytryptamine (Roberts & Straughan, 1967). Sotalol has been found to be an effective antagonist of noradrenaline on cortical neurones (Johnson, Roberts, Sobieszek & Straughan, 1969). We wish to report some further experiments which show that responses to monoamines can also be potentiated by methysergide and sotalol.

Spontaneously active neurones were studied in the somatosensory cortex of the halothane-anaesthetized cat. All the drugs were applied by microelectrophoresis. All the cells included in this study responded with excitation to noradrenaline, 5-hydroxytryptamine and mescaline. Repeated responses to noradrenaline, 5-hydroxytryptamine and mescaline were compared before, during and after a prolonged application of methysergide or sotalol.

The effect of methysergide was studied on 20 cells. On 15 of these cells, responses to the monoamines were reduced in the presence of methysergide. On five cells, potentiation of the effects of the monoamines was also seen. This potentiation was only observed when methysergide was applied with low ejecting currents and was always superseded by antagonism when the intensity of the ejecting current was increased. Similar results were obtained with sotalol. On 14 cells antagonism alone was seen; on three cells potentiation was also observed. Responses to noradrenaline, 5-hydroxytryptamine and mescaline were affected similarly in the presence of methysergide and sotalol; responses to acetylcholine did not change.

The dual action of methysergide and sotalol on responses to the monoamines can be interpreted in terms of two independent mechanisms: a lower concentration of methysergide or sotalol may affect a more sensitive 'potentiating' mechanism only, whereas a higher concentration may activate an 'antagonistic' mechanism as well.

A similar dual action on responses to the monoamines has been observed with the tricyclic antidepressants (Bradshaw, Roberts & Szabadi, 1973). In the case of the antidepressants, potentiation might be explained in terms of uptake blockade, while antagonism may be due to the blockade of post-synaptic receptors. However, this explanation is less plausible in the case of methysergide and sotalol, since methysergide has little uptake blocking activity (Born, Juengjaroen & Michal, 1972). Moreover, mescaline has only a very low affinity for uptake mechanisms in the periphery (Iversen, 1967).

Another possibility is that potentiation of excitatory responses to the monoamines results from the blockade of masked inhibitory receptors. Excitatory and inhibitory monoamine receptors have been found to co-exist on some invertebrate neurones (Gerschenfeld, 1973). It has been suggested that this may also be the case on some mammalian central neurones (Szabadi & Bradshaw, 1973).

References

BORN, G.V.R., JUENGJAROEN, K. & MICHAL, F. (1972). Relative activities on, and uptake by, human blood platelets of 5-hydroxytryptamine and several analogues. *Br. J. Pharmac.*, **44**, 117-139.

BRADSHAW, C.M., ROBERTS, M.H.T. & SZABADI, E. (1973). Comparison of the effects of imipramine and desipramine on single cortical neurones. *Br. J. Pharmac.*, **48**, 358-359P.

GERSCHENFELD, H.M. (1973). Chemical transmission in invertebrate central nervous systems and neuromuscular junctions. *Physiol. Revs.*, **53**, 1-119.

IVERSEN, L.L. (1967). The uptake and storage of noradrenaline in sympathetic nerves. (Cambridge University Press.)

JOHNSON, E.S., ROBERTS, M.H.T., SOBIESZEK, A. & STRAUGHAN, D.W. (1969). Noradrenaline sensitive cells in the cat cerebral cortex. *Int. J. Neuropharmac*, **8**, 549-566.

ROBERTS, M.H.T. & STRAUGHAN, D.W. (1967). Excitation and depression of cortical neurones by 5-hydroxytryptamine. *J. Physiol., Lond.*, **193**, 269-294.

SZABADI, E. & BRADSHAW, C.M. (1973). The role of physical and biological factors in determining the time course of neuronal responses. *Neuropharmacology*, (in press).