THE ACTION OF INDORAMIN AND OTHER COMPOUNDS ON THE UPTAKE OF NEUROTRANSMITTERS INTO RAT CORTICAL SLICES

R.F. SUGDEN

Wyeth Institute of Medical Research, Huntercombe Lane South, Taplow, Maidenhead, Berks

Indoramin has been tested for its ability to inhibit the uptake of tritiated (−)-noradrenaline and 5-hydroxytryptamine into rat brain cortical slices. Other α-blocking agents and tricyclic antidepressants were included for comparison. Activity against noradrenaline uptake is probably not important in the therapeutic action of indoramin. However, inhibition of 5-hydroxytryptamine uptake may be responsible for the sedation in high dosage noted by some investigators,

The compound indoramin is an α-adrenoceptor blocking agent with hypotensive properties; the dose limiting factor clinically is the tendency to cause sedation (Lewis, George & Dollery 1973). α-Adrenoreceptor blocking agents are known to inhibit the re-uptake of noradrenaline and 5-hydroxytryptamine (5-HT) at high concentration (Iversen, 1965) and conversely certain uptake inhibitors, such as the tricyclic antidepressants, imipramine and desipramine, will block α-receptors at high concentration (Theobald, Buch, Kunz, Morpurgo, Stenger & Wilhelmi, 1964). For this reason it was thought worthwhile to compare the noradrenaline and 5-HT uptake inhibiting, α-receptor blocking and 5-HT receptor blocking properties of certain α-adrenoceptor blocking agents and tricyclic antidepressants. The compounds selected were the α-blockers indoramin, phentolamine, thymoxamine and chlorpromazine, the tricyclic antidepressants imipramine and desipramine and the highly selective inhibitor of noradrenaline uptake, Wy 23409 (10-(*m*-chlorophenyl)-2,3,4,10-tetrahydropyrimidol[1,2a]indol-10-ol hydrochloride) (Beckett, Southgate & Sugden, 1973).

Methods The method of preparing the tissue used for measuring the uptake of tritium labelled (−)-noradrenaline or 5-hydroxytryptamine was similar to that described by Iversen & Neal (1968). Rat brain cortical slices (10 mg) were suspended in 4.5 ml Krebs solution and were preincubated for 15 min at 27° C. The inhibitory drug and the amine under study were added in 0.5 ml and the incubation was continued for 20 minutes. The final concentration of the amine was 10^{-7} M and the concentration of each inhibitor was varied as appropriate. Each experiment was run as a six point assay with three concentrations of imipramine, which was used throughout as a reference standard, being compared with three concentrations of one of the other drugs. A control uptake group and a background group were included in each assay. There were four samples in each group. Percentage inhibition of uptake for each sample was calculated as:

$$\frac{\text{(Mean control}-\text{test sample)}}{\text{(Mean control}-\text{mean background)}} \times 100$$

Each compound was run in at least three assays, the results of which were grouped together. A best fit straight line of percentage inhibition against log molar concentration was then calculated by the least squares method so that 50% inhibition concentrations (IC_{50}) could be derived.

The radioactivity bound by the tissue was assumed to be largely unchanged amine. Hamberger & Tuck (1973) showed that 90% of the radioactivity retained by brain slices was unchanged 5-HT under similar conditions and incubation times. Jonsson, Hamberger, Malmfors & Sachs (1969) showed that less than 10% of noradrenaline taken up by rat iris was metabolized after 15 minutes. Accordingly, no correction was made to the figures obtained for total uptake.

Results The results for the compounds used are shown in Table 1a. It is apparent that, against noradrenaline uptake, indoramin is more active than the other α-blockers but is still rather less active than imipramine. Against 5-HT uptake, however, indoramin shows activity close to that of imipramine.

The pA_2 values for α-adrenoreceptor blockade are shown in Table 1b for comparison. The values for the antidepressant class are lower than those for the α-blockers. The pA_2 values for 5-HT receptor blockade are also given in Table 1b. There is no clear distinction between the two classes of compound for this property.

Discussion Indoramin is a potent α-blocking agent with a pA_2 value of 7.4 on guinea-pig aorta. It also inhibits the uptake of (−)-noradrenaline by

Table 1 Comparison of amine uptake inhibition with peripheral receptor blockade

(a) *Uptake inhibition*

Drug	*IC_{50} against noradrenaline (M)*	*Drug*	*IC_{50} against 5-HT (M)*
Desipramine	2×10^{-8}	Imipramine	8×10^{-7}
Imipramine	1×10^{-7}	Indoramin	2×10^{-6}
Wy 23409	1×10^{-7}	Desipramine	6×10^{-6}
Chlorpromazine	2×10^{-6}	Chlorpromazine	1×10^{-5}
Indoramin	2×10^{-6}	Phentolamine	2×10^{-5}
Phentolamine	3×10^{-5}	Wy 23409	2×10^{-5}
Thymoxamine	3×10^{-5}	Thymoxamine	7×10^{-5}

(b) *pA_2 values for receptor blockade*

Drug	*pA_2 for α-receptors*	*Drug*	*pA_2 for 5-HT receptors*
Chlorpromazine	8.3	Chlorpromazine	Non-competitive, potent
Phentolamine	7.6	Imipramine	6.9
Indoramin	7.4	Phentolamine	6.6
Thymoxamine	6.9	Desipramine	6.2
Imipramine	6.6	Indoramin	6.0
Desipramine	5.6	Thymoxamine	5.9
Wy 23409	$\ll 5.0$	Wy 23409	$\ll 5.0$

IC_{50} = drug concentration giving 50% inhibition of uptake of the amine which was present at 10^{-7} M concentration.

pA_2 values for α-receptors were determined on guinea-pig aorta. pA_2 values for 5-hydroxytryptamine (5-HT) receptors were determined on rat ileum. pA_2 values taken from Collis & Alps (1973), otherwise personal communication from Dr J.F. Waterfall.

rat brain cortical slices but at higher concentrations than are required for the tricyclic antidepressants. At synapses containing α-receptors, therefore, the α-blocking effect of indoramin would be expected to override any opposing effect due to accumulation of noradrenaline by inhibition of its uptake.

It has been suggested that the inhibition of 5-HT uptake plays a significant part in the pharmacology of the tricyclic antidepressants (Carlsson, Fuxe & Ungerstedt, 1968). Indoramin is nearly as active as imipramine in inhibiting 5-HT uptake (potency ratio 1 : 2.5) but less active as an inhibitor of post-synaptic 5-HT receptors (potency ratio 1 : 8). It is likely, therefore, that indoramin will share with imipramine those properties, if any, attributable to inhibition of 5-HT uptake. This reasoning requires that the post-synaptic 5-HT receptors of the rat ileum, used for determining the pA_2 values, are good models for 5-HT receptors elsewhere and that the concentration of indoramin achieved is sufficient to affect 5-HT neuronal systems.

It is of interest to note that those tricyclic antidepressants with most sedative action are those that are most active against 5-HT uptake (Hollister, 1969; Lidbrink, Jonsson & Fuxe, 1971). The possibility arises that the sedative action of indoramin seen clinically in high dosage results from the inhibition of 5-HT uptake.

References

BECKETT, P.R., SOUTHGATE, P.J. & SUGDEN, R.F. (1973). The pharmacology of Wy 23409, a new antidepressant. *Naunyn-Schmiedebergs Arch. Pharmac.*, **279**, Suppl., 27.

CARLSSON, A., FUXE, K. & UNGERSTEDT U. (1968). The effect of imipramine on central 5-hydroxytryptamine neurones. *J. Pharm. Pharmac.*, **2**, 150-151.

COLLIS, M.G. & ALPS, B.J. (1973). The evaluation of the α-adrenoreceptor blocking action of indoramin, phentolamine and thymoxamine on the rat and guinea-pig isolated mesenteric vasculature and aortic spiral preparations. *J. Pharm. Pharmac.*, **25**, 621-628.

HAMBERGER, B. & TUCK, J.R. (1973). Effect of tricyclic antidepressants on the uptake of noradrenaline and 5-hydroxytryptamine by rat brain slices incubated in buffer or human plasma. *Europ. J. clin. Pharmac.*, **5**, 229-235.

HOLLISTER, L.E. (1969). Clinical use of psychotherapeutic drugs. Current status. *Clin. Pharmac. Ther.*, **10**, 170-198.

IVERSEN, L.L. (1965). The inhibition of noradrenaline uptake by drugs. *Adv. Drug Res.*, **2**, 5-23.

IVERSEN, L.L. & NEAL, M.J. (1968). The uptake of (^{3}H) GABA by slices of rat cerebral cortex. *J. Neurochem.*, **15**, 1141-1149.

JONSSON, G., HAMBERGER, B., MALMFORS, T. & SACHS, C. (1969). Uptake and accumulation of ^{3}H-noradrenaline in adrenergic nerves of rat iris. Effect of reserpine, monamine oxidase and tyrosine hydroxylase inhibition. *Europ. J. Pharmac.*, **8**, 58-72.

LEWIS, P.J., GEORGE, C.F. & DOLLERY, C.T. (1973). Clinical evaluation of indoramin, a new antihypertensive agent. *Europ. J. clin. Pharmac.*, **6**, 211-216.

LIDBRINK, P., JONSSON, G. & FUXE K. (1971). The effect of imipramine-like drugs and antihistamine drugs on uptake mechanisms in the central noradrenaline and 5-hydroxytryptamine neurons. *Neuropharmacology*, **10**, 521-536.

THEOBALD, W., BUCH, O., KUNZ, H.A., MORPURGO, C., STERGER, E.G. & WILHELMI, G. (1964). Vergleichende pharmakologische Untersuchungen mit Tofranil, Pertofran und Insidon. *Archs int. Pharmacodyn. Ther.*, **148**, 560-596.

(Received May 1, 1974)