The activation of pineal hydroxyindole-*O*-methyltransferase by psychotomimetic drugs

Schizophrenia has long been associated with abnormal methylation (Osmond & Smythies, 1952; Kety, 1965). A methylating enzyme, hydroxyindole-*O*-methyltransferase (HIOMT) which catalyses the formation of melatonin (Axelrod & Weissbach, 1961) occurs uniquely in the pineal gland. Consequently, the latter has been implicated in the disease (Altschule, 1957; McIsaac, Khairallah & Page, 1961; Jones, McGeer & Greiner, 1969; Greiner, 1970).

In animal studies, haloperidol (Naylor & Olley, 1969), a drug used in the treatment of the disease and lysergic acid diethylamide (lysergide) (Diab, Freedman & Roth, 1971), a psychotomimetic compound, have been shown to be concentrated in the rat pineal gland. Recently, we demonstrated *in vitro* (Hartley & Smith, 1972) that haloperidol and fluphenazine, another neuroleptic drug, inhibited bovine pineal HIOMT. We now report on the activation of this enzyme by psychotomimetic drugs.

Incubations were at 37° for 1 h, the mixture contained in 2·25 ml: *S*-adenosyl-5'-[^{14}C]methionine chloride (0·5mCi mmol^{-1}) 0·025 μCi, *N*-acetyl-5-hydroxytryptamine $9{\cdot}2 \times 10^{-5}$M, phosphate buffer (pH 7·9) 538 μM and pineal homogenate prepared by the method of Axelrod & Weissbach (1961) 13·3 mg tissue, equivalent to 350 μg enzyme (Lowry, Rosebrough & others, 1951). In parallel experiments, each psychotomimetic drug in 0·25M phosphate buffer pH 7·9 was added to the above mixture to give a final concentration of $1{\cdot}2 \times 10^{-4}$M. Controls from which *N*-acetyl-5-hydroxytryptamine was omitted were carried out to demonstrate that no [^{14}C]labelling of the drug occurred. Melatonin was extracted and assayed by the method of Axelrod & Weissbach (1961).

The figures in Table 1 show that dimethyltryptamine at $1{\cdot}2 \times 10^{-4}$M stimulates bovine pineal HIOMT by almost 30%. At the same concentration, the other psychotomimetic compounds produce about 15% activation while lysergic acid gives only a 10% increase. However, Shein, Wilson & others (1971), who used rat pineal cultures, reported that neither mescaline nor lysergide affected melatonin levels whereas mescaline increased 5-hydroxytryptamine levels by stimulating pineal tryptophan hydroxylase.

It is not yet possible to correlate clinical potency of hallucinogenic compounds with their *in vitro* stimulation of pineal HIOMT; however, should these drugs accelerate the enzyme *in vivo*, a new mechanism must be considered. A hyperactive pineal HIOMT

Table 1. *Effect of psychotomimetic and related agents* (*at* $1{\cdot}2 \times 10^{-4}$M) *on bovine HIOMT.*

Agents	% increase or decrease in activation of bovine HIOMT as melatonin
Dimethyltryptamine (DMT)	+27·83 ± 1·44 (4)
Methoxybufotenin	+16·52 ± 2·47 (5)
Lysergide (tartrate)	+14·23 ± 3·32 (3)
Mescaline HCl	+14·06 ± 1·92 (4)
Amphetamine SO_4	+12·50 ± 2·18 (6)
3,4-Dimethoxyphenethylamine† (DMPEA)	+10·11 ± 1·59 (5)
N-Acetyl-3,4-dimethoxyphenethylamine† (NADMPEA)	+8·70 ± 1·15 (3)
Dopamine†	−12·26 ± 1·78 (4)
Lysergic acid†	+9·88 ± 1·52 (4)
Melatonin†	+6·03 ± 0·80 (2)

+ Activation; − Inhibition.
Standard errors are shown and number of determinations are indicated in brackets.
† non-psychotomimetic agents in man.

would produce high melatonin levels which may either increase 5-hydroxytryptamine levels in such areas of the brain as the hypothalamus or the mid-brain (Anton-Tay & Wurtman, 1969) or be converted by cyclic dehydration into hallucinogenic carboline derivatives (McIsaac & others, 1961).

Psychotomimetic compounds produce psychoses in normal subjects similar to those observed in schizophrenia. The fact that all the hallucinogenic compounds examined *in vitro* increase the amounts of melatonin is particularly relevant since we have recently shown (Hartley & Smith, 1972) that neuroleptic drugs used in the treatment of the disease inhibit the *in vitro* formation of melatonin. However, some increased amount of melatonin is observed with lysergic acid, a reputedly non-psychotomimetic compound.

Also, Table 1 demonstrates that 3,4-dimethoxyphenethylamine (DMPEA) and *N*-acetyl-3,4-dimethoxyphenethylamine (NADMPEA) at $1{\cdot}2 \times 10^{-4}$M produce a 10% increase in the formation of melatonin. The unmethylated dopamine gives a 10% decrease which is in good agreement with Weiss (1968). Both DMPEA and NADMPEA have been controversially implicated in schizophrenia (Himwich, 1971) and have been shown to produce behavioural changes in animals similar to those caused by mescaline (Bindler, Sanghvi & Gershon, 1968; Shulgin, Sargent & Naranjo, 1969). In schizophrenic patients, Greiner (1970) has proposed that pineal HIOMT may be congenitally defective, whilst we have suggested (Hartley & Smith, 1973) that the enzyme might be out of phase with its normal substrate since we demonstrated that *in vitro* pineal HIOMT will act on abnormal substrates to produce NADMPEA. It is possible therefore, that such abnormally methylated catecholamines are produced in schizophrenia and thus effect psychoses by a similar mechanism to that suggested above for mescaline.

Postgraduate School of Studies in Pharmaceutical Chemistry,
School of Pharmacy, University of Bradford,
Great Horton Road,
Bradford BD7 1DP, Yorkshire, U.K.

R. HARTLEY
J. A. SMITH

March 29, 1973

REFERENCES

ALTSCHULE, A. D. (1957). *New Engl. J. Med.*, **257**, 919–924.
ANTON-TAY, F. & WURTMAN, R. J. (1969). *Nature, Lond.*, **221**, 474–475.
AXELROD, J. & WEISSBACH, H. (1961). *J. biol. Chem.*, **236**, 211–213.
BINDLER, E., SANGHVI, I. & GERSHON, S. (1968). *Archs int. Pharmacodyn. Thér.*, **176**, 1–6.
DIAB, I. M., FREEDMAN, D. X. & ROTH, L. J. (1971). *Science*, **173**, 1022–1024.
GREINER, A. C. (1970). *Can. Psychiat. Assoc.*, **15**, 433–447.
HARTLEY, R. & SMITH, J. A. (1972). *J. Pharm. Pharmac.*, **24**, 100P–103P.
HARTLEY, R. & SMITH, J. A. (1973). *Biochem. Pharmac.*, in the press.
HIMWICH, H. E. (1971). *Biochemistry, Schizophrenias and Affective Disorders.* Chapter 5. Baltimore. The Williams and Wilkins Co.
JONES, R. L., MCGEER, P. L. & GREINER, A. C. (1969). *Clin. Chem. Acta*, **26**, 281–283.
LOWRY, O. H., ROSEBROUGH, N. J., FARR, A. L. & RANDALL, R. J. (1951). *J. biol. Chem.*, **193**, 265–275.
KETY, S. S. (1965). *Int. J. Psychiat.*, **1**, 409–415.
MCISAAC, W. M., KHAIRALLAH, P. A. & PAGE, I. H. (1961). *Science*, **134**,. 674–675.
NAYLOR, R. J. & OLLEY, J. E. (1969). *Br. J. Pharmac.*, **36**, 208–209.
OSMOND, H. & SMYTHIES, J. R. (1952). *J. ment. Sci.*, **98**, 309–315.
SHEIN, A. N., WILSON, S., LARIN, F. & WURTMAN, R. J. (1971). *Life Sci., 10*, Part 2, 273–282.
SHULGIN, A. T., SARGENT, T. & NARANJO, C. (1969). *Nature*, **221**, 537–541.
WEISS, B. (1968). *Advances Pharmac.*, **6**, 152–155.