EFFECT OF PSYCHOTROPIC DRUGS ON THE RELEASE OF SEROTONIN INDUCED BY ELECTRICAL STIMULATION OF MIDBRAIN RAPHE IN RATS

W. KOSTOWSKI and E. GIACALONE

Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea 62, Milan, Italy

The electrical stimulation of the midbrain raphé (MR) results in a marked increase of 5-hydroxyindoleacetic acid (5HIAA) and a simultaneous slight decrease of 5-hydroxytryptamine (5HT) in the forebrain of rats (Aghajanian *et al.*, 1967). It was therefore interesting to investigate the effect of several drugs on this experimental condition by using unanaesthetized animals chronically implanted with electrodes in the MR (see Table I). Pentobarbital anaesthesia prevented the decrease of 5HT and only partially the increase of 5HIAA.

Desipramine and chlorpromazine induced a complete blockade of the biochemical effects induced by MR stimulation.

The case of amphetamine at relatively low doses is more complicated because it already induces an increase of 5HIAA in the forebrain. However, there was a tendency to block the decrease of 5HT and even more to prevent the increase of 5HIAA after stimulation.

Eserine produced a similar effect as amphetamine but much less marked; however, it did not prevent the rise of 5HIAA in stimulated rats. LSD25 prevented the decrease of 5HT without changing the increase of 5HIAA. Reserpine considerably increased the level of 5HIAA and it induced the known fall of 5HT in normal rats. In stimulated animals the effect of reserpine was more marked on brain 5HT than in non-stimulated rats.

The results obtained do not allow a simple classification of the tested drugs in relation with their known pharmacological effects, but they add further data in the complex picture of the interaction of psychotropic drugs with 5HT metabolism.

In particular the effect of desipramine and chlorpromazine may be related to the fact that these drugs inhibit the uptake (Iversen 1965; Manara *et al.*, 1967) and the efflux (Manara *et al.*, 1966) of biogenic amines in the brain. Gey and Pletscher (1961) have found that chlorpromazine decreases the release of 5HT induced by reserpine and the rise of 5HT due to monoamineoxidase inhibitors. The fact that drugs like chlorpromazine and desipramine behave similarly on this experimental condition does not mean that the final effect of 5HT activity must be the same, because chlorpromazine is a strong antagonist of 5HT (Gyermek *et al.*, 1956; Garattini and Valzelli, 1955, 1965) while desipramine is rather a potentiator (Gyermek, 1966).

The effect of amphetamine is difficult to explain because this drug is supposed to be a competitive monoamineoxidase inhibitor (Blaschko *et al.*, 1937), an effect which should lead to a decrease of 5HIAA.

LSD is known to decrease the release of 5HT from electrically stimulated brain slices (Chase *et al.*, 1967) and from brain of animals treated with reserpine (Freedman, 1960), probably because it increases 5HT synthesis in brain (Diaz *et al.*, 1967).

The effect of reserpine was interesting because it adds evidence to the observation that the depletion of amines by reserpine is more rapid when the structure is under nervous stimulation (Carlsson, 1966).

REFERENCES

AGHAJANIAN, G. K., ROSENCRANS, J. A. and SHEARD, M. H. (1967): Serotonin: release in the forebrain by stimulation of midbrain raphé. *Science, 156*, 402.

BLASCHKO, H., RICHTER, D. and SCHLOSSMAN, H. (1937): The oxidation of adrenaline and other amines. *Biochem. J., 31*, 2187.

TABLE I

No. of rats	Treatment (mg/kg i.p.)		Brain content (γ/g ± S.E.)					
			5HT			5HIAA		
			Non-stimulated	Stimulated	Change (%)	Non-stimulated	Stimulated	Change (%)
41	Saline		0.381 ± 0.01	0.288 ± 0.02*	−24	0.252 ± 0.01	0.396 ± 0.02***	+57
23	Pentobarbital	40.0	0.352 ± 0.02	0.360 ± 0.01°	—	0.291 ± 0.01	0.350 ± 0.01*	+21
32	DMI	10.0	0.390 ± 0.02	0.328 ± 0.03	−16	0.276 ± 0.01	0.293 ± 0.01°°	+ 6
24	CPZ	5.0	0.354 ± 0.03	0.342 ± 0.03	—	0.278 ± 0.01	0.278 ± 0.03°°	—
21	LSD	0.1	0.350 ± 0.02	0.392 ± 0.01°°°	+12	0.238 ± 0.01	0.348 ± 0.02**	+46
26	Amphetamine	2.0	0.437 ± 0.03	0.365 ± 0.03°	−16	0.381 ± 0.02°°°	0.328 ± 0.04	−15
21	Eserine	1.0	0.421 ± 0.01	0.362 ± 0.01	−14	0.318 ± 0.02°°°	0.434 ± 0.01**	+36
24	Reserpine	2.5	0.134 ± 0.01°°°	$0.082 \pm 0.00^{°°°}_{***}$	−39	0.605 ± 0.06°°°	0.590 ± 0.07°°°	—

* = $p < 0.01$ between stimulated and non-stimulated animals. ° = $p < 0.02$ as compared to saline.
** = $p < 0.005$ between stimulated and non-stimulated animals. °° = $p < 0.01$ as compared to saline.
*** = $p < 0.0025$ between stimulated and non-stimulated animals. °°° = $p < 0.005$ as compared to saline.

Sprague-Dawley female rats 160–180 g, 13–15 days after implantation, were used. Drugs or saline were injected 30 min. before stimulation (biphasic pulses 10 c/sec., 2 ms, 5–7 volts) with the exception of pentobarbital given at the beginning of the stimulation. During stimulation animals were placed into a special container to avoid movements of the head. After stimulation, animals were sacrificed, their forebrains were removed by precollicular section (caudally to hypothalamus), quickly frozen and submitted to extractions. 5HT and 5HIAA were measured spectrofluorimetrically in the same sample (Giacalone, unpublished) or separately according to Shore (1959) for 5HT and to Giacalone and Valzelli (1966) for 5HIAA.
Statistical analysis was performed by conventional methods.

CARLSSON, A. (1966): Pharmacological depletion at catecholamine stores. *Pharmacol. Rev.*, *18*, 541.
CHASE, T. N., BREESE, G. R. and KOPIN, I. I. (1967): Serotonin release from brain slices by electrical stimulation: regional differences and effect of LSD. *Science*, *157*, 1461.
DIAZ, P., NGAI, S. H. and COSTA, E. (1967): The effect of LSD on the metabolism of rat brain serotonin (5HT). *Pharmacologist*, *9*, 251.
FREEDMAN, D. (1960): LSD-25 and brain serotonin in reserpinized rat. *Fed. Proc.*, *19*, 266.
GARATTINI, S. and VALZELLI, L. (1955): Antagonismo tra serotonina da un lato e cloropromazina e reserpina dall'altro. *Boll. Soc. ital. Biol. sper.*, *31*, 1648.
GARATTINI, S. and VALZELLI, L. (1965): *Serotonin*, p. 88, Elsevier Publishing Company, Amsterdam.
GEY, K. F. and PLETSCHER, A. (1961): Einfluss von Chlorpromazin und Chlorprothixen auf den Monoaminstoffwechsel des Rattenhirns. *Helv. physiol. pharmacol. Acta*, *19*, C22.
GIACALONE, E. and VALZELLI, L. (1966): A method for the determination of 5-hydroxyindolyl-3-acetic acid in brain. *J. Neurochem.*, *13*, 1265.
GYERMEK, L. (1966): The pharmacology of imipramine and related antidepressants. *Int. Rev. Neurobiol.*, *9*, 117.
GYERMEK, L., LÁZÁR, G. and CSÁK, Z. (1956): The antiserotonin action of chlorpromazine and some other phenothiazine derivatives. *Arch. int. Pharmacodyn.*, *107*, 62.
IVERSEN, L. L. (1965): The inhibition of noradrenaline uptake by drugs. *Advanc. Drug Res.*, *2*, 5.
MANARA, L., SESTINI, M. G., ALGERI, S. and GARATTINI, S. (1966): On the ability of desipramine to interfere with reserpine induced noradrenaline release. *J. Pharm. Pharmacol.*, *18*, 194.
MANARA, L., ALGERI, S. and SESTINI, M. G. (1967): Some modifications of the adrenergic mechanism induced by DMI-reserpine interactions. In: *Proceedings, I International Symposium on Antidepressant Drugs, Milan, 1966*, pp. 51-60. ICS 122, Excerpta Medica, Amsterdam.
SHORE, P. A. (1959): A simple technique involving solvent extraction for estimation of noradrenaline. *Pharmacol. Rev.*, *11*, 276.