The pressor action of 2,5-dimethoxy-4-methylamphetamine in rats

The hallucinogen, 2,5-dimethoxy-4-methylamphetamine (DOM or STP) increases the systolic blood pressure and exerts other autonomic effects in man (Snyder, Faillace & Hollister, 1967). The effects of STP on biogenic amines in animal brains have also been studied. In rats, it caused an increase of the level of 5-hydroxytryptamine (5-HT) with a concomitant decrease of that of 5-hydroxyindoleacetic acid (5-HIAA) (Freedman, Gottlieb & Lovell, 1970), and a decrease in 5-HT turnover (Andén, Corrodi, Fuxe & Meek, personal communication). Increases in the concentration of 5-HT and, even more profoundly, that of noradrenaline were also observed in young chickens (Wallach, Friedman & Gershon, 1972); however, no marked changes of either 5-HT or noradrenaline concentrations resulted from the administration of STP to mice (Idänpään-Heikkilä & McIsaac, 1970). In view of the above findings which have demonstrated the influence of STP on neurotransmitters, possibly also on their receptors, we undertook to study effects of STP on the blood pressure of animals.

Male Sprague-Dawley rats, 300 to 380 g, were anaesthetized by intraperitoneal injection of 50 mg/kg of pentobarbitone sodium in saline. Arterial pressure was recorded from a polyethylene cannula placed in the left common carotid artery and connected to a Linear-Core pressure transducer (Model P-1000) and a E & M physiograph (Type DNP-4A). Injections of drugs were made through a polyethylene cannula in the right jugular vein. Pithed rats were prepared according to the method of Gillespie & Muir (1967). Reserpine (5 mg/kg) was injected intraperitoneally to animals 6 h before the measurement of blood pressure. Where artificial respiration was needed, a Harvard rodent respirator (Model 680) was used; output (400 ml/kg)/min.

STP exhibited a potent pressor action in rats (Table 1). The increase of systolic pressure was greater than that of the diastolic pressure. The effect was transient: after a dose of 50 μg/kg *via* the jugular vein a peak was reached within 15 s, and the blood pressure returned to normal in 30 min. When STP was given to man, the systolic pressure was also increased; however, in contrast to the observation in rats, the diastolic pressure was unaffected.

Table 1. *Effects of varying concentrations of STP on the blood pressure of rats.*

STP dose (μg/kg)	Increase in blood pressure (mm Hg)	
	Mean	Systolic
10	15·5 ± 1·6	24·8 ± 1·6
25	25·8 ± 2·7	41·3 ± 3·9
50	37·8 ± 2·4	70·3 ± 4·4

Each value represents the mean ± s.e. of 6 animals.

Table 2. *Effects of pithing or reserpine on STP pressor action.*

STP dose (μg/kg)	Increase in blood pressure (mm Hg)		
	Nontreated	Pithed	Reserpinized
10	15·5 ± 1·6 (6)	26·0 ± 5·9 (4)	25·6 ± 3·7 (5)
50	37·8 ± 2·4 (6)	56·5 ± 12·2 (4)	48·6 ± 5·2 (5)

Each value represents the mean ± s.e. The numbers of animals are given in parentheses.

Table 3. *Effects of phentolamine, hexamethonium and cinanserine on STP pressor action.*

STP dose (μg/kg)	Increase in blood pressure (mm Hg) Phentolamine			Hexamethonium			Cinanserine		
	Before	After	block-ade%	Before	After	block-ade%	Before	After	block-ade%
10	15·8 ±1·5 (5)	5·8 ±1·7 (5)	76	18·0 ±2·2 (4)	16·5 ±5·2 (4)	10	15·7 ±1·7 (4)	0·5 ±1·0 (4)	97
50	37·6 ±1·0 (5)	19·2 ±2·7 (5)	55	34·0 ±7·4 (4)	37·8 ±11·6 (4)	−12	32·5 ±6·8 (4)	1·8 ±1·3 (4)	94

Each value represents the mean ± s.e. The numbers of animals are given in parentheses.

STP produced an increase in blood pressure even in the reserpinized or pithed rats (Table 2). The elevation of blood pressure after pithing implied that the pressor action of STP was not mediated through the cns. The failure of hexamethonium hydrochloride (20 mg/kg, *via* the cannula) to block the increase of blood pressure by STP indicated that it did not exert its action by stimulating autonomic ganglia. Furthermore, this pressor action was independent of biogenic amines as pretreatment of reserpine (5 mg/kg, i.p.) did not prevent the elevation of blood pressure. All these results suggested that STP may exert a direct stimulation of receptors of biogenic amines in the cardiovascular system.

To further differentiate the involvement of noradrenaline and 5-HT receptors, selective blockers of the two systems were then used. The α-adrenoceptor blocking agent, phentolamine hydrochloride (10 mg/kg), blocked 75 and 55% of the STP pressor action produced by 10 and 50 μg/kg respectively (Table 3). At doses higher than 10 mg/kg phentolamine was able to block also the 5-HT receptors (Offermeier & Ariëns, 1966). For the blockade of 5-HT receptors, cinanserine hydrochloride [2-(3-dimethylaminopropylthio)cinnamanilide] was chosen. This agent has been demonstrated to inhibit 5-HT effect on the blood pressure of phenobarbitone anaesthetized dogs (Rubin, Piala & others, 1964). In the present study, a 1 mg/kg dose of cinanserine blocked only the pressor action of 5-HT but not its depressor action or the pressor action of noradrenaline in pentobarbitone-anaesthetized rats. The same dose also caused a completed blockade of the pressor action of STP in animals (Table 3). Our results, therefore, suggest that STP exhibits its pressor action by stimulating 5-HT receptors in the cardiovascular system. In conjunction with this, the reported decrease of 5-HT turnover in rat brains has been related to the stimulation of 5-HT receptors by STP by Andén & his colleagues.

Texas Research Institute of Mental Sciences,
Houston, Texas 77025, *U.S.A.*

JEN-TZAW HUANG
BENG T. HO

May 15, 1972

REFERENCES

FREEDMAN, D. X., GOTTLIEB, R. & LOVELL, R. A. (1970). *Biochem. Pharmac.*, **19**, 1181–1188.
GILLESPIE, J. S. & MUIR, T. C. (1967). *Br. J. Pharmac. Chemother.*, **30**, 78–87.
IDÄNPÄÄN-HEIKKILÄ, J. E. & MCISAAC, W. M. (1970). *Biochem. Pharmac.*, **19**, 935–937.
OFFERMEIER, J. & ARIËNS, E. J. (1966). *Archs int. Pharmacodyn. Thér.*, **164**, 192–215.
RUBIN, B., PIALA, J. J., BURKE, J. C. & CRAVER, B. N. (1964). *Ibid.*, **152**, 132–143.
SNYDER, S. H., FAILLACE, L. & HOLLISTER, L. (1967). *Science*, **158**, 669–670.
WALLACH, M. B., FRIEDMAN, E. & GERSHON, S. (1972). *Eur. J. Pharmac.*, **17**, 259–269.