Effect of 2,5-dimethoxy-4-methylamphetamine on heart and smooth muscle contraction

We have previously reported that 2,5-dimethoxy-4-methylamphetamine (DOM or STP) produces an increase of blood pressure in rats (Huang & Ho, 1972). This pressor action was not attenuated by destroying the central nervous system of animals yet it was blocked by cinanserin, a 5-HT receptor blocker, suggesting the possible involvement of STP with the 5-HT receptors on peripheral tissues. To elucidate this possible mechanism, we have examined the action of STP on the isolated perfused heart and aorta strip preparations, as well as the rat stomach fundus strip preparation.

Male Sprague-Dawley rats, 300 g, were killed, the heart was removed and a cannula tied into the aorta. Perfusion was in oxygenated Ringer-Locke solution at 60 cm water. The method was that of Langendorff adapted for rat heart. A myograph Type A transducer (Narco Biosystems, Houston, Texas), connected to a physiograph (Type DNP-4A, Narco Biosystems) was attached to the apex of the heart for recording amplitude and rate of contraction. Coronary flow was recorded by a drop counter connected to the physiograph. STP (0·1 or 1 mg) in 0·2 ml of Ringer-Locke solution was injected through the cannula.

The fundus area was dissected from the stomach of the same rats, opened longitudinally and cut into a strip about 2 cm in length, according to Vane (1957). Contraction of the strip in 5 ml of Krebs solution was recorded by the myograph Type A connected to the physiograph.

The rabbit aorta strip was studied according to Furchgott & Bhadrakom (1953). The aorta from a male rabbit, 3 kg, was spirally cut to produce a continuous strip about 3 mm in width and 2 cm in length. The apparatus and procedure were the same as described for the stomach fundus strip.

Table 1 shows that during 4 min of perfusion of rat heart, 1 mg of STP produced 100% increase in amplitude of contraction: a non-significant 20% increase was observed with 0·1 mg. The rate of contraction was not affected by 0·1 mg of STP but was significantly decreased by 1 mg of the compound after 1 min of perfusion (control 100 ± 7·4; treated 82·6 ± 8·2, $P < 0.05$). No change in coronary flow was observed with either dose of STP during 4 min. The increase of contraction amplitude produced by 1 mg of STP resembles the effect of 5-HT on isolated heart, but the rate of contraction differed. STP either decreased or did not affect rate of contraction while 5-HT increased it (Douglas, 1970).

STP produced a contraction of rabbit aorta strip, the magnitude being that 0·8 μg ml^{-1} of STP is equivalent to about 1·0 ± 0·05 g (n = 4). The development of the contraction was rather slow and reached a maximum in about 30 min, as did the recovery process. After washing the contracted aorta strip, it took about 60 min to

Table 1. *Effects of STP on the isolated perfused rat heart.*

STP (mg)	Control	Percent of control			
		Time (min)			
		1	2	3	4
		Amplitude of contraction			
0·1	100 ± 10·4	114·5 ± 5·3	107·6 ± 8·6	121·3 ± 9·6	107·8 ± 6·6
1·0	100 ± 16·1	132·0 ± 9·5	172·3 ± 20·3	200·0 ± 27·8	157·2 ± 20·9

Each value represents mean ± s.e. of five animals. Control values were taken 1 min before starting perfusion of STP.

return to its original base-line. A greater magnitude of contraction was produced by 100 μg ml^{-1} of STP. The recovery in this case required several hours and no contraction was produced after the strip was re-exposed to STP. However, cold storage of the strip at 5° overnight restored the response of the strip to STP (100 μg ml^{-1}). STP (100 μg ml^{-1}) relaxed the contraction of the aorta strip produced by noradrenaline but failed to relax the contraction producd by 5-HT; instead an augmentation was observed.

Cinanserin (2 μg ml^{-1}) blocked or relaxed the contraction of aorta strip produced by STP or 5-HT, but in the same concentration it failed to block the contractions produced by noradrenaline. These results suggest that STP stimulates 5-HT receptors in the aorta strip. The contraction produced by noradrenaline could only be blocked by cinanserin at a concentration 100 times that which blocked the contraction produced by 5-HT.

In rat stomach fundus, 100 μg ml^{-1} of STP produced a contraction equivalent to about 3·6 $\pm$ 0·1 g (n = 3); a similar contraction was produced by 0·05 μg ml^{-1} of 5-HT or 0·1 μg ml^{-1} of acetylcholine. There was no synergistic action of acetylcholine with STP. Noradrenaline (2 μg ml^{-1}) either prevented or relaxed the contraction produced by STP. After STP was washed from the contracted strip the fundus strip slowly returned to its original level with the exception of an increase in the spontaneous contraction frequency and magnitude. Cinanserin (100 μg ml^{-1}) blocked the contraction produced by STP and partly blocked that produced by acetylcholine.

Amphetamine (Innes, 1962), like STP, was reported to produce a contraction of rat stomach fundus strip. This is in contrast to other sympathomimetic amines which tend to relax the stomach fundus. Using a receptor protection method, Innes also demonstrated that amphetamine caused stimulation of 5-HT receptors in the stomach fundus. Although both STP and amphetamine produced a stomach fundus contraction by stimulation of 5-HT receptors, and both exert pressor action, yet the action of the two drugs can be differentiated by cinanserin which is capable of blocking pressor action of STP but fails to block that of amphetamine (Huang & Ho, to be published). The results of the present study further indicate that the pressor action of STP is likely to be the result of contraction of the heart muscle and constriction of the blood vessels via stimulation of 5-HT receptors.

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July 26, 1973

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