SIMILARITY BETWEEN D-SEROTONIN RECEPTORS AND α-ADRENERGIC RECEPTORS

I. I. Abramets

UDC 612.18

Experiments were carried out on isolated strips of the stomach and seminiferous ducts of rats, and on whole rats in which the blood pressure in the abdominal aorta was recorded, using methods of crossed tachyphylaxis with serotonin and selective protection of specific receptors with noradrenalin and serotonin against dibenamine block. They showed that sympathomimetic substances possessing methoxyl groups (mescaline, compound T-7), act mainly on D-serotonin receptors of smooth muscles. A weaker action of this type is possessed by sympathomimetic drugs not containing hydroxyl groups (amphetamine). Sympathomimetics possessing only one hydroxyl group act mainly on α-adrenergic receptors. The results indicate structural similarity between D-serotonin receptors and α-adrenergic receptors.

Serotonin was discovered as a vasoconstrictor drug of noncatecholamine nature in the blood serum [7]. It was later found that the effects of catecholamines and of serotonin on certain organs are competitively blocked by the same antagonists [1,3,6,9]. Vane [8], working with a sympathomimetic drug (amphetamine), found that this substance acts on D-serotonin receptors of smooth muscles of the rat stomach. Innes [4,5] developed Vane's idea and concluded that in some organs (the cat spleen) the effects of catecholamines and serotonin are brought about through the same type of receptors.

EXPERIMENTAL METHOD

Experiments were carried out on isolated strips of the stomach and the isolated seminiferous ducts of rats and on anesthetized rats (blood pressure recorded in the abdominal aorta) to investigate the possibility of crossed tachyphylaxis between several sympathomimetic drugs and serotonin and to examine the degree of protection given by serotonin and noradrenalin against irreversible dibenamine block of the receptors through which the specific effects of sympathomimetics are brought about.

In the first group of experiments, changes in responses to the test drug were investigated on a strip of the rat stomach after reproduction of tachyphylaxis to serotonin in the strip. When crossed tachyphylaxis was present, the reaction to the tested agonist was absent under these conditions or considerably reduced. In the experiments on the seminiferous ducts and on rats, tachyphylaxis was produced by injection of the tested drugs, and the serotonin effects were investigated against this background.

Experiments on protection of the receptor were carried out on a strip of stomach and on the seminiferous ducts of rats by Furchgott's method [2]. Dibenamine in a concentration of $1 \cdot 10^{-7}$–$5 \cdot 10^{-6}$ g/ml was used as unbalanced blocking agent, and serotonin ($1 \cdot 10^{-4}$ g/ml) and noradrenalin ($5 \cdot 10^{-5}$ g/ml) were used as protective substances.

EXPERIMENTAL RESULTS

A typical experiment on a rat is illustrated in Fig. 1. After tachyphylaxis to mescaline had been obtained, the reaction to serotonin was virtually absent. In this case a crossed tachyphylaxis to both mescaline and serotonin was observed. In the experiments of this series, similar results were obtained with compound T-7 and with amphetamine, but not with ephedrine, pedrolone, and compound T-4.

In the experiments on the isolated seminiferous ducts of rats, crossed tachyphylaxis with serotonin was also produced by mescaline, compound T-7, and amphetamine; these sympathomimetics either possess

Department of Pharmacology, A. M. Gor'kii Donetsk Medical Institute (Presented by Academician of the AMN SSSR V. V. Zakusov). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 67, No. 2, pp. 63-65, February, 1969. Original article submitted March 26, 1968.

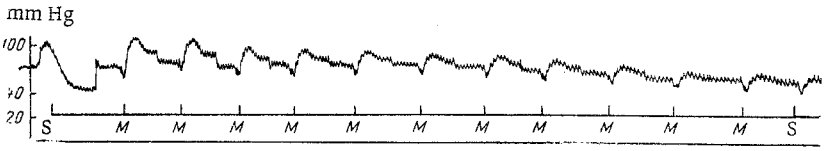

Fig. 1. Crossed tachyphylaxis to mescaline and serotonin in an experiment in which the blood pressure was recorded in the abdominal aorta of a rat. From top to bottom: arterial pressure, marker of injection, zero line. S, intravenous injection of serotonin in a dose of 10 μg/kg; M, intravenous injection of mescaline in a dose of 300 μg/kg.

TABLE 1. Mean Values of Residual Responses (in %) after Dibenamine Block (experiments on isolated rat organs)

Drug	Isolated seminiferous duct		Strip of stomach
	protection by serotonin	protection by noradrenalin	protection by serotonin
Noradrenalin	25.1	71.7	
Serotonin	84.6	48.2	90.7*
Amphetamine	30.5	40.8	89.1
Ephedrine	11.3	69.1	
Pedrolone	4.3	51.4	
Compound T-4	0	51.5	
Compound T-7	79.5	28.5	88.5
Mescaline	78.0	35.5	86.1

*Remaining sympathomimetics caused a contraction of the strip of stomach which was too small to estimate or they caused relaxation.

no hydroxyl groups (amphetamine) or they do possess methoxyl groups. The remaining investigated sympathomimetics did not give rise to crossed tachyphylaxis.

On a strip of rat stomach, amphetamine, compound T-7, mescaline, and pedrolone caused contractions in contrast to catecholamines which caused relaxation of the smooth-muscle strip of the rat stomach [6].

The ability of the drugs mentioned above to cause contraction of smooth muscles of the stomach is due to their effect on D-serotonin receptors, as was confirmed by the presence of crossed tachyphylaxis between these substances and serotonin. Crossed tachyphylaxis to serotonin was not obtained with compound T-4 and ephedrine.

The presence of crossed tachyphylaxis with serotonin indicates the possibility that phenylalkylamines (mescaline, compound T-7, and amphetamine) may act upon D-serotonin receptors of the smooth muscles of blood vessels, the seminiferous duct, and the stomach of rats, thus indicating common features in the structure of adrenergic and D-serotonin receptors of these organs.

The structural similarity between the receptors implies the possibility of their crossed protection against irreversible blocking by dibenamine and other haloethylamines.

Table 1 shows that noradrenalin effectively protected the α-adrenergic receptors (residual response 71.7%), but gave much weaker protection to the D-serotonin receptors (residual response 48.2%). Serotonin protected the serotonin receptors (84.6%) and also, to some extent, the α-adrenergic receptors (25.1%). The results given in Table 1 also show that, with the exception of compound T-4, all sympathomimetic drugs to some extent acted upon both α-adrenergic receptors and D-serotonin receptors. However, mescaline, compound T-7, and amphetamine caused contraction of the rat seminiferous duct, acting mainly on D-serotonin receptors, as shown by the high residual responses of these agonists during protection of the receptors by serotonin. On the other hand, noradrenalin, ephedrine, pedrolone, and compound T-4 produced the same effect by acting mainly upon α-adrenergic receptors of the smooth muscles of the seminiferous duct.

The effects of amphetamine, compound T-7, and mescaline on the strip of stomach were connected with their action upon D-serotonin receptors.

These results are supplementary to those obtained by Vane [8], because he worked only with the stomach and intestine of rats and rabbits. Phenylalkylamines possessing methoxyl groups in the ring possessed the greatest effect on D-serotonin receptors of smooth muscles, and phenylalkylamines without hydroxyl groups gave a weaker effect. Amines possessing only one hydroxyl group acted mainly on α-adrenergic receptors.

The results confirm the hypothesis of similarity between active centers of D-serotonin receptors and α-adrenergic receptors of smooth muscles, but they suggest an absence of structural identity.

LITERATURE CITED

1. I. M. Samoilovich, Pharmacological Analysis of Serotonin-Sensitive Structures, Candidate dissertation, Donetsk (1966).
2. R. F. Furchgott, J. Pharmacol. Exp. Ther., 111, 265 (1954).
3. K. H. Ginzell,and K. A. Kottegoda, Quart. J. Exp. Physiol., 38, 225 (1953).
4. I. R. Innes, Brit. J. Pharmacol., 19, 427 (1962).
5. I. R. Innes, Brit. J. Pharmacol., 21, 427 (1963).
6. J. Offermeier and E. J. Ariens, Arch. Internat. Pharmacodyn., 164, 192 (1966).
7. M. M. Rapport, A. A. Green, and I. H. Page, Science, 108, 329 (1948).
8. J. R. Vane, in: Ciba Foundation Symposium on Adrenergic Mechanisms, London (1960), p. 356.
9. D. W. Woolley and E. Shaw, Fed. Proc., 12, 239 (1953).