PHARMACOLOGICAL ANALYSIS OF SOME ADRENOMIMETIC EFFECTS OF SEROTONIN

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UDC 615.217.22:547.756

It was shown with the aid of D-, M-, and T-antagonists of serotonin (LSD-25, indocarb, tipindole), the sympatholytic agent bretylium, the α-adrenoblocker droperiodol, and also of imipramine that contractions of the isolated rat vas deferens induced by serotonin are unconnected with direct excitation of serotoninergic and adrenergic structures, but can be explained by liberation of catecholamines through the action of serotonin.

KEY WORDS: serotonin; liberation of noradrenalin.

In the modern view the effect of serotonin on the mammal can be explained not only by its interaction with serotoninergic structures, but also by its ability to liberate catecholamines and also to interact directly with adrenergic structures [4]. As regards the mechanism of the adrenomimetic action of serotonin on the isolated rat vas deferens, data in the literature are extremely contradictory. Some workers [10] claim that serotonin can directly excite the α-adrenergic structures of the vas, whereas others [9], on the basis of experiments with reserpine and guanethidine, state that the effect of serotonin is mediated by catecholamines liberated under its influence from sympathetic nerve endings. However, it has been concluded from data showing the different effects of chelating agents, enzymes, and certain other substances on contractions of the vas evoked by noradrenalin and serotonin that the response of the vas to serotonin is due to excitation of the D-serotoninergic structures of its smooth muscles [1, 3].

In this investigation an attempt was made to explain the mechanism of the spasmogenic effect of serotonin on the rat vas deferens.

EXPERIMENTAL METHOD

Male albino rats weighing 180-250 g were decapitated. The vasa deferentia were isolated and placed in 20-ml jars filled with aerated Krebs' solution at 32°C [7]. After incubation for 1.5 h, during which the nutrient solution was changed 7 or 8 times, the original responses to serotonin and noradrenalin were recorded on the tape of a kymograph. After each response had been recorded the organ was rinsed with 100 ml Krebs' solution. The magnitude of the original responses to serotonin or noradrenalin was compared with the magnitudes of responses to administration of the same amines and after preincubation for 15 min either with serotonin antagonists (LSD-25, tipindole, indocarb) or with substances affecting the neuronal uptake of biogenic amines or possessing sympatholytic or α-adrenolytic properties (imipramine, bretylium, droperidol). The concentrations of the antagonists and agonists are indicated in the text. The total number of experiments was 52.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that noradrenalin induces contraction of the isolated rat vas deferens starting from concentrations of $0.5 \cdot 10^{-6}$-$1 \cdot 10^{-6}$ M and serotonin with concentrations 100-400 times higher –

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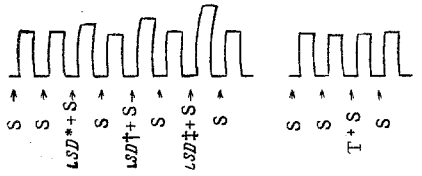

Fig. 1

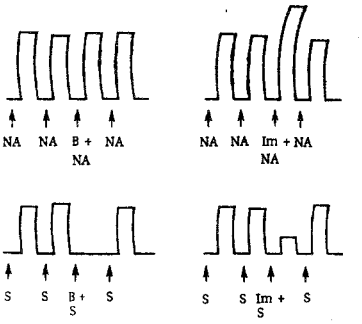

Fig. 2

Fig. 1. Effect of LSD-25 and tipindole on contractions of isolated rat vas deferens induced by serotonin. S) Addition of serotonin (final concentration 10^{-4} M); LSD* – addition of LSD-25 ($3 \cdot 10^{-9}$ M); LSD† – ditto ($3 \cdot 10^{-8}$ M); LSD‡ – ditto ($3 \cdot 10^{-7}$ M); T) addition of tipindole ($5 \cdot 10^{-5}$ M).

Fig. 2. Effect of bretylium and imipramine on contractions of isolated rat vas deferens induced by noradrenalin and serotonin. NA – Addition of noradrenalin (final concentration 10^{-6} M); S – addition of serotonin (10^{-4} M); B) addition of bretylium (10^{-4} M); Im – addition of imipramine ($3.2 \cdot 10^{-7}$ M).

$1 \cdot 10^{-4}$ to $2 \cdot 10^{-4}$ M. When noradrenalin was used contractions appeared after 1-2 sec, but in the experiments with serotonin they developed much more slowly – in the course of 2-3 min. This suggested that the mechanisms of development of contractions of the vas in response to serotonin and noradrenalin are different. However, the next experiments showed that the classical serotonin antagonist LSD-25, in concentrations blocking D-serotoninergic structures ($1 \cdot 10^{-9}$ M), and also in doses 10-100 times greater [5], not only does not reduce but, on the contrary, increases the response of the vas to serotonin. For instance, with a concentration of the antagonist of $3 \cdot 10^{-9}$ M the response was increased on the average by 15%, in a concentration of $3 \cdot 10^{-8}$ M it was increased by 29%, and in $3 \cdot 10^{-7}$ M by 57%. LSD-25 had a similar effect on contractions of the vas produced by noradrenalin. Neither indocarb, in concentrations blocking D- and M-serotoninergic structures [6], nor tipindole in a concentration of $5 \cdot 10^{-5}$ M (sufficient to block serotoninergic structures of D-, M-, and T-types) reduced the response of the vas to serotonin (Fig. 1). The results indicate that D-, M-, and T-serotoninergic structures do not participate in the production of contractions of the vas in response to serotonin.

Meanwhile experiments with the α-adrenolytic droperidol confirmed the view that α-adrenergic structures participate in the formation of this response. In a concentration of $1 \cdot 10^{-7}$ M, for instance, droperidol depressed the response of the vas to noradrenalin and to serotonin equally (results of 10 experiments). To discover whether serotonin causes contractions of the vas as a result of direct interaction with α-adrenergic structures or through the liberation of catecholamines, bretylium and imipramine were used.

In a concentration of $1 \cdot 10^{-4}$ M bretylium has a marked sympatholytic action but does not affect α-adrenergic structures [2]. The experiments showed that bretylium, in the above concentration, did not alter the response of the vas to noradrenalin but completely inhibited contractions to serotonin (Fig. 2). This could be connected with the ability of bretylium to block the serotonin-induced liberation of catecholamines from nerve endings. The results of these experiments also show that the response of the vas to serotonin was not due to the direct action of the latter on α-adrenergic structures. The effect of imipramine, which blocks monoamine uptake, on contractions to serotonin and noradrenalin was studied in other experiments. Imipramine in a concentration of $3.2 \cdot 10^{-7}$ M reduced contractions of the vas to serotonin by 66%. The response to noradrenalin, on the other hand, was increased under these circumstances by 50% (Fig. 2). This last effect could be due to an increase in the concentration of mediator in the region of the receptors as a result of blocking of its reverse transport in nerve endings [8]. Depression of the response of the organ to serotonin by imipramine was evidently due to the ability of imipramine to prevent serotonin from entering the nerve fibers and liberating the mediator.

The results thus indicate that serotoninergic structures of D-, M-, and T-types play no part in the formation of "serotonin" contractions on the isolated rat vas deferens. No direct excitatory effects of

serotonin on α-adrenergic structures could be discovered in these experiments. The mechanism of the mimetic action of serotonin on the isolated rat vas deferens is evidently that it liberates noradrenalin from sympathetic fibers, and this then interacts with the α-adrenergic structures.

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