Bol. Zool. e Biol. Mar., N.S., n.º 30, pp. 81-86, São Paulo, 1973

THE SEROTONIN-LIKE ACTIONS OF SOME HALLUCINOGENS ON A MOLLUSCAN HEART

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AÇÃO SEROTONINA-MIMÉTICA DE ALGUNS ALUCINÓGENOS NO CORAÇÃO DE UM MOLUSCO

RESUMO:

Algumas substâncias psicodélicas representando diferentes classes de alucinogênios mimetizam mais a ação da serotonina do que as catecolaminas no coração isolado de *Mercenaria mercenaria*.

ABSTRACT

Several psychedelic substances representing different classes of hallucinogens mimic the action of serotonin rather than the catecholamines on the isolated heart of *Mercenaria mercenaria*.

It is a privilege for us to participate in this tribute to Professor Sawaya on the occasion of this retirement. One of us (J.H.W.) has enjoyed a long acquaintance with Professor Sawaya and came to know Brasil during a period of research in his Department.

The mode of action of hallucinogens at cellular and biochemical levels is poorly understood. While there is rather general agreement that most of them act by way of monoaminergic neurotransmitter systems, opinions differ regarding which system — serotonin (5-HT) or catecholamine — may be involved.

The complexity of the mammalian CNS makes the study of the pharmacology of identifiable neurons and synapses peculiarly difficult and 5-HT-containing neurons, except those to the pineal gland, appear

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Número especial em homenagem ao Prof. Dr. Paulo Sawaya, no ano jubilar de seu magistério.

to be absent from the mammalian peripheral nervous system. In some invertebrate animals, however, there are central and peripheral monoaminergic neurons whose junctions are more conveniently accessible for pharmacological study. For example, molluscan hearts are innervated by 5-HT-containing neurons and probably by dopaminergic neurons as well [1]. Certain of the hallucinogens (e.g. LSD-25) have earlier been shown to mimic the action of 5-HT on molluscan hearts [2]. Since the pharmacology of the heart of the clam, *Mercenaria* (= *Venus*) *mercenaria,* has been extensively studied, it was chosen for a more complete survey of the actions of a series of hallucinogens. Included in this, or in earlier studies, were the following compounds: (a) the indole derivatives — bufotenine, psilocybin, dimethyltryptamine (DMT), and diethyltryptamine (DET); (b) the indole-containing substances — d-lysergic acid diethylamide (LSD-25) and d-1-acetyl lysergic acid diethylamide (ALD-52); (c) the phenylethylamine derivatives — mescaline and 2,5-dimethoxy-4-methyl-amphetamine (DOM; "STP").

Answers to the two following questions have been sought: (1) do these hallucinogens act like 5-HT or like the catecholamines on the *Mercenaria* heart, and (2) what are their relative potencies? The procedure has been similar to that used in earlier studies of LSD on this heart [3]. The isolated heart was bathed in a 10 ml. volume of sea water to which the hallucinogen was added, and the response of the heart compared with its response to 5-HT or to the catecholamines (dopamine, norepinephrine, epinephrine). Over most of its effective range (10^{-9} to 10^{-5} M), 5-HT increases the amplitude of beat of the *Mercenaria* heart with little increase in tonus, while the catecholamines are active only at higher concentrations (near 10^{-5} M) and they increase the frequency of beat and tonus until hearts stop in systole. 1-Methyl-d-lysergic acid butanolamide (methysergide; UML) is a highly effective antagonist of 5-HT on the *Mercenaria* heart [3] but does not block the action of the catecholamines. The efficacy of UML as an antagonist of the hallucinogens was therefore determined.

To estimate relative potencies of the several hallucinogens, an effort was made to find the molar concentration of each that would produce a response of the heart that was only slightly above threshold. This could not be done with a high degree of accuracy for a number of reasons. Chief among these was that what appeared to be a near threshold dose after an exposure of 10 to 20 min. might, if left in

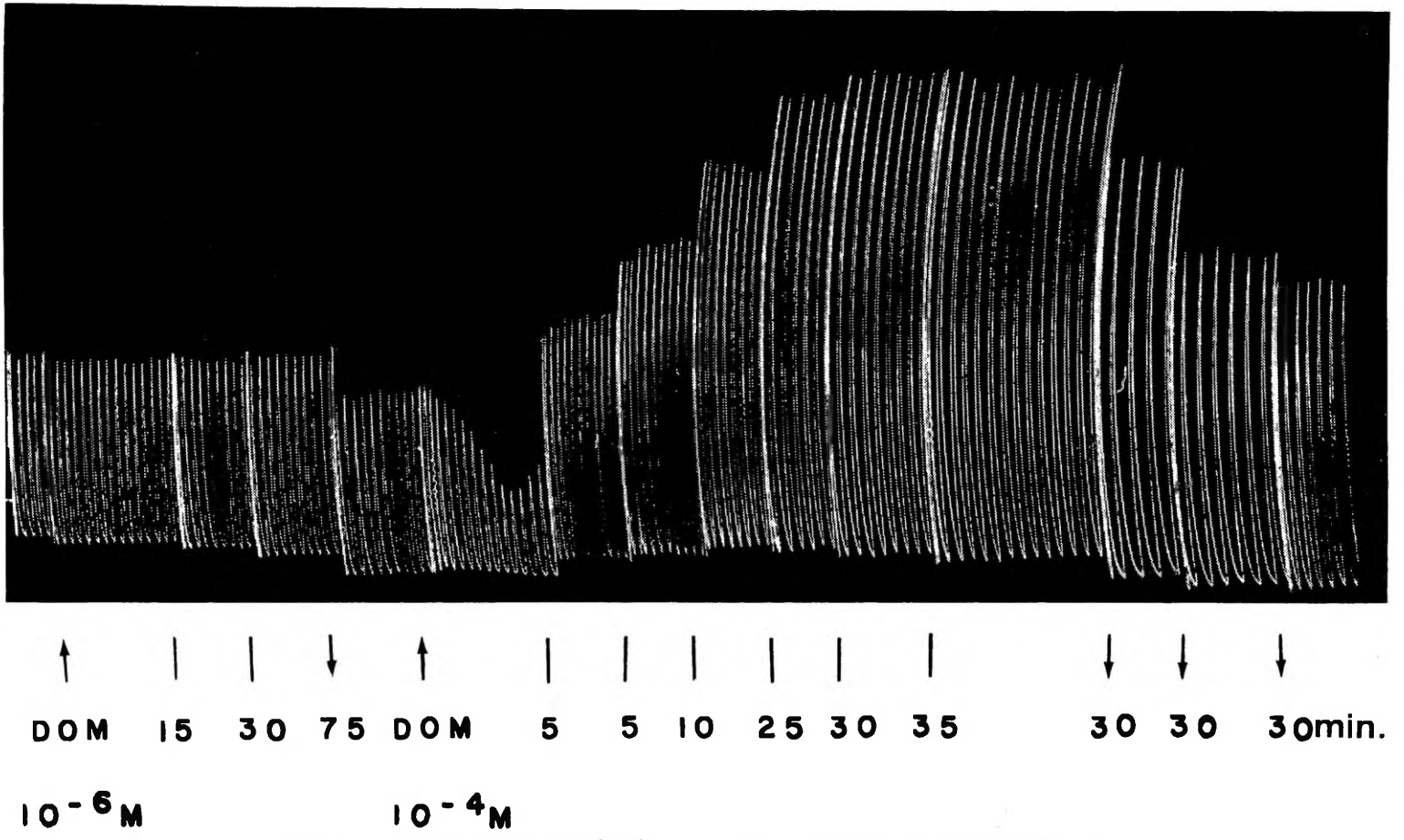

Fig. 1 — Kymograph record showing responses of *Mercenaria* heart to 10^{-6} M and 10^{-4} M 2,5-dimethoxy-4-methyl-amphetamine (DOM). At the vertical bars, the drum was stopped for the minutes indicated while the DOM remained in the bath. At each ↓ the drum was stopped and the heart washed with several changes of sea water during the minutes indicated. The decrease in amplitude with 10^{-4} M DOM was atypical.

the bath for 1 to 3 hours, produce a maximal response. This had been observed earlier for LSD [3], and for bufotenine, DMT and DET [4] Also, all of the hallucinogens are difficult to wash out of the heart; requiring from 30 minutes to many hours depending on the particular hallucinogen and the concentration used. Even when the beat returned to its original amplitude and frequency, the hearts were usually tachyphylactic to the same hallucinogen. For these reasons it was usually necessary to use a fresh heart for each concentration of each hallucinogen studied. This introduced a further variable, namely individual and seasonal variation in sensitivity of *Mercenaria* hearts to their normal cardioregulators and, though not systematically studied, apparently also to the hallucinogens.

It was known from earlier studies that LSD-25, ALD-52, bufotenine, DMT and DET all mimic the action of 5-HT on the heart of *Mercenaria* [3, 4]. Their primary effect is to increase amplitude of beat, sometimes accompanied by an increase in frequency, but little or no increase in tonus except at high concentrations. The same was found to be true for psilocybin and yohimbine. These substances are close analogs of 5-HT or contain the indole ring. The finding that mescaline and DOM also closely mimic the actions of 5-HT on the *Mercenaria* heart was not anticipated although from the results of Greenberg [4] this might have been predicted. Figure 1 is a record of the actions of 10^{-6} and 10^{-4} M DOM and illustrates a rather typical response to any of the hallucinogens studied. 10^{-6} M DOM was near threshold for this heart, while 10^{-4} M DOM produced a near-maximal response after an exposure of 80 minutes. After three periods of washing during 90 minutes, the amplitude of beat had not returned to the original level.

A further indication that mescaline and DOM are probably active at 5-HT receptors, was the observation that UML blocked them as effectively as it blocked 5-HT and the other hallucinogens. That amphetamines act on 5-HT receptors in mammalian smooth muscle was already known (Vane, 1960; Innes, 1963).

The approximate relative activities on the *Mercenaria* heart of the hallucinogens that have been used in the present or earlier studies are given in Table I. The molar concentrations are those that produced measurable increases in amplitude of beat after exposures of 10 to 20 minutes. The range of concentrations is an indication of the usual variation in sensitivity of different hearts. LSD is the most active of the hallucinogens on the *Mercenaria* heart. As little as 10^{-17} M pro-

TABLE 1

Ranges of molar concentrations of several hallucinogens required for near-threshold, 5-HT-like action on *Mercenaria* hearts.

Hallucinogens	Number of hearts	Range of near-threshold concentrations
		Molar
LSD-25	40	10^{-17} — 10^{-12}
Mescaline	10	10^{-12} — 10^{-10}
Bufotenine [a]	7	10^{-10} — 5×10^{-10}
[5-HT [b]	100 +	10^{-9} (av.) I
Psilocybin	7	10^{-10} — 10^{-8}
DET [c]	7	10^{-9} — 1.2×10^{-8}
DMT [c]	6	1.7×10^{-9} — 3×10^{-8}
DOM ("STP")	10	10^{-7} — 10^{-6}
ALD-52	3	10^{-6}
Yohimbine	3	10^{-6} — 10^{-5}

[a] Includes data from Greenberg (1960b).
[b] Mean threshold concentration of 5-HT for comparison.
[c] Values from Table I, Greenberg (1960b).

duces a maximal increase in amplitude of beat in some hearts if allowed to act for 2-3 hours. At 10^{-7} to 10^{-6} M, LSD produces a maximal effect in about 10 minutes. A plot of time required for maximal action against the logarithm of molar concentration of LSD, between 10^{-6} M and 10^{-17} M, yields a straight line. The effect of LSD is very slowly reversed by washing. With some hearts, continuous washing for 15 hours has failed to bring the amplitude of beat back to its original level. Untreated hearts washed for such a period of time show a gradual decrease in strength of beat. *Mercenaria* hearts are made up of about 100,000 smooth muscle cells[4]. 10^{-17} M LSD in 10 ml of bathing fluid would provide less than one molecule per muscle cell. It is difficult to conceive of a mechanism of action of LSD that would account for such potency and prolonged action.

Mescaline at near threshold doses acts more rapidly than LSD but the amplitude of beat does not increase significantly with prolonged exposure. Hearts also appear to become tachyphylactic to mescaline more rapidly than to other hallucinogens.

Bufotenine, psilocybin, DMT and DET have similar patterns of action and their thresholds are not very different. Bufotenine, the most active, has been found by others to be 10 to 50 times as potent as 5-HT on the *Mercenaria* heart [4, 6].

Although ALD-52 was found to be equipotent with LSD as a psychotomimetic [7], it, and yohimbine, are the least active of the hallucinogens on the *Mercenaria* heart.

DOM or "STP" is a new hallucinogen which is reported to be about one-thirtieth as potent as LSD in man and about 100 times as potent as mescaline [8]. On the *Mercenaria* heart, it is far less active than LSD or mescaline. It is obvious from a comparison of the relative activities of DOM and ALD-52 on man and on the *Mercenaria* heart that there must be marked differences such as in rates of penetration, destruction or removal, or of combination with receptors in these quite unlike test situations. This is not unexpected but more important to a better understanding of the mechanism of action of the hallucinogens is the observation that those tested all appear to act like 5-HT on *Mercenaria* heart cells which are normally excited by this neurotransmitter. However, this is not meant to imply that this is the mode of action of the hallucinogens in the brain of man, only that it is a possibility.

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9. Supported by Grant, 2-RO1-NB 00623, from USPHS.