ROLE OF CENTRAL SEROTONINERGIC PROCESSES IN THE HEAD-TWITCHING PHENOMENON INDUCED BY TRYPTOPHAN IN MICE AND RATS

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Injection of tryptophan (100-200 mg/kg) into mice and rats whose monoamine oxidase activity is inhibited by phenelzine (15-50 mg/kg) produces the head-twitching phenomenon. The serotonin antagonists BOL-148 and deseryl, in a dose of 1 mg/kg, if injected 30 min after tryptophan, as well as the tryptophan-hydroxylase inhibitor parachlorophenylalanine, injected in a dose of 300 mg/kg 1 h before tryptophan, diminished or completely prevented this phenomenon. The serotonin concentration in the brain of animals showing the head-twitching phenomenon was increased by more than 3 times above the control level.

Tryptophan, in conjunction with monoamine oxidase (MAO) inhibitors, gives rise to the head-twitching phenomenon in mice and rats [4, 11]. A similar motor response arises in mice through the action of 5-hydroxytryptophan (5-HT), the immediate precursor of serotonin.

Since head twitching, like the other behavioral effects of 5-HT, is due to elevation of the serotonin level in the brain [8, 9], and also since tryptophan is an initial product of serotonin biosynthesis and the immediate precursor of 5-HT, it was decided to investigate the role of central serotoninergic processes in the genesis of head twitching by the action of tryptophan.

Interest in this phenomenon is also due to the fact that, because head twitching can be recorded quantitatively, this phenomenon can be used as a model to evaluate the effect of psychotropic drugs on central serotoninergic processes [9]. Great importance is attached to these latter in the pathogenesis of depression and in the mechanism of the thymoanaleptic effect [1, 6, 7, 10, 13].

EXPERIMENTAL METHOD

Experiments were carried out on albino mice of both sexes and on male albino rats. All drugs were injected intraperitoneally. Head twitching was counted for each animal every 30 min for 2 h after injection of tryptophan [4]. Immediately after recording of the head twitches, the animals were decapitated and the serotonin concentration in the brain determined fluorometrically by a modified ninhydrin method [3]. One mouse brain (without the cerebellum) or one rat brain stem, obtained by the method described previously [5], was used for each determination. The results were subjected to statistical analysis by the Fisher–Student method.

EXPERIMENTAL RESULTS

The head twitching phenomenon was observed in all mice and rats receiving tryptophan after preliminary injection of phenelzine. The serotonin receptor blocking agents BOL-148 (2-bromolysergic acid diethylamide) and deseryl (1-methyl-D-lysergic acid butanolamide) considerably reduced the intensity of the

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TABLE 1. Effect of Deseryl, BOL-148, and PCPH on Number of Head Twitches Evoked by Tryptophan in Mice

Drugs and doses (in mg/kg)	Total no. of head twitches in group		
	M ± m (n)		P
Phenelzine (50) + tryptophan (200)	15.84 ± 4.70	(10)	
Phenelzine (50) + tryptophan (200) + deseryl (1)	0.0		
Phenelzine (50) + tryptophan (200)	12.30 ± 2.46	(10)	< 0.001
Phenelzine (50) + tryptophan (200) + BOL-148 (1)	2.20 ± 0.72		
Phenelzine (50) + tryptophan (200)	28.60 ± 2.36	(10)	< 0.001
Phenelzine (50) + PCPH (300) + tryptophan (200)	3.60 ± 2.20		

Note. Phenelzine and PCPH were injected 1 h before tryptophan, and deseryl and BOL-148 30 min after tryptophan. Number of animals given in parentheses.

TABLE 2. Effect of Combined Administration of Phenelzine and Tryptophan on Brain Serotonin Concentration in Rats and Mice

Species of animals	Group No.	Drugs and doses (in mg/kg)	Serotonin concentration (in μg/g brain tissue)				Phenomenon of head twitching
			M ± m (n)		%	P	
Mice	1	Water	0.79 ± 0.02	(18)	100		Absent
	2	Phenelzine (50) + tryptophan (150)	3.01 ± 0.02	(12)	380	0.01	Present
Rats	3	Water	0.42 ± 0.02	(23)	100		Absent
	4	Phenelzine (20) + tryptophan (150)	1.55 ± 0.05	(6)	340	0.01	Present
	5	Phenelzine (15) + tryptophan (100)	1.34 ± 0.07	(9)	297	0.01	Present
	6	The same	0.98 ± 0.07	(14)	218	0.01	Absent

Notes. 1) In these experiments head twitches were counted in an alternative form.
2) $P_{4-5} < 0.002$ (rats receiving equal doses of phenelzine and tryptophan were divided into 2 subgroups depending on the presence or absence of head twitches).

head twitching or prevented it altogether when tryptophan was injected after phenelzine (Table 1). Parachlorophenylalanine (PCPH), an inhibitor of tryptophan hydroxylase, the enzyme controlling the rate of the whole process of serotonin biosynthesis [12], also reduced the number of head twitches (Table 1).

In mice receiving tryptophan (150 mg/kg) after the preliminary injection of phenelzine (50 mg/kg) and in rats receiving a combination of tryptophan with phenelzine in a dose of 20 mg/kg, the brain serotonin level was more than 3 times higher than normal (Table 2). Head twitches were observed under these conditions in 100% of animals.

If the dose of phenelzine was reduced to 15 mg/kg and that of tryptophan to 100 mg/kg, head twitching developed in only some of the rats. In these animals the brain serotonin concentration was increased by 3 times, while in the rats in which head twitching was absent the increase was only 2.2 times ($P < 0.05$).

The results suggest that the head twitching produced by tryptophan against the background of MAO inhibition is due to increased activity of central serotoninergic processes and that at least the initial appearance of this motor response is associated with an increase in the brain serotonin concentration up to a certain threshold level. In the present investigation no attempt was made to study the relationship between the brain serotonin concentration and the intensity of head twitching. These results do not agree with those obtained by Hess and Doefner [11], who observed no correlation between elevation of the brain serotonin level and the presence of head twitching. Comparison of the experimental techniques used does not yet permit any definite conclusions to be drawn regarding the reasons for these differences.

In the discussion on the mechanism of this phenomenon, the view shared by certain writers [2, 12] that it is mediated not through serotonin, but through one of its metabolites, must be considered. Recent work has demonstrated the presence of N-methyl-transferase, an enzyme catalyzing the conversion of serotonin into bufotenine, in the brain tissue of man, rats, and chickens. Bufotenine is known to have the property of causing head twitching in animals [8]. It can be postulated that the formation of bufotenine from serotonin takes place during blocking of deamination, the main pathway of serotonin metabolism, by MAO inhibitors. However, the hypothesis regarding the role of serotonin metabolites in the mechanism of the behavioral effects of tryptophan against the background of MAO inhibition requires direct experimental verification.

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