EFFECT OF IMIPRAMINE-LIKE ANTIDEPRESSANTS ON HEAD TWITCHING IN MICE INDUCED BY 5-HYDROXYTRYPTOPHAN

E. L. Shelkunov

UDC 615.214.32.015.4:612.822.1.018.577.175.823

When head twitching (HT) in mice in response to administration of 5-hydroxytryptophan (5-HTP) was used as a "serotoninergic" model the antidepressants chlorimipramine and imipramine, and also chlorpheniramine (suprastin), exhibited a serotonin-positive action in doses of 1.0, 5.0, and 1.0 mg/kg respectively. Quipazine had a serotoninomimetic action, desipramine an ambivalent action in doses of 1-20 mg/kg, whereas iprindole and morphaphen were ineffective in doses of up to 20 mg/kg. Amitryptiline, noveril (dibenzepine), melitracene, trimeprimine (trimipramine), and ludiomil (maprotiline) exhibited an antiserotonin action in doses of 0.5, 1.0, 20.0, and 20.0 mg/kg respectively. The results are discussed in the light of the concept of a complex spectrum of mediator activity of the imipramine-like antidepressant.

KEY WORDS: antidepressants; anti- and proserotonin action; screening; 5-hydroxytryptophan; head twitching.

It is now generally accepted that an essential biochemical mechanism of the antidepressive action of the imipramine-like antidepressants is their serotonin-positive action [7, 9], due to inhibition of reverse transport of serotonin into the terminals of serotoninergic neurons [7, 13].

Head twitching (HT), caused by injection of 5-hydroxytryptophan (5-HTP) into mice [8], is widely used to assess the effect of drugs on central serotoninergic processes.

In the investigation described below a series of imipramine-like antidepressants was tested on this relatively simple and convenient serotoninergic model.

EXPERIMENTAL METHOD

The number of HT in mice was counted by a modified method [5] for 1 min after every 6.5 min in the course of 52 min after intraperitoneal injection of D,L-5-HTP in a dose of 200 mg/kg. The total number of HT per experiment was counted for each mouse. Antidepressants or distilled water (H_2O) in the control were injected intraperitoneally simultaneously with 5-HTP in a volume of 0.1 ml/20 g body weight. The significance of the difference between the number of HT in the control and experimental groups in each experiment was determined by Student's t-test. One control and five experimental groups (eight mice in each group) were included in each experiment. The minimal effective doses (MED) of antidepressants causing inhibition or potentiation of HT were taken to be the smallest doses which gave a statistically significant effect in at least half of the experiments (not less than four experiments per dose). The doses of the antidepressants were varied by a factor of 2 in the successive experiments. Altogether 2950 mice were used.

EXPERIMENTAL RESULTS

The results of two typical experiments are given in Table 1. Of the series of antidepressants tested only chlorimipramine (anafranil) and imipramine, which have the strongest blocking action on serotonin reassimilation, clearly increased HT. Their MED were 1 and 5 mg/kg respectively. The antihistamine drug chloropheniramine (suprastin), which blocks the reverse transport of serotonin into the neurons [10] but has significant adrenopositive action [5], also increased HT in doses starting from 1 mg/kg. Quipazine, with the properties of a serotoninomimetic, and suggested for use as an antidepressant [12], induced HT in doses of 0.1-20.0 mg/kg. The action of desipramine was irregular: in some doses it potentiated HT, in others it inhibited it.

Laboratory of Psychopharmacology, V. M. Bekhterev Leningrad Psychoneurological Research Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 9, pp. 304-306, September, 1978. Original article submitted January 13, 1978.

TABLE 1. Effect of Antidepressants on HT Induced by 5-HTP (results of experiments)

Year and date of experiment	Drug	Dose, mg/kg	Interval, min*	Number of HT	P‡
9/19/1973	H_2O		30	2,1±0,93	
	Imipramine	5,0	30	7,4±1,02	<0,002
	Chlorpheniramine	2,5	30	14,6±3,03	<0,01
	H_2O		0	0,9±0,61	
	Imipramine	5,0	0	16,4±3,96	<0,01
	Chlorphenira mine	2,5	0	8,5±1,91	<0,01
5/30/1974	H_2O		0	10,8±1,96	
	Melitracene	2,5	0	13,4±1,51	
	Melitracene	10,0	0	6,0±2,01	<0,1
	Melitracene	20,0	0	1,1±0,74	<0,001
	Chlorimipramine	2,5	0	25,5±5,94	<0,05
	Chloromipramine	5,0	0	51,7±10,71	<0,002

*Between injection of drug and 5-HTP.
†Relative to control for that particular experiment.

In the last series of experiments desipramine potentiated HT very slightly but only in a dose of 10 mg/kg in three experiments ($P < 0.1$; < 0.1, < 0.05). After administration of desipramine in a dose of 20 mg/kg HT was potentiated in two of six experiments, there was no effect in three, and antagonism was observed in one experiment. In a dose of 5 mg/kg there was no effect in two experiments, antagonism was observed in one, and synergism in 1 ($P < 0.1$).

The other imipramine-like antidepressants did not potentiate HT but, on the contrary, could inhibit it when the dose was increased, and so exhibited antagonism against 5-HTP. The antidepressants were investigated in this test over a range of doses from 0.5 to 20.0 mg/kg. The data are summarized in Table 2.

In the first investigation [8] in which an alternative method of assessing HT was used, the inhibitory effect of amitryptiline, desipramine, imipramine, and chlorpheniramine on HT was observed; the action of amitryptiline, ED_{50} for which was 1.4 mg/kg, was 8.6 times stronger than that of desipramine and 42 times stronger than that of imipramine and chlorpheniramine. The results show that counting the number of HT can also reveal a serotonin-positive action, but only for drugs which exhibit such an action strongly (chlorimipramine, chlorpheniramine, imipramine). For most antidepressants, however, a serotonin-positive action could not be detected on this model, and such drugs as amitryptiline and noveril showed a strong serotonin-negative action.

When these data are interpreted it must be noted that, besides serotonin-positive components, due to inhibition of serotonin transport into the terminals of the serotoninergic neuron, the antidepressants also have several other neuromediator effects [14, 15]. In particular, they have an antiserotonin action, which is particularly marked in the case of amitryptiline [15]. The integral "mediator equivalent" of each drug will therefore depend on the relationship between the various aspects of its activity [14]. For drugs of the desipramine and noveril type, with a strong adrenopositive action, it is particularly important to take into account also the antagonism between adrenergic and serotoninergic systems [6, 14], in the body as a whole. On such a model the present writer also found that adrenomimetics have a powerful inhibitory action on HT.

The data on the integral serotonin-positive effect (serotonin-positive equivalent) of some antidepressants and the serotonin-negative or neutral action of others are in good agreement with data in the literature on these compounds [11] and, in particular, with data showing the very weak blocking of reverse serotonin transport by antidepressants such as trimeprimine, ludiomil, iprindole (one-thousandth as strong as chlorimipramine), desipramine, and noveril (one-hundredth as strong) [7, 11, 13], so that in vivo adequate inhibition of serotonin uptake into brain slices is practically never achieved (ED_{50} greater than 60 mg/kg] [13].

TABLE 2. Effect of Antidepressants on HT Induced by 5-HTP (summary of data)

Drug	Effect	MED, mg/kg
Chlorimipramine	S	1,0
Imipramine	S	5,0
Chlorpheniramine	S	1,0
Desipramine	Irregular (A-S)(A—F)	
Quipazine	Induces HT	0,1—20
Amitryptiline	A	0,5
Noveril (dibenzepine)	A	1,0
Melitracene	A	20,0
Trimeprime	A	20,0
Ludiomil (maprotiline)	A	20,0
Iprindole	0	
Morphaphen (L-90)	0	

Legend. S) Synergism, A) antagonism, 0) no effect.

On the other hand, when tests are carried out on frogs for antidepressant screening [2], a serotonin-positive action is evidently detected [3] in most antidepressants. It seems likely that in these tests mainly a presynaptic (based on inhibition of reassimilation) serotonin-positive component of the action of antidepressants and neuroleptics is found, because of the functional characteristics of the nervous system and (or) the righting reflex of the frog used in this case. A special feature of these tests for screening is evidently that in this respect they approximate closely biochemical methods which reveal inhibition of serotonin transport into the serotoninergic neuron [13] and also into platelets [2].

To conclude, it can be said that the serotoninergic response of HT in mice to injection of 5-HTP provides a concrete model in which different types of synapses play a definite role. Other serotoninergic models on the whole animal may reveal a rather different resultant effect of the drugs on pre- and postsynaptic processes of neuromediation in mammals [14]. However, in mammals and on other physiological models on the animal as a whole, of all the known imipramine-like antidepressants only chlorimipramine and imipramine potentiated the central effects of serotonin [1, 5], and in some models only inhibition of serotoninergic processes was found [1, 4].

LITERATURE CITED

1. A. P. Gilev, V. Zh. Kurilenko, T. M. Vysokovskii, et al., in: The Pharmacological Basis of the Antidepressive Effect [in Russian], Leningrad (1970), p. 75.
2. I. P. Lapin, G. F. Oksenbrug, I. V. Ryzhov, et al., Farmakol. Toksikol., No. 2, 144 (1976).
3. G. F. Oksenkrug, S. V. Osipova, and N. V. Uskova, in: Serotoninergic Processes in the Action of Psychotropic Drugs [in Russian], Leningrad (1970), p. 47.
4. E. Zh. Shelkunov, in: Serotoninergic Processes in the Action of Psychotropic Drugs [in Russian], Leningrad (1970), p. 150.
5. E. L. Shelkunov, in: Depressions and Their Treatment [in Russian], Leningrad (1973), p. 131.
6. B. B. Brodie and P. A. Shore, Ann. New York Acad. Sci., 66, 631 (1957).
7. A. Carlsson, H. Corrodi, K. Fuxe, et al., Europ. J. Pharmacol., 5, 357 (1969).
8. S. J. Corne and R. W. Pickering, Psychopharmacologia (Berlin), 11, 65 (1967).
9. I. P. Lapin and G. F. Oxenkrug (G. F. Oksenkrug), Lancet, 1, 132 (1969).
10. P. Lidbrink, G. Jonsson, and K. Fuxe, Neuropharmacology, 10, 521 (1971).
11. A. Randrup and C. Braestrup, Psychopharmacology, 53, 309 (1977).
12. R. Rodrigues, J. A. Rojas-Ramirez, and R. R. Drucker-Colin, Europ. J. Pharmacol., 24, 164 (1973).
13. S. B. Ross and A. L. Renyi, Europ. J. Pharmacol., 7, 270 (1969).
14. E. L. Schelkunov (E. L. Shelkunov), Activ. Nerv. Sup. (Prague), 9, 207 (1967).
15. W. Theobald, A. Büsch, and H. A. Kunz, Arzneimittel-Forsch., 15, 117 (1965).