EFFECT OF 3-HYDROXYPYRIDINE DERIVATIVES ON THE CENTRAL NERVOUS SYSTEM

A. V. Val'dman,* T. A. Voronina,
L. D. Smirnov, U. M. Tilekeeva,
and K. M. Kyumaev

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In the modern view [3, 9, 11], antioxidant inhibitors can be used as potential protective agents against various noxious factors and, in particular, as agents protecting biological membranes against injuries due to activation of lipid peroxidation (LPO). The most promising natural and synthetic antioxidants are α-tocopherol, sterically hindered phenols, 1,4-dihydropyridines, and derivatives of 3-hydroxypyridine.

Among these substances the water-soluble antioxidants which are 3-hydroxypyridine derivatives [9], structurally close to compounds of vitamin B_6 group, are of definite interest from the pharmacologic point of view. It has been shown that 3-hydroxypyridines possess a broad spectrum of biological action (radioprotective [2], heteroprotective [12]) and that they can protect blood against mechanical trauma [10].

The writers showed previously [8] that in experiments on animals 3-hydroxypyridine derivatives have an anticonvulsant, sedative, and muscle-relaxing action. Later, the anticonvulsant action of 3-hydroxypyridines was confirmed by other investigations [1, 5]. Meanwhile the effects of these substances on the CNS have not been studied.

Accordingly, the investigations described below was undertaken with the aim of an experimental study of the spectrum of psychotropic effects of 3-hydroxypyridines in order to obtain an idea of the particular effect of these substances on the CNS.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino mice weighing 18-24 g and rats weighing 150-250 g, by methods usually used for the detection and evaluation of manifestations of action of psychotropic drugs. To study the anxiolytic effect the conflict situation method was used, specifically with conflict between food and defensive reflexes. The antiagressive effect was determined as the threshold of the agressive response of a pair of mice to electric shock administered through the floor. The antihypoxic action was tested under conditions of hypobaric hypoxia (ascent to 11,000 m) and of hypoxia with hypercapnia in an airtight chamber. The antiamnesic action was studied by the passive avoidance test, using maximal electric shock as the amnesic agent. The effect of drugs on orienting-investigative behavior ("open field" test) also was studied, and their anticonvulsant action (antagonism with metrazol, maximal electric shock text) and their toxicity were assessed. The techniques used were described in [4]. Drugs were injected intraperitoneally 40 min before the beginning of the experiment.

The following compounds were studied:

*Academy of Medical Sciences of the USSR.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 99, No. 1, pp. 60-62, January, 1985. Original article submitted January 13, 1984.

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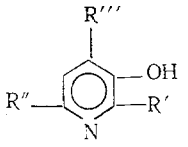
TABLE 1. Comparative Psychotropic Activity of Some 3-Hydroxypyridine Derivatives

Action	Compounds					
	I	II	III	IV	V	VI
Anxiolytic	+		+			+
Antiaggressive	—				—	
Antihypoxic	+	+	+	+	+	+
Antiamnesic	+	—	+	—	—	—
Inhibition of orienting reflexes	—	—	+	—	—	+
Inhibition of investigative behavior	—	+	+		—	+
Potentiation of hexobarbital sleep	—	+	+	+	—	
Antagonism to metrazol	Effect observed in dose of 200 mg/kg or more					
Abolition of convulsions during elec. shock	Same					
Disturbance of movement coordination	Effect observed in a dose of 300 mg/kg or more					

Legend. Anxiolytic action studied in experiments on rats, in all other cases experiments were done on mice. +) Action present in 50% of animals or more, or reduction of effect by half when all compounds used in a dose of 100 mg/kg; —)no action.



I. $R' = R'' = R''' = H$;

II. $R' = R'' = CH_3$; $R''' = H$;

III. $R' = C(CH_3)_3$; $R'' = R''' = H$;

IV $R' =$  ; $R'' = R''' = H$;

V $R' = C(CH_3)_3$; $R'' = CH_3$; $R''' = H$;

VI $R' = C(CH_3)_3$; $R'' = CH_2N$  O;

$R''' = H$;

EXPERIMENTAL RESULTS

Experiments on the animals showed that 3-hydroxypyridines have a wide spectrum of psychotropic action (Table 1). The action of these substances was exhibited most clearly on experimental models of neurotic and neurosis-like states and, in particular, when a conflict situation, based on inability to satisfy the dominant need during collision between two motivations, the basic methods of evaluation of antineurotic, tranquilizing drugs, were used. Under the influence of 3-hydroxypyridines (compounds I, II, III, IV, V, VI) in doses of 50-200 mg/kg a distinct anxiolytic effect was observed, with abolition of emotional strain and anxiety, an increase (by more than twice) in the number of attempts to satisfy the demand for food, despite consequent painful stimulation, normalization of the appropriateness of response to provocative test stimuli, and recovery of autonomic manifestations affecting the cardiovascular and respiratory systems, disturbed by the conflict situation.

By the direction and character of their tranquilizing (anxiolytic) action 3-hydroxypyridines resemble tranquilizers of the benzodiazepine series (diazepam, chlordiazepoxide), although they are much weaker (5 times or more) in their absolute activity as reflected in ED_{50} values. The distinguishing feature of the action of 3-hydroxypryidines compared with benzodiazepines is absence of muscle relaxing effects, during manifestation of the tranquilizing effect. In addition, unlike benzodiazepines hydroxypyridines induce a weak antiagressive effect.

All 3-hydroxypyridine derivatives studied, in doses of 100-200 mg/kg, had a marked antihypoxic action, prolonging the animals' survival considerably during exposure to conditions of both hyperbaric hypoxia and hypoxia with hypercapnia in an airtight chamber. Some of the compounds tested (I, II, V, VI), if injected in doses of 100-200 mg/kg 40 min before a single training session in the passive avoidance method in a dark and light chamber, had an antiamnesic action, preventing "obliteration" of the memory trace by electric shock, and restoring the disturbed learning.

Some compounds (II, III, IV, V) not only caused the effects mentioned above, but also had a general sedative action on behavior, inhibiting motor activity and orienting reflexes, and potentiating the hypnotic action of hexobarbital, which is a feature of psychotropic drugs with depressant type of action.

The anticonvulsant action of the 3-hydroxypyridines was exhibited in antagonism with metrazol tests and the maximal electric shock test as a rule in doses of over 200 mg/kg, whereas signs of neurologic impairment, detected as disturbances of motor coordination, were observed with doses of 350 mg/kg or more. LD_{50} (in mice) for individual compounds of the series varied from 300 to 1000 mg/kg.

Derivatives of 3-hydroxypyridine thus have tranquilizing, anticonvulsant, antiagressive, sedative, and also antihypoxic, and antiamnesic action under experimental conditions.

We know that antioxidants, being LPO inhibitors, under stress conditions prevent accumulation of hydroperoxides and thereby help to prevent the development of a stressor response [6, 7].

The mechanism of the psychotropic action of 3-hydroxypyridine derivatives is not yet clear. Their psychopharmacologic properties are evidence of a complex, multicomponent mechanism, probably connected primarily with structural changes in the membranes and modification of the physicochemical properties and permeability, and with other factors.

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