DISTRIBUTION OF THE ADRENOBLOCKING DRUG PYRROXAN IN ALBINO RATS

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The distribution of the adrenoblocking drug pyrroxan in the blood plasma and organs of albino rats was investigated. Pyrroxan was shown to appear rapidly in the brain, liver, kidneys, and other organs and to accumulate selectively in the hypothalamus. The use of a spectrofluorometric method showed that unchanged pyrroxan molecules disappear from the plasma and organs in the course of 2 h. In studies with pyrroxan–^{14}C, radioactivity was detected in the organs for 24 h, but in the plasma for several days, indicating the formation of metabolites of pyrroxan or its complexes with plasma proteins and with structural elements of the organs. The high effectiveness of pyrroxan in different forms of hypothalamic disturbances accompanied by symptoms of overexcitation of the sympathetic nervous system can be explained by its selective accumulation in the hypothalamus.

KEY WORDS: adrenoblockers; pyrroxan; distribution; hypothalamus.

Pyrroxan, a compound obtained at the Institute of Toxicology, Ministry of Health of the USSR [3], has a marked peripheral and central adrenoblocking action and is an effective agent for the treatment and prevention of states based upon an excessive increase of sympathetic tone.

The object of this investigation was to study the distribution of pyrroxan in the blood plasma and organs of rats.

EXPERIMENTAL METHOD

Experiments were carried out on male and female SHP albino rats weighing 170-230 g. Pyrroxan from the "Farmakon" Factory and pyrroxan labeled at the carbon atom of the carbonyl group (pyrroxan–^{14}C, specific radioactivity 2 mCi/g) were used. Aqueous solutions of pyrroxan and pyrroxan–^{14}C were injected intraperitoneally into the rats in doses of 60 and 20 mg/kg, respectively. The animals were decapitated 5, 15, and 30 min and 1, 2, 4, and 24 h after injection of the preparations. The concentration of pyrroxan in the plasma, brain, liver, and kidneys was determined by a spectrofluorometric method. For this purpose tissues were homogenized in 3 volumes of 0.01 N HCl, the pH of the homogenate and plasma was adjusted to 8.7, and the pyrroxan was extracted with 2 volumes of heptane containing 1% isoamyl alcohol. Pyrroxan was extracted from the organic phase with 0.01 N HCl. The pyrroxan concentration in the acid extracts was determined on the Hitachi spectrofluorometer with excitation wavelength of 320 nm and fluorescence of 430 nm. The results were expressed in μg pyrroxan/g tissue or /ml plasma. In the animals receiving pyrroxan–^{14}C radioactivity was determined in samples of plasma, heart, liver, kidneys, adrenals, spleen, lungs; and also of the hypothalamus, cortex, and subcortical structures of the brain. The radioactivity of the samples was measured on a Packard liquid scintillation spectrometer in dioxan scintillator. The results were expressed in counts/min/mg dry weight.

EXPERIMENTAL RESULTS

Within a few minutes after the injection of pyrroxan the drug was found in the brain, liver, and kidneys (Table 1), evidence of its high penetrating power through tissue barriers, including the blood–brain barrier.

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TABLE 1. Distribution of Pyrroxan in Blood Plasma (in μg/ml) and Organs (in μg/g) of Rats (M ± m)

Oxygen	Time after injection						
	5 min	15 min	30 min	1 min	2 min	4 min	24 min
Plasma	1,98±0,27 (12)	3,77±1,29 (16)	0,72±0,21 (9)	0,13±0,8 (10)	Traces (5)	Traces (5)	Traces (5)
Brain	6,77±2,64 (11)	21,5±5,44 (16)	10,3±3,56 (9)	4,76±0,93 (9)	1,26±1,35 (5)	Traces (5)	Traces (5)
Liver	32,0±6,46 (12)	37,5±7,78 (11)	9,8±1,94 (8)	—	Traces (5)	Traces (5)	Traces (5)
Kidneys	12,9±3,44 (12)	18,3±4,55 (17)	10.8±2.45 (10)	4,68±0,94 (7)	3,57±0,69 (4)	Traces (5)	Traces (5)

Legend. Here and in Table 2 number of animals shown in parentheses.

TABLE 2. Distribution of Pyrroxan–^{14}C in Blood Plasma and Organs of Rats (in counts/min/mg; M ± m)

Organ	Time after injection						
	5 min	15 min	30 min	1 h	2 h	4 h	24 h
Plasma	67±9 (4)	281±45 (8)	282±80 (6)	137±17 (4)	121±36 (4)	49±5 (4)	44±13 (4)
Cortex	72±14(4)	175±31 (8)	107±7 (6)	44±11 (4)	22±2 (4)	7±2 (4)	Следы (4)
Subcortex	55±13 (4)	131±24 (8)	87±5 (6)	39±4 (4)	17±4 (4)	6±1 (4)	Следы (4)
Hypothalamus	60±13 (4)	132±23 (8)	180±26 (5)	289±70 (4)	47±5 (4)	12±2 (4)	10±3 (4)
Liver	419±30 (4)	516±93 (8)	443±27 (4)	283±17 (4)	125±27 (4)	47±6 (4)	14±1 (4)
Kidneys	207±10 (4)	713±99 (8)	561±99 (6)	271±42 (4)	136±20 (4)	69±12 (4)	22±2 (4)
Adrenals	167±29 (4)	241±59 (8)	193±20 (6)	69±8 (4)	57±6 (4)	18±2 (4)	8±3 (4)
Heart	119±5 (3)	119±19 (8)	91±8 (4)	39±4 (4)	28±5 (4)	16±1 (4)	7±2 (4)
Lungs	337±59 (4)	519±99 (8)	329±50 (6)	230±1 (3)	183±58 (4)	29±11 (4)	33±7 (4)
Spleen	308±30 (3)	351±69 (8)	209±24 (6)	188±49 (4)	61±15 (4)	16±1 (4)	5±3 (4)

The greatest accumulation of pyrroxan in the liver after 5 min can be explained on the grounds both that the liver is the first organ to which the substance passes through the portal vein system when injected intraperitoneally, and also that it is in the liver that the main metabolic conversions of foreign compounds take place [2].

By the spectrofluorometric method it is possible to judge whether the samples contain unchanged molecules of the substance being determined [4], i.e., molecules which have not undergone metabolic conversion and are not stable complexes with components of the plasma and organs. The results obtained by this method indicate rapid disappearance of the unchanged pyrroxan molecules from the plasma and organs. For instance, after 1 h less than 5% of the maximal concentration of pyrroxan remained in the plasma, and only traces were present after 2 h. In the brain 22% remained after 1 h and only 6% of the maximal concentrations after 2 h in that organ.

Experiments in which pyrroxan–^{14}C was injected also showed rapid accumulation (within 15 min) of the label in most organs. In the hypothalamus, radioactivity reached a maximum after 1 h, whereas in other regions of the brain and in other organs the peak of radioactivity appeared 15-30 min after the injection of pyrroxan–^{14}C (Table 2). Pyrroxan, with definite affinity for central adrenergic structures [1], is evidently selectively retained in the hypothalamus, the posterior part of which contains mainly noradrenergic neurons [5]. It must be noted that radioactivity still persisted in the blood plasma, brain, liver, and kidneys at times after injection when pyrroxan could no longer be determined spectrofluorometrically. The level of radioactivity in the plasma after 24 h was 15% of the maximal level, and it thereafter fell very slowly: Traces of radioactivity (about 3%) were still found 10 days after the injection of pyrroxan–^{14}C. These results may indicate that the plasma and organs contained metabolic products of pyrroxan or that stable complexes of pyrroxan were formed with the plasma proteins and the structural components of the organs.

The rapid appearance of pyrroxan in the plasma and organs explains the development of the therapeutic effect during the first 5-15 min after injection of the drug; the longer stay of pyrroxan in the hypothalamus accounts for the high efficacy of this substance in the treatment of various forms of hypothalamic disorders (crises and paroxysms), associated with symptoms of overexcitation of the sympathetic nervous system [3].

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