EFFECT OF STELAZINE ON OXIDATIVE METABOLISM IN VARIOUS STRUCTURES OF THE CAT BRAIN

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A statistically significant change in oxidative metabolism is observed in the tissues of the cerebral cortex and mesencephalic reticular formation of the cat following administration of stelazine (trifluperazine). Oxidative metabolism in the cortex is reduced in acute experiments by doses of stelazine of 1 and 20 mg/kg, but is practically unchanged in chronic experiments (dose of stelazine 3 mg/kg by mouth for one month). Oxidative processes in the reticular formation are stimulated in both acute and chronic experiments.

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Under the influence of neuroleptics (phenothiazine derivatives), especially those like chloropromazine, the oxidative metabolism of the brain is modified [2-4, 6, 9]. Recently, the drug stelazine has been used clinically on a wide scale with good results in the treatment of hallucinatory states [1, 7]. This substance is a phenothiazine derivative with a side chain including a piperazine ring [1]. It could be postulated that stelazine may also produce changes in oxidative metabolism in the brain.

However, there is no information in the literature concerning the action of stelazine on oxidative metabolism whether of the brain as a whole or of individual formations differing in structures and function. According to available data [8], injection of stelazine in large doses inhibits incorporation of S^{35}- and C^{14}-galactose into the lipids of the rat brain. This neuroleptic lowers the surface tension of artificial membranes more than the other phenothiazines [12].

The object of the present investigation was to study the effect of stelazine on the intensity of respiration and oxidative phosphorylation in the tissues of various structures of the cat brain.

EXPERIMENTAL METHOD

Experiments were conducted on the brain of 20 male cats weighing 3-3.5 kg. The preparation of stelazine (of Soviet manufacture) was injected intramuscularly in a dose of 1 or 20 mg/kg. The animals were sacrificed 3-3.5 h after injection of the drug. In chronic experiments the drug was given daily by mouth in a dose of 3 mg/kg for 30 days. The animals were sacrificed 24 h after the last dose. In all experiments an experimental and a control animal of equal weight were sacrificed simultaneously. The following brain structures were investigated: cerebral cortex – motor, visual, and auditory areas (altogether), the geniculate bodies, corpora quadrigemina, and mesencephalic reticular formation. All operations of extracting and preparing the tissues after decapitation of the animal were performed in a cold room at 3-5°. The intensity of tissue respiration of these brain structures (tissue sample weighing 300 mg) was measured manometrically in a Warburg apparatus in an atmosphere of air at −26°. An incubation mixture of the following composition was used: oxidation substrate (0.1 M succinate), phosphate buffer (0.67 M), glucose (0.1 M), NaF (1.0 M), $MgCl_2$ (0.008 M), Tris-buffer (0.12 M), ADP (0.04 M), hexokinase (0.6 mg per sample). The volume of the sample was 2 ml, and its pH 7.3.

Respiration was recorded for 20 min, after which the content of bound inorganic phosphate in a trichloroacetic extract was determined by a photoelectric colorimeter with a No. 4 red filter by the method of Lowry and Lopez [10] as modified by Skulachev, Peel, and Lohmann [5]. The intensity of oxygen absorption and phosphate utilization was expressed in μatoms oxygen and inorganic phosphorus/300 mg moist

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TABLE 1. Intensity of Respiration and Oxidative Phosphorylation in Tissues of Various Cat Brain Structures (in μatoms/sample) after Administration of Stelazine

Experimental conditions, dose of stelazine	Cerebral cortex				Mesencephalic reticular formation				Geniculate bodies				Corpora quadrigemina			
	P_H	O_2	P/O	No. of expts.	P_H	O_2	P/O	No. of expts.	P_H	O_2	P/O	No. of expts.	P_H	O_2	P/O	No. of expts.
Control	13,2±0,59	8,46±0,56	1,6±0,12	7	7,78±0,18	4,64±0,27	1,68±0,11	6	9,04±0,25	5,0±0,46	1,8±0,14	7	10,62±0,89	5,0±0,28	2,1±0,12	7
Acute expt., 1 mg/kg	8,42±1,33 $t=3,28$	4,66±0,83 $t=3,8$	1,8±0,57 $t=0,34$	5	11,0±1,24 $t=2,67$	7,71±1,04 $t=2,86$	1,42±0,16 $t=1,37$	5	9,8±1,46 $t=0,51$	5,25±0,83 $t=0,26$	1,87±0,61 $t=0,11$	5	9,72±2,21 $t=0,38$	5,6±1,04 $t=0,55$	1,74±0,19 $t=1,61$	5
Acute expt., 20 mg/kg	10,7±1,24 $t=2,0$	4,9±0,28 $t=6,3$	2,04±0,23 $t=1,7$	3	5,85±0,09 $t=9,6$	3,8±0,18 $t=2,6$	1,54±0,10 $t=0,93$	3	8,8±0,26 $t=0,67$	4,33±0,07 $t=1,4$	2,0±0,0 $t=1,4$	3	9,2±1,2 $t=0,95$	5,29±0,01 $t=1,04$	1,73±0,23 $t=1,42$	3
Chronic expt., 3 mg/kg by mouth daily for 30 days	15,0±0,93 $t=1,63$	8,1±0,72 $t=0,36$	1,84±0,17 $t=1,15$	4	14,33±1,27 $t=5,1$	8,2±0,19 $t=11,0$	1,75±0,2 $t=0,3$									

Note. Differences statistically significant when $t > 2$.

weight of tissue/20 min. The P/O ratio was calculated as a measure of the coupling of oxidation and phosphorylation. The total protein content in the tissues of these parts of the brain was determined by Lowry's method [11].

EXPERIMENTAL RESULTS

It is clear from Table 1 that in the acute experiments the intensity of respiration and oxidative phosphorylation showed changes which varied in degree from one brain structure to another. In the cerebral cortex the intensity of respiration and phosphorylation fell significantly after administration of stelazine in a dose of 1 mg/kg (by 45 and 36% respectively). Conversely, respiration and oxidative phosphorylation in the reticular formation tissues were activated with this dose (by 66 and 41% respectively). After administration of stelazine in a dose of 20 mg/kg, both processes were inhibited in the cortical tissues, and this also occurred with a dose of 1 mg/kg. In the reticular formation no activation of oxidative processes was observed with a dose of 20 mg/kg, as with a dose of 1 mg/kg, but on the contrary, they were inhibited (the intensity of respiration fell by 18%, the utilization of phosphate by 24%). Both processes showed no significant change from the control level in the tissues of the corpora quadrigemina and geniculate bodies of the experimental animals.

In the animals receiving stelazine in chronic experiments, a tendency for the level of phosphorylation to rise was observed in the cortical tissues. In the reticular formation marked activation of both respiration and phosphorylation was observed (by 77 and 84% respectively), while the total protein content showed no statistically significant change under the influence of stelazine.

These results demonstrate the selective character of action of stelazine on different brain structures.

Maintenance of the normal intensity of oxidative processes in the cerebral cortex and the increase in their activation in the mesencephalic reticular formation under the influence of chronic administration of stelazine may perhaps reflect a definite functional modification of the interaction between these brain structures with the object of restoring normal cortical function. This is in agreement to some extent with the results of investigations showing improvement of logical thinking and memory in patients after prolonged administration of stelazine [7].

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