S.we.20.4

The effects of pentobarbital on complex brain function in rhesus monkeys as measured by performance in an operant test battery

Paule, M.G. and Gillam, M.P.

Pharmacodynamics Branch, Division of Reproductive and Developmental Toxicology, National Center for Toxicological Research, Jefferson, Arkansas 72079-9502, U.S.A.

The effects of the general anesthetic pentobarbital (1.0-15.0 mg/kg) on several complex brain functions were studied simultaneously by monitoring it's effects on the performance of 5-8 adult male rhesus monkeys in an operant test battery (OTB). The OTB included five different tasks that are thought to engender responding associated with aspects of motivation, color and position discrimination, learning, short-term memory and attention, and time perception. The specific tasks designed to monitor these functions, the maximum times allowed for their completion, and the number of subjects performing them each session were: Progressive Ratio 10 min, n = 8; Conditioned Position Responding 5 min, n = 8; Incremental Repeated Acquisition 35 min, n = 8; Delayed Matching-To-Sample 30 min, n = 6; and Temporal Response Differentiation 20 min, n = 5. The presentation of the tasks alternated such that on one test day, subjects were presented with the learning, color and position discrimination, and motivation tasks and on the next test day with the short-term memory and attention and the time perception tasks. Each session lasted 50 min and began 15 min after the iv administration of pentobarbital or saline (control injections). Measures of response rates and percent task completed were collected for all tasks. Response accuracies were measured in all tasks except for the motivation task. For the time perception task, 5.6 mg pentobarbital/kg significantly decreased accuracy but did not affect overall response rate. In the learning task, this same dose significantly decreased response rate but did not affect accuracy. Significant decreases in performance of the short-term memory task (decreases in both response rate and accuracy) and the motivation task (decreased response rate) were noted at doses of 10.0 mg/kg and higher whereas responding in the color and position discrimination task was not significantly disrupted at doses less than 15.0 mg/kg pentobarbital. Thus, performance in the time perception task and learning tasks is approximately equal in sensitivity to disruption by pentobarbital, with accuracy in the time perception task being more sensitive than accuracy in the learning task. Performance in the short-term memory and attention, and the motivation tasks is the next sensitive with performance in the color and position discrimination task being the least sensitive. These data indicate that the simultaneous assessment of several behaviors thought to reflect specific brain functions allows the determination of which behaviors are the most sensitive to drug effects.

S.we.20.5

The effect of 3-month administration of nootropics (pyritinol, piracetam) and methoxytacrin on the behaviour and brain variables in old rats

Benešová, O., Tejkalová, H., Krištofíková, Z., Binková, B. and Michalíková *, S.

*Psychiatric Research Institute, 181 03 Prague 8 and * Institute for Experimental Endocrinology, 833 06 Bratislava, Czechoslovakia*

In order to evaluate adequately the effects of nootropics used for the treatment of mental decline in senescence, an animal model was established using old rats and long-term peroral administration of the drug with final assessment of behaviour (open field, T-maze) and a battery of neurobiochemical markers characterizing the progress of degenerative processes in aging brain and endocrine system (Benešová et al., 1989). In this model situation, the action of two nootropics – pyritinol and piracetam – was compared with the effects of methoxytacrin, the cholinesterase inhibitor.

The experiments were carried out in 48 male rats, strain Wistar, aged 14.5 months at the start of the study. They were divided in 4 groups, each comprising 12 animals. The drugs were mixed in standard food pellets prepared freshly

twice a week in concentrations adjusted for realizing daily intake of following doses which were chosen in relation to the clinical dosage: pyritinol 40 mg/kg, piracetam 80 mg/kg, methoxytacrin 5 mg/kg. Three groups were experimental, the fourth were controls fed standard pellets. In the course of 3-month experiment, the rats were regularly followed-up for weight, food and water consumption and health condition. In the last two weeks, behaviour of all animals was tested in open field (spontaneous activity, habituation) and in T-maze (light discrimination performance). At the age of 17.5 months, the rats were decapitated, pathomorphology of the body and organs was evaluated including the histological examination of the liver. In addition, the assessments of ascorbic acid in adrenals and of liver enzymes in blood serum were performed. Brains were dissected in 6 parts (cortex, hippocampus, hypothalamus, striatum, brainstem, cerebellum) and following neurobiochemical variables were estimated: (1) marker for cholinergic neuronal activity – high affinity choline uptake (HACU), (2) markers for monoaminergic transmission – concentrations of noradrenaline, dopamine, serotonin and their metabolites HVA and 5-HIAA, (3) markers for free radical membrane damage: a) lipid peroxidation, b) protein insolubilization, (4) markers for cell number and size – concentrations of DNA, RNA, proteins.

Both nootropics improved the performance of the rats in T-maze without any change of open field activity. A deceleration of brain aging processes may be seen after pyritinol treatment, when considering the decreased fraction of insoluble proteins in the cortex and higher concentrations of noradrenaline and serotonin in the brain stem. Positive effects of piracetam seem to be reflected in the rise of total proteins in the cortex, in higher amount of ascorbic acid in adrenals and in the increase of body weight, indicating an anabolic character of drug action. The rats treated with methoxytacrin revealed a deterioration of T-maze discrimination in comparison to the controls and a significantly raised activity in the first minute of the open field test (hyperreactivity on external stimuli). Brain analysis showed a decrease of HACU hippocampal synaptosomes. This result may be interpreted as a reduction of acetylcholine synthesis induced by longlasting rise of synaptic transmitter concentration resulting in activation of M_2 autoreceptors and feedback inhibition. No signs of liver damage were found in any of the tested groups.

Reference

Benešová, O. et al., 1989, Activ. nerv. sup. (Prague) 3, 231–234.

S.we.20.6

Effects of new ergoline dopamine agonists on the cholinergic memory impairment

Borsy, J., Vitális, B., Tapfer, M., Horváth, K., Király, I. and Magó-Karácsony, E.

Institute for Drug Research, PO Box 82, 1325 Budapest, Hungary

We have shown previously that two new ergoline compounds (GYKI-32 887: /(N-2-azido-ethyl-N-methyl-sulphonylamino)methyl/-6-methylergol-8-ene maleate and GYKI-35 064: the 2-chloro-derivative of the former) are potent dopamine D_2 receptor agonists, but their pharmacological profiles are different. One of them, GYKI-32 887, like bromocriptine, proved to be a mixed dopamine agonist in inducing pre- and postsynaptic activation of dopaminergic structures in the brain. However, its chloro derivative, GYKI-35 064, exhibited some selectivity to the dopamine autoreceptor of D_2 type. (Borsy 1985, Borsy et al., 1988, Borsy et al., 1989)

Considering the evidence for the existence of muscarinic and dopaminergic heteroreceptors in the brain, in this study we investigated the possible cholinergic linkage of the two ergoline compounds.

The findings of the present experiments show that both compounds had a moderate binding affinity to the muscarinic receptors in the cortex rat membrane. IC_{50} values were found nearly the same (17 μM for GYKI-35 064 and 20 μM for GYKI-32 887). However, in vivo experiments indicated that dopamine D_2 autoreceptor agonist, GYKI-35 064, was more potent muscarinic compound than the mixed agonist, GYKI-32 887. In mice the oxotremorine induced tremor was potentiated most effectively by the administration of GYKI-35 064 (3-10 mg/kg ip.) and lower potentiation was obtained by the treatment of the other ergoline. Both dopamine agonists failed to modify the peripheral muscarinic response, i.e. salivation induced by oxotremorine. In rats the antiamnestic effect of the