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THE ROLE OF CEREBRAL BLOOD FLOW IN MIGRAINE DEVELOPMENT

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ABSTRACT: Relevance of the topic. The search for and study of pharmacological agents for the treatment of patients with migraine is one of the priority problems of modern medicine, since migraine is one of the most widespread and socially significant diseases. In developed countries of Europe and America, migraine affects 3 to 16% of the population, and according to some data, up to 30%. Migraine affects 18% of women, 6% of men, and 4% of children (Stewart W.F. et al., 1994; Rasmussen B.K., 1994; Vein A.M. et al., 1995; Silberstein S.D. et al., 1998; Yakhno H.H. et al., 2001; Amelin A.V. et al., 2001; Chernyak Z.V. et al., 2003). It has been shown that people of working age - 35-40 years old - suffer from migraine more often. Research in recent years has revealed a tendency towards an increase in the number of migraine patients (Stewart W.F. et al., 1994; Amelin A.V. et al., 2001; Yakhno N.N. et al., 2001; Yakhno N.N., Shtulman D.R., 2003).

The important role of the genetic factor in the occurrence of migraine has been confirmed in numerous molecular biological and clinical studies. Therefore, migraine is considered a disease caused by a hereditarily determined dysfunction of vasomotor regulation, manifested by paroxysmal attacks of pulsating headache, usually in one half of the head (Alekseev V.V., Yakhno N.N., 1997; Amelin A.V. et al., 2001). Numerous studies are devoted to the study of migraine and there is significant progress in understanding the pathogenesis of this disease, however, many aspects of this affliction remain unclear (Pietrobon D., Stressing J. 2003). It has been established that the neurotransmitter serotonin plays a significant role in the pathogenesis of this disease (Chugani D.C. et al., 1999). Serotonin, on the one hand, has a pronounced effect on cerebral vessels, on the other hand, it participates in the conduction of pain impulses (Prusinsky A., 1979;). The following hypotheses of the formation of a migraine attack are currently being discussed. The vascular hypothesis of the development of a migraine attack, which has not lost its relevance today, was proposed by Wolff H.G. and co-workers (1963), according to whom an attack of migraine is characterized by an initial increase in the tone of the cerebral vessels with its subsequent decrease. The neurogenic hypothesis, based on the correlation of changes in cerebral circulation with the spreading cortical depression of Leao, was proposed by Olesen J. B. and co-authors (1981). Finally, according to the trigeminovascular hypothesis proposed by Moskowitz M. A. (1984), the trigeminal nerve system is responsible for the interaction between the central nervous system and the vessels of the brain during a migraine attack. Consequently, despite the differences in ideas about the formation of a migraine attack, most researchers point to the significant role of serotonin and brain vessels in the pathogenesis of this disease. The only question that is in doubt is the primary or secondary significance of the brain vessels in the implementation of a migraine attack. In accordance with the above, pathogenetically justified treatment of patients with migraine is the use of drugs that act on serotonin receptors - 5HT1b/id" agonists and 6HT1c receptor antagonists. However, these

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drugs are not always effective enough and have pronounced undesirable side effects. Therefore, the search for new drugs for the prevention and treatment of migraine attacks is the most important task of modern pharmacology and medicine. Given the important role of cerebral circulation and serotonin in the pathogenesis of a migraine attack, when searching for new anti-migraine drugs, it is necessary to identify substances that have the ability to act on serotonin receptors of the brain vessels.

Earlier, an original serotonin receptor antagonist, Tropoxin, was created at the V.V. Zakusov Research Institute of Pharmacology, Russian Academy of Medical Sciences. By blocking 5HT2 receptors, it prevents the development of constrictor reactions of the brain vessels caused by serotonin. Tropoxin is one of the tropane derivatives that were synthesized in the Chemistry Department of the State Research Institute of Pharmacology named after V.V. Zakusov, Russian Academy of Medical Sciences, by leading researcher, PhD in Chemistry L.M. Kostochka. Therefore, we considered it appropriate to conduct a search for new anti-migraine drugs among tropane derivatives. In order to understand the pathogenesis of migraine, it is of interest to study in more detail the mechanism of action of drugs used to treat migraine. Therefore, it seemed important to conduct further study of the mechanisms of anti-migraine activity of the drug - Tropoxin, as well as to study the cerebrovascular serotonergic activity of the known anti-migraine drug - sumatriptan.

Purpose of the study. Search for new anti-migraine drugs among tropane derivatives and study the mechanism of action of Tropoxin and sumatriptan.

CONCLUSIONS

1. The study of the relationship between structure and serotonergic cerebrovascular activity among new tropane derivatives allowed us to identify compounds with antagonist and agonist activity. Compound JIK-728 has a pronounced antiserotonin cerebrovascular activity comparable to tropoxin, while LK-769, on the contrary, enhances the reactions of brain vessels to serotonin, which indicates its agonist properties in relation to serotonin, characteristic of the well-known anti-migraine drug - sumatriptan.

2. Sumatriptan and compound JIK-769, unlike serotonin, have a biphasic effect on the blood supply to the cerebral cortex of intact animals - an initial decrease in the level of blood supply to the brain is replaced by a subsequent increase, which plays an important role in the mechanism of the anti-migraine effect of sumatriptan.

3. Using microiontophoretic technology, it was established that Tropoxin is a blocker of 5HT receptors of the excitatory (depolarizing) type, which are localized on neurons of the sensorimotor cortex of the brain.

4. For maximum manifestation of the neurotropic antiserotonin activity of Tropoxin, it is necessary to maintain the conformation of the entire molecule, since the inhibitory effect of its fragments is expressed to a lesser extent.

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5. In vitro and ex vivo experiments, Tropoxin exhibits pronounced antiaggregatory activity comparable to dipyridamole.

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