vious experiments, the intensity of fast flash in a plasma-containing model system is an integral characteristic strongly dependent on the presence of antioxidants: scavengers of free radicals and active oxygen species, complexons for transition metals, etc. Since niphtholid in millimolar concentrations lowers the amplitude of fast flash in this model, it can be hypothesized that its antioxidant activity is mediated by another mechanism.

The finding that these antiandrogens differ considerably in antioxidant activity is important for their use in clinical practice. Recent investigations showed that antiandrogens are useful in the treatment of oncologic diseases accompanied by hormonal disturbances, for example, bone sarcoma [3]. In this case, antiandrogens should be tested for the compatibility with conventional chemotherapeutic agents, since some of them act via the initiation of FRO [1].

It has been generally recognized that antioxidant preparations increase the organism's resistance to various damaging factors; therefore, niphtholid may have a wide therapeutic application. However, further experimental and clinical studies are necessary to clarify this issue.

REFERENCES

1. E. B. Burlakova and N. P. Pal'mina, *Vopr. Onkol.*, **36**, No. 10, 1155-1162 (1990).
2. G. I. Klebanov, I. V. Babenkova, Yu. O. Teselkin, *et al.*, *Lab. Delo.*, No. 5, 59-62 (1988).
3. N. E. Kushlinskii and V. N. Mitin, *Vopr. Onkol.*, **38**, No. 5, 571-576 (1992).
4. P. V. Sergeev, A. G. Belykh, S. A. Chukaev, and B. M. Gukasov, *Eksp. Klin. Farmakol.*, **55**, No. 2, 60-62 (1992).
5. M. Breckwoldt (Ed.), *Diagnosis and Therapy of Androgenisation*, Berlin (1992).
6. H. Wiseman, *Trends Pharmacol. Sci.*, **15**, No. 3, 83-89 (1994).

Analgesic Action of the New Drug Semax

M. V. Koroleva, E. E. Meizerov, V. N. Nezavibat'ko, A. A. Kamenskii, V. A. Dubynin, and Yu. B. Yakovlev

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 122, No. 11, pp. 527-529, November, 1996
Original article submitted September 1, 1995

Intranasal administration of the new regulatory peptide Semax (0.5 mg/kg) relieves migraine headache and pain caused by dental plexalgia. The analgesic effect of Semax is due to spasmolytic and general regulatory activities but not to its influence on pain sensitivity system.

Key Words: *pain; rheoencephalogram; adrenocorticotropic hormone fragments*

Considerable investigative effort has been focused on the development of drugs based on endogenous regulatory peptides or their synthetic analogs. The interest in peptide drugs is motivated by the following reasons. First, peptides are effective in very low doses. Second, enzyme systems that can rapidly inactivate peptides are present in the body. Third, peptides produce no significant side effects. There are a number of immunostimulating, nootropic, analgesic, and other drugs based on regulatory peptides. Dalargin, oxytocin, vasopressin, and thymogen have been successfully used in this country. Clinical trials of the analog of the adrenocorticotropic hormone fragment 4-10 have been started. This heptapeptide (O_2 MEHF-PGP, Semax) was developed at the Institute of Molecular Genetics (Russian Academy of Sciences). Semax exerts prolonged (up to 24 h) beneficial effects on the function of the forebrain: it improves attention and accelerates learning [1,4].

Institute for Research on Traditional Methods of Therapy, Ministry of Health; Institute of Molecular Genetics, Russian Academy of Sciences, Moscow; Department of Human and Animal Physiology, Moscow State University

0007-4888/96/0011-1107$15.00

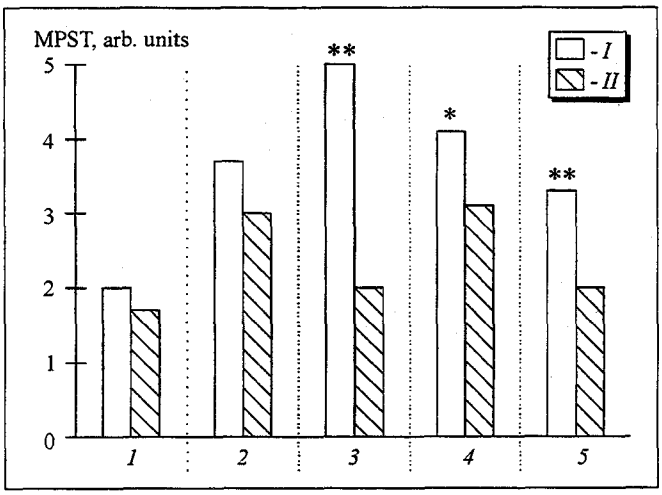

Fig. 1. Results of the modified pain sensitivity test in patients with migraine headache before and after administration of Semax.

Here and in Fig. 2: *1*) frequency of pain attacks; *2*) duration of pain attacks; *3*) severity of pain; *4*) scale for rating sensory characteristics of pain; *5*) scale for rating subjective perception of pain. Before (*I*) and after (*II*) administration of Semax. *$p<0.05$; **$p<0.01$.

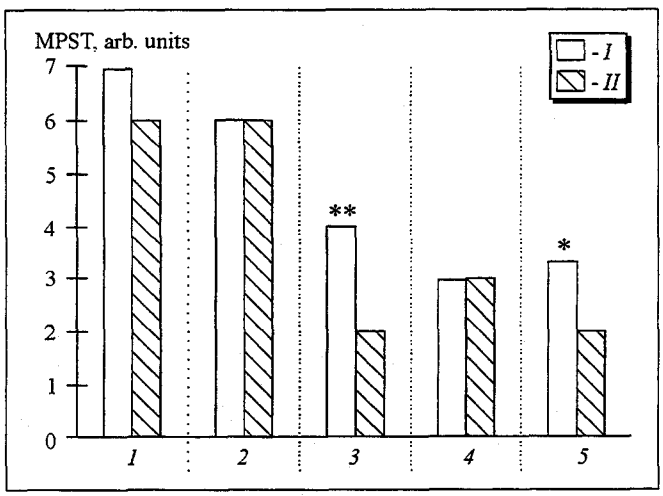

Fig. 2. Results of the modified pain sensitivity test in patients with dental plexalgia before and after administration of Semax.

However, therapeutic activity of this peptide is not limited by the influence on mnestic abilities of humans. Clinical trials revealed analgesic effects of Semax in a number of pain syndromes. In this study we examined the analgesic effects of this peptide.

MATERIALS AND METHODS

The analgesic activity of Semax was studied in three groups of patients with headache of vascular origin or facial pain. Group 1 consisted of 12 patients (10 women and 2 men aging 19-56 years) with migraine headache, group 2 included 16 patients (12 women and 4 men, 45-65 years) with typical trigeminal neuralgia, and group 3 consisted of 9 patients (3 women and 6 men, 15-52 years) with dental plexalgia. Semax was administered once intranasally in a dose of 0.5 mg/kg body weight. Pain was analyzed in the modified pain sensitivity test (MPST), which involved the use of scales for rating pain severity as well as duration and frequency of pain attacks and scales for assessing sensory and psychoemotional attitude of pain. In group 1, rheoencephalogram (REG) was recorded from the internal carotid arteries (because pain was localized predominantly in this area) before and 5, 15, and 30 min after administration of Semax. In groups 2 and 3, thresholds of sensation and pain in response to electrostimulation of the skin in symmetrical areas of the face on healthy and affected sides as well as trigeminal somatosensory evoked potentials (TSEP) in leads C3'-Fz and C4'-Fz according to the 10-20 system [3] were recorded. These records were made before and 5, 15, and 30 min after Semax administration.

RESULTS

The REGs recorded in group 1 before treatment with Semax showed changes characteristic of different phases of a migraine attack [2]. In 5 patients, rheoencephalographic changes of type 1 were observed, including increased tone of large and small arteries, decreased pulse filling (more pronounced on the affected side), and slightly increased venous tone. Seven patients showed rheoencephalographic changes of type 2 characterized by increased pulse filling and markedly elevated venous tone with signs of hindered venous outflow. The total MPST score in this group was 78%; the patients described their pain as very severe, compressing, pulsing, and/or excruciating.

The REGs of group 1 patients recorded 5 min after Semax administration differed from those recorded before it, the differences being most pronounced 30 min after the drug administration. Decreased vascular tone, increased pulse filling, and lesser hemispheral asymmetry (as a result of improved venous drainage and a greater increase in the rheographic index on the painful side) were observed in the patients with type 1 rheoencephalographic changes. The effect of Semax was weaker in patients with type 2 changes, manifesting itself as improved venous outflow predominantly on the affected side.

By the 30th min after Semax administration, the intensity of pain decreased in all patients of group 1. The total score in the MPST was 32%. Patients reported that pain became more diffuse and less severe (Fig. 1); their psychoemotional attitude to it changed. This effect was more pronounced in patients with type 1 rheoencephalographic changes. Complete cessation of pain 90-120 min after Semax

administration was reported by 4 out of 5 patients. In patients with type 2 changes, pain was not eliminated but became less severe. Psychoemotional attitude of the patients to pain changed. These results suggest that Semax relieves pain in patients with migraine by exerting vasodilatory (predominantly spasmolytic) effects.

In patients with typical trigeminal neuralgia (group 2), Semax induced no significant changes in sensation or pain thresholds and TSEP. There were no significant changes in the characteristics of pain in the MPST.

In patients with the trigeminal pain syndrome due to dental plexalgia (group 3), the amplitudes and latencies of the first two cortical components of TSEP (N14/P23 and N32/P41) were greater when the affected side of the face was stimulated before treatment with Semax (in comparison with stimulation of the healthy side). Such differences are characteristic of this syndrome [3]. The total score for pain was 82%. The patients described pain as severe, aching, pressing, and excruciating.

After administration of Semax, pain disappeared in 6 patients, 3 patients reported a decrease in pain severity, and their perception of pain changed (Fig. 2). It is noteworthy that in 4 patients suffering from pain for 1-3 months, pain did not recur during a 3-month period after treatment with Semax (none of the patients was followed-up for a longer period), but the thresholds for sensation and pain in response to the test stimulus remained the same, and no significant changes in TSEP were observed after a single intranasal administration of Semax. This observation indicates that Semax does not exhibit analgesic activity by itself.

Thus, Semax alleviated or eliminated pain in half of patients with migraine or dental plexalgia without eliciting direct analgesic effect. Our results suggest that an integrative neuromodulatory mechanism whereby the metabolism of neurotransmitters is optimized and adaptive processes are accelerated is responsible for the effect of Semax. Since this peptide produces no adverse effects, it can be used in the treatment of migraine headache and dental plexalgia.

REFERENCES

1. L. V. Antonova, A. A. Kamenskii, T. I. Vlasova, *et al.*, *Byull. Eksp. Biol. Med.*, **102**, No. 11, 569-571 (1986).
2. L. R. Zenkov and M. A. Ronkin, in: *Functional Diagnosis of Nervous Diseases* [in Russian], Moscow (1991), pp. 7-146.
3. E. E. Meizerov, V. K. Reshetnyak, V. E. Grechko, and Yu. V. Grachev, *Zh. Nevropatol. Psikhiatr.*, No. 4, 12-17 (1989).
4. M. A. Ponomareva-Stepnaya, V. N. Nezavibat'ko, L. V. Antonova, *et al.*, *Khim.-Farm. Zh.*, No. 7, 790-795 (1984).