Antimotion Effect of Nooglutyl and Its Neuronal Mechanism

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Experiments on rats demonstrate that nooglutyl exhibits pronounced vestibular-protective properties and by its antimotion activity does not rank below classic vestibular protectors, such as scopolamine and diprazine. Electrophysiological experiments on cats show that nooglutyl alters spontaneous activity in 80% of cortical neurons (somatosensory zone I and area 5 of the parietal association cortex) and considerably weakens effects caused by motion sickness: activation of single unit activity of somatosensory zone I and inhibition of neuron responses to somatic stimulation. This property of the preparation is believed to form the basis of its antimotion effect.

Key words: *nooglutyl; motion sickness; cortical neurons*

Nooglutyl (N-5-[oxynicotinoyl]-L-glutamic acid) is an original nootropic agent recently developed at the Research Institute of Pharmacology, Russian Academy of Medical Sciences [1,4]. We showed earlier [5] that a number of traditional nootropic agents (piracetam, oxiracetam, etc.) exhibit vestibular-protective activity, and this provided the impetus for the present study, where the vestibular-protective activity of nooglutyl was assessed and the possible neuronal mechanism of its antimotion effect was elucidated.

MATERIALS AND METHODS

Behavioral experiments were conducted on male Wistar rats of body weight 190-250 g. Motion sickness was induced in rats on a modified set-up (NASA, USA) [6], which allowed for rotation of the animals in two perpendicular planes at a frequency of 0.33 Hz. The degree of motion sickness was determined by the amount of food taken by the animals within 2 and 24 h after rotation [2]. Scopolamine (Sigma) and diprazine (pipolphen, Hungary), standard vestibular protectors, were used in the study besides nooglutyl. The preparations were administered intraperitoneally 25-40 min prior to rotation.

Standard microelectrode technology was used for decoding the antimotion effect of nooglutyl on the neuronal level. Experiments were carried out on 12 curarized male cats of body weight 3-4 kg kept under conditions of artificial lung ventilation. Body temperature was maintained on a stable level by an electric heating pad. Preliminary surgery (tracheotomy, scalping, etc.) was performed under narcosis (sodium ethaminal in a dose of 35 mg/kg intraperitoneally). Glass microelectrodes filled with 3 M NaCl solution (resistance less than 10 MΩ) were used for extracellular recording of the electrical activity of some cortical neurons that was initiated 8-10 h after administration of sodium ethaminal. Data on spontaneous and induced (electrical stimulation of the hind limbs: 20-40 V, 0.5 msec) neuron activity were processed on a personal computer. Nooglutyl (3.7×10^{-3} M solution) was applied to the cortex through a thin polyethylene

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tube connected to a hydraulic micromanipulator. Two sites of the cortex were selected for investigation: somatosensory zone I (S1) and area 5 (according to Brodmann) of the parietal association cortex. The choice of these sites was dictated by our findings [3,5] that they are involved in motion sickness pathogenesis. The technique of inducing motion sickness in cats was described by us earlier [3].

RESULTS

Table 1 shows that nooglutyl in a dose of 50 mg/kg exhibits pronounced vestibular-protective properties. Its antimotion activity is found to be not less than that of classic vestibular protectors: scopolamine in a dose of 0.1 mg/kg and diprazine in a dose of 50 mg/kg.

In the next series of experiments on cats we attempted to decode the mechanism of the antimotion effect of nooglutyl on the neuronal level. Spontaneous activity of neurons of the S1 zone of the cortex was considerably transformed under conditions of motion sickness, the frequency of action potentials significantly increasing in 26 out of 37 neurons (70%). In seven cases (19%) motion sickness produced an inhibitory effect and in four (11%) it caused no noticeable shifts in single unit activity.

The effect of nooglutyl on spontaneous activity was analyzed in 19 neurons of the S1 zone. Three cells (16%) did not react to local application of the preparation. The nootropic activated single unit activity in 13 cases (68%) and inhibited it in 3 cases (16%). Neurons of area 5 of the parietal association cortex reacted to nooglutyl in a similar manner: stimulative and inhibitory effects were observed in 70% and 12% of cases, respectively, and no effect was found in 18% of cases. The duration of the effect ranged from 30 to 60 min.

It is of interest to note that nooglutyl is capable of considerably weakening activation of single unit activity of zone S1 neurons induced by motion sickness. This property of the preparation may well form the basis of its antimotion effect.

A marked inhibition of induced reactions of zone S1 neurons was observed under conditions of motion sickness. Early (short-latent) induced responses were found to be maximally reduced (by 50% or more). The direction of induced responses or their separate components did not always coincide with the direction of changes in cell spontaneous activity. As a rule, nooglutyl diminished the effect of motion sickness with respect to induced neuron responses.

Table 1. Comparative Antimotion Activity of Some Neurotropic Agents Determined by Food Intake by Rats ($M \pm m$)

Agent, mg/kg	Food intake after motion sickness, % of baseline
Control (0.9% NaCl solution)	63±6
Nooglutyl (50)	89±6*
Scopolamine (0.1)	86±7*
Diprazine (50)	81±5*

Note: 6–10 animals were used. Food intake prior to motion sickness (the baseline level) was taken as 100%. Asterisk shows significance of differences compared to the control, $p<0.05$ (Student's t test).

The results of the current study invite the following conclusions. First, nooglutyl exhibits a pronounced vestibular-protective activity. Second, a considerable proportion of cortical neurons (more than 80%) show sensitivity toward the nootropic, a fact which may lie at the basis of the mechanism of its action on the higher integrative brain functions. Third, nooglutyl is able to correct spontaneous and induced activity of cortical neurons under conditions of motion sickness.

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