CHANGES IN PAIN SENSITIVITY INDUCED BY RAISED ATMOSPHERIC PRESSURE

Yu. D. Ignatov,* A. A. Myasnikov, Yu. N. Vasil'ev, and N. N. Vinnichuk

UDC 616.8-009.7-02:612.274]-07

KEY WORDS: pain; analgesia; naloxone; yohimbine; atropine

For more and more people a hyperbaric medium has become a condition of their occupational activity, and this has necessitated the study of functioning of the different organs and systems of the body, and of the body as a whole, under raised pressure. Activity of the CNS has been shown to change under the influence of extremal factors of a hyperbaric medium, as shown by disturbance of the integrative function, of mental working capacity, attention, and memory [1, 9, 10]. The mechanisms of regulation of pain at normal pressure have now been studied in fair detail [4, 6-8], but virtually no attempt has been made to study changes in pain sensitivity in a hyperbaric atmosphere.

The aim of this investigation was to study the effect of a raised atmospheric pressure and a helium–oxygen mixture on pain sensitivity and its changes under the influence of drugs modifying the processes of neurochemical mediation.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 200-240 g in a compression–decompression chamber, one valve of which we replaced by a special device for introducing electrical conductors. Compression was carried out uniformly at the rate of 0.2 MPa/min, and the duration of isobaric pressure was 60 min. Carbon dioxide was removed by preliminary insertion of containers with soda lime absorbent into the pressure chamber. The temperature was kept between 21 and 23°C and humidity at 68-82%. Pain sensitivity was evaluated during electrical stimulation of the base of the tail through needle electrodes, with stimuli of increasing voltage from 1 to 15 V, from an ÉSL-1 stimulator, up to the vocalization threshold in animals partially immobilized in special containers, before the rise of pressure and after 2, 20, 40, and 60 min of isobaric pressure. Pain sensitivity in the animals was studied during a rise of atmospheric pressure up to 1.1 MPa with an interval of 0.1 MPa. The test preparations were injected intraperitoneally: naloxone 1 mg/kg, atropine 1 mg/kg, yohimbine 1 mg/kg, prazocin 1 mg/kg, all 1-3 min, and parachloramphetamine 5 mg/kg 48 h before the beginning of compression. Investigations on male subjects (24-32 years old) were carried out in a PDK-2 pressure chamber with a capacity of 7 m^3. Pressure was raised smoothly up to 0.4 MPa in the course of 7-8 min, and to 0.7 MPa in the course of 12-14 min. The temperature in the chamber was kept at 25-27°C and the humidity at 80-90%. No rise of CO_2 concentration was permitted. By means of a needle adhesimeter of our own design, the subjects' threshold of pain perception and threshold of pain endurance were determined in the epigastric region 1-1.5 cm below the xiphoid process, 30-60 min before the beginning of compression, and 10 and 60 min, and also 8 h after the rise of pressure. The numerical results were subjected to statistical analysis by Student's test and by the use of nonparametric statistical methods, both for tied (signs test, maximum test) and untied values (Kolmogorov–Smirnov test). In some cases, Spearman's rank correlation coefficient was used.

*Corresponding Member of the Russian Academy of Medical Sciences.

Department of Pharmacology, Naval Department, Academician I. P. Pavlov St. Petersburg Medical Institute.
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 114, No. 8, pp. 157-159, August, 1992. Original article submitted February 11, 1992.

0007-4888/92/0008-1123$12.50 ©1993 Plenum Publishing Corporation

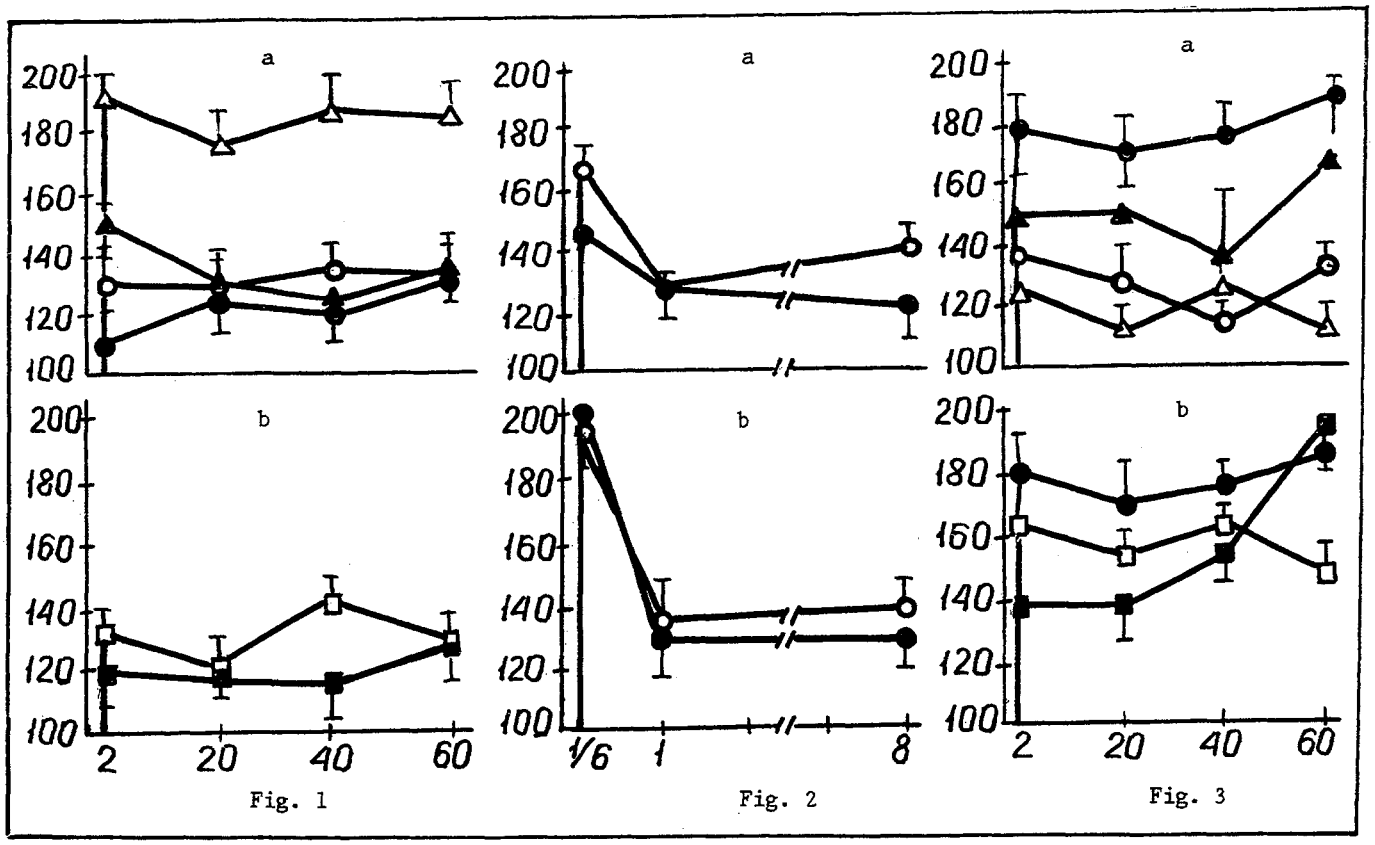

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Changes in vocalization threshold of rats subjected to raised pressures of air (a) and heliox (b). Ordinate, change in pain threshold (in % of initial value); abscissa, time of isobaric pressure (in min); filled circles – pressure 0.5 MPa, empty circles and filled squares 0.7 MPa, filled triangles 0.9 MPa, empty triangles and squares 1.1 MPa.

Fig. 2. Changes in pain sensitivity in human subjects exposed to raised atmospheric pressure of 0.4 MPa (a) and 0.7 MPa (b). Abscissa, time of isobaric pressure (in h); filled circles – threshold of pain perception, empty circles – threshold of intolerable pain. Remainder of legend as to Fig. 1.

Fig. 3. Effect of naloxone, parachloramphetamine, atropine (a), yohimbine, and prazocin (b) on analgesic effect of a raised atmospheric pressure of 1.1 MPa. Filled circles – control, empty circles – naloxone 1 mg/kg, filled triangles – parachloramphetamine 5 mg/kg, empty triangles – atropine 1 mg/kg, filled squares – yohimbine 1 mg/kg; empty squares – prazocin 1 mg/kg. Remainder of legend as to Fig. 1.

EXPERIMENTAL RESULTS

The experiments showed that rats in a hyperbaric atmosphere developed hypoalgesia, the severity and course of which depended on the level of hyperbaric pressure (Fig. 1a). With an increase of pressure to 0.5 MPa the vocalization threshold was found to be raised throughout the period of isobaric pressure, and with peak values as a rule toward its end. Starting from a pressure of 0.7 MPa, the pain thresholds rose sharply during the first minutes of isobaric pressure, and then fell a little. The most marked analgesia occurred at a pressure of 1.0 and 1.1 MPa. Strong coefficients of correlation 0.925 and 0.83 respectively were discovered at the 2nd and 40th minutes at isobaric pressure, followed by moderately strong positive correlation between the rise of vocalization thresholds and the hyperbaric pressure level at the 20th and 60th minutes.

Very probably the change in pain sensitivity in a hyperbaric atmosphere was due to elevation of the partial pressure of nitrogen, which is known to play a key role in the disturbance of synaptic transmission and integrative activity of the CNS [3, 9]. The validity of this hypothesis was confirmed by the results of our experiments in which

nitrogen was replaced by an equal volume of helium. In animals in a helium–oxygen medium (heliox; 79.1% helium and 20.9% oxygen) under a pressure of 0.7 and 1.1 MPa, hypoalgesia developed, but its intensity was significantly less than at the corresponding air pressures (Fig. 1b). The hypoalgesia arising at raised pressures of heliox was virtually independent on the level of hyperbaric pressure, possibly in connection with the hyperoxia that accompanies a raised atmospheric pressure and which can raise pain thresholds [6]. This hypoalgesia may also have been partly due to stress on account of the experimental conditions. In experiments with simulation of a rise of pressure, but with all the remaining parameters of the experiment preserved, an increase in vocalization threshold by 16-46% was observed, corresponding to the effect of a raised heliox pressure. However, the leading factor causing depression of pain sensitivity in a hyperbaric atmosphere of air must nevertheless be considered to be a raised partial pressure of nitrogen.

We found that hypoalgesia at raised atmospheric pressure varied in different animals, so that they could accordingly be divided into two groups. In the first group (72%) marked analgesia developed with elevation of the atmospheric pressure, and at a pressure of 0.7 MPa their vocalization threshold rose by 95-100%. In the second group pain sensitivity changed very little. For instance, at a pressure of 0.7 MPa the vocalization threshold of these rats rose by only 15%. It is interesting to note that the animals differed also in their degree of stress-induced analgesia. During simulation of a raised pressure the pain thresholds in the first group increased by 1.5-2 times, but in the second group they were virtually unchanged.

A similar time course of pain sensitivity was found in man also (Fig. 2). Hypoalgesia was discovered when the air pressure was raised by only 0.4 MPa, especially in the first minutes at isobaric pressure, and the threshold of intolerable pain was most clearly raised. At a pressure of 0.7 MPa the threshold of pain perception and the threshold of intolerable pain were both equally raised. As regards individual changes in pain sensitivity under an air pressure of 0.7 MPa, all the subjects likewise could be divided into two groups. In the first group (67%) the threshold of pain perception and the threshold of intolerable pain were increased by 1.5-2 times. In the second group (33%) the thresholds were raised by only 15-25%. These differences in the change of nociceptive sensation may in all probability be due to individual levels of activity of the antinociceptive systems of the brain and (or) the content of endogenous ligands of opiate receptors [4, 13, 14].

Involvement of the opioidergic system in realization of the analgesic action of a raised atmospheric pressure was confirmed by evidence showing that naloxone considerably reduced hyperbaric analgesia (Fig. 3a). It is difficult at present to define precisely the mechanism of involvement of opiate receptors in the analgesic effect of an increased partial pressure of nitrogen. However, the possibility cannot be ruled out that during hyperbaric analgesia increased release of endogenous receptor ligands takes place, and (or) the nitrogen interacts directly with opiate receptors, as has been suggested for nitrous oxide [12].

It is worth noting that hyperbaric analgesia, unlike stimulation-, acupuncture-, and morphine-induced analgesia [5, 11, 13], was reduced to a lesser degree by parachloramphetamine, and by a much greater degree by atropine (Fig. 3a). An essential role in the formation of hyperbaric analgesia is played also by the adrenergic system, which realizes its effect mainly through α_2-adrenoreceptors, just as in analgesia of other genesis [2, 8], as is indicated by the greater depressant action of the α_2-adrenoreceptor antagonist yohimbine compared with the α_1-antagonist prazocin (Fig. 3b). It is very difficult to imagine that a raised partial pressure of nitrogen changes the ligand-receptor properties of different neurochemical systems. It is more probable, in our view, to suggest that under hyperbaric conditions the endogenous antinociceptive brain systems, which inhibit pain sensitivity by rather different neurochemical mechanisms than in opiate-, stimulation-, and acupuncture-induced forms of analgesia, are activated.

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EFFECT OF PROPRANOLOL ON CIRCADIAN RHYTHM OF DURATION OF THE HYPNOGENIC ACTION OF DIAZEPAM AND HEXOBARBITAL

É. B. Arushanyan and P. Botvev Orkhii

UDC 615.214.24.015.2].015.4.07

KEY WORDS: propranolol; circadian rhythm; pharmacogenic sleep

The hypnogenic effect of general anesthetics and sedatives varies in its intensity throughout the 24-h period [8]. The time course of pharmacogenic sleep is significantly affected by administration of melatonin [1], the principal hormone of the pineal gland, which is involved in the organization of circadian rhythms [9]. Nervous control of the activity of this cerebral gland depends entirely on a sympathetic nerve, which has beta-adrenoreceptors distributed on its endings. The search for ways of controlling deep pharmacogenic sleep through modulation of pineal activity is an interesting problem.

In the investigation described below the character of the action of the beta-adrenoblocker propranolol on the circadian rhythm of the effect of diazepam and hexobarbital was studied.

EXPERIMENTAL METHOD

Altogether 48 groups of experiments were carried out on 288 male albino mice weighing 20-30 g, during May. The animals were kept under standard conditions (as regards number to a cage, diet, ambient temperature), with a fixed ratio (1:1) of light and darkness, the period of light being from 8 a.m. to 8 p.m. The latent period of assumption of the side position by the animals, and its duration, after injection of a standard dose of diazepam (50 mg/kg, intraperitoneally – the other drugs in the same way) and of hexobarbital (75 mg/kg) were estimated. In the experimental series, administration of these substances was preceded (30 min previously) by injection of propranolol (5 mg/kg), but in the control series by injection of the same volume of physiological saline. The results were subjected to statistical analysis by Student's test and the Wilcoxon–Mann–Whitney test.

Department of Pharmacology, Medical Institute, Stavropol'. (Presented by Academician of the Russian Academy of Medical Sciences D. A. Kharkevich.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 114, No. 8, pp. 159-161, August, 1992. Original article submitted February 6, 1992.

 0007-4888/92/0008-1126$12.50 ©1993 Plenum Publishing Corporation