EFFECT OF MORPHINE AND NALOXONE ON SENSITIVITY OF RATS TO PAIN AFTER RADIATION INJURY

Yu. D. Ignatov, A. A. Abdrakhmanov,
N. N. Lashkul, and A. A. Zaitsev

UDC 615.212.7.015.4:612.884.014.481].076.9

KEY WORDS: radiation injury; analgesia; opioids

Ionizing radiation in high and very high doses causes a wide variety of functional disturbances, including depression of the reactivity of experimental animals to nociceptive stimuli of thermal genesis [4]. The neurotransmitter mechanisms of this analgesia have virtually not been studied, and the role of various, mainly opioidergic, systems in the formation of the analgesic effect after radiation injury, integrated at the segmental and suprasegmental brain levels are not yet clear. All that is known is that after irradiation the levels of endogenous morphine-like substances in the CNS are raised [3].

Accordingly, in the investigation described below changes in nociceptive responses were investigated in different tests and at different times after irradiation of rats with ionizing radiation and during blockade and activation of the opioidergic mechanisms of the brain by naloxone and morphine, respectively.

EXPERIMENTAL METHOD

Experiments were carried out on 108 waking rats in which nociceptive responses to thermal and electrical stimulation were studied in "tail-flick," tail contraction, and vocalization tests [1]. The animals were irradiated with gamma-quanta from the source of a "RKhM-gamma-20" apparatus in a dose of 150 Gy and a dose rate of 4 Gy/sec. The state of pain sensitivity was assessed in the control and 1, 3, 6, and 24 h after irradiation. The effect of naloxone (Narcan, from "Endo," USA) in doses of 0.1 and 1 mg/kg and of morphine hydrochloride in a dose of 5 mg/kg was determined 10 and 30 min, respectively, after their intraperitoneal injection.

EXPERIMENTAL RESULTS

Irradiation led to clear and opposite changes in nociceptive sensitivity in different tests (Table 1). In the thermal pain test, throughout the 24-h period of observation highly significant analgesia was observed, and reached a maximum 6 h after irradiation. At this time the latent periods of vocalization in response to thermal stimulation of the rats' tail and the tail withdrawal reflex in the "tail-flick" test were lengthened by 180-220%. A different time course was observed in response to electrical nociceptive stimulation. The threshold of the vocal response was significantly lowered in the first 3 h and 24 h after irradiation, and not until 6 h after irradiation did this parameter exceed the control values, although not significantly. Basically the same changes were observed in the threshold of contraction of the rats' tail.

Naloxone in a dose of 0.1 mg/kg did not change the sensitivity to pain of the intact animals, but in a dose of 1 mg/kg it lowered the threshold of nociceptive responses to painful electrical stimulation. After irradiation naloxone, in a dose of 0.1 mg/kg, reduced the analgesic effect of radiation damage in the tail withdrawal test, but in a dose of 1 mg/kg it completely abolished this effect. However, naloxone, throughout its dose range, had no definite effect on sensitivity to pain, measured in response to electrical stimulation of the rats' tail.

Academician I. P. Pavlov First Leningrad Medical Institute. Radiobiology Group, Institute of Nuclear Physics, Academy of Sciences of the Kazakh SSR, Alma-Ata. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 108, No. 10, pp. 453-454, October, 1989. Original article submitted December 28, 1988.

TABLE 1. Effect of Ionizing Radiation, Naloxone, and Morphine on Nociceptive Responses in Rats

Experimental conditions	Latent period of tail withdrawal, sec	Threshold of contraction of tail, mA	Threshold of vocalization, mA
Before irradiation (control)	100	100	100
After irradiation:			
1 h	165*	56*	68*
» 3 h	152*	87	78*
» 6 h	321*	100	135*
» 24 h	142*	56*	43*
Naloxone (0.1 mg/kg) before irradiation	114	106	111
after irradiation:			
1 h	124*	91	94
» 6 h	123*	66*	104
Naloxone (1 mg/kg) before irradiation	106	77*	84*
after irradiation:			
1 h	89*	75*	61*
» 6h	88*	67*	63*
Morphine (5 mg/kg) before irradiation	237*	114	179*
after irradiation:			
1h	264*	128*	183*
» 3 h	209*	80*	72*
» 6 h	403*	89*	134*
» 24 h	362*	104	184*

Legend. *$p < 0.05$ compared with control. Results of experiments given as percentages of control, taken as 100%.

Morphine in a dose of 5 mg/kg, in intact rats, raised the thresholds of the vocal response evoked by electrical and thermal stimulation equally, lengthened the latent period of tail withdrawal, but did not significantly change the tail contraction reflex. The analgesic action of morphine in the "tail-flick" test was completely preserved after radiation injury, and after 6 and 24 h it was expressed even more strongly than in unirradiated animals. Meanwhile the effect of morphine or of painful electrical stimulation virtually did not develop 3 and 6 h after irradiation.

The results showed that ionizing radiation induces phasic changes in nociceptive sensitivity not only to thermal [4], but also to electrical nociceptive stimulation. In addition, irradiation changes the mechanisms of pain regulation differently, depending on its genesis, but not on the level of integration in the CNS, for exposure to radiation led to opposite changes in tests involving thermal (analgesia) and electric (hyperalgesia) pain. We know that the contraction and tail-withdrawal reflexes studied in this investigation are closed mainly at the spinal cord level, for vocalization is integrated by suprasegmental structures of the CNS [2].

Very probably analgesia after irradiation is realized chiefly through the opioidergic systems of the suprasegmental and segmental levels of the spinal cord, as shown by its abolition by naloxone. In the study already cited above [4], the postulated inhibition of the nociceptive response in the "hot plate" test also is explained by activation of the endogenous opiate system, in agreement with data showing abolition, by naloxone, of postradiation locomotor hyperactivity in mice [3]. The leading role in these opioidergic systems may be played by μ-opiate receptors. This hypothesis is supported by the fact that naloxone, in a dose as low as 0.1 mg/kg, which virtually completely abolished analgesia after irradiation, in this dose blocks comparatively selectively μ-opiate receptors, but only in a dose of 1 mg/kg or more does it block opiate receptors of other types [5]. Meanwhile opioidergic mechanisms do not play a key role in the formation of hyperalgesic effect of radiation, for it is not blocked by naloxone.

It is noteworthy that irrespective of the genesis of the painful stimuli, analgesia was observed 6 h after irradiation. Probably this 6 hour period is necessary for the body

to restore its endogenous opiate systems and to exhibit their maximal antinociceptive effect under conditions of exposure to damaging radiation of this particular intensity. It is also evident that gamma quanta in a dose of 150 Gy selectively "injure" the opioidergic mechanisms regulating pain of electrical nature. Otherwise it is difficult to explain preservation of the analgesic activity of morphine in thermal pain tests and, at the same time, the development of hyperalgesia against the background of morphine during painful electrical stimulation in the same irradiated animals. Thus a change in activity of the opioidergic systems largely determines the direction and the phasic character of changes in nociceptive sensitivity during radiation injury. From the practical point of view it is important to note that opiates completely exhibit their analgesic action at different periods of time during the first 24-h period after irradiation. Meanwhile the need for a differential approach to their use, allowing for the genesis of the stimuli evoking the pain syndrome, during exposure to ionizing radiation will be evident.

LITERATURE CITED

1. A. A. Zaitsev and Yu. D. Ignatov, The Neuropsychopharmacology of Pain-Relieving Substances [in Russian], Leningrad (1986), pp. 30-43.
2. E. E. Hahn, Meth. Find. Exp. Clin. Pharmacol., 7, 373 (1985).
3. G. A. Mickley, K. E. Stevens, G. A. White, and G. L. Gibbs, Science, 220, 1185 (1983).
4. G. C. Teskey and M. Kavaliers, Life Sci., 35, 1547 (1984).
5. F. C. Tortella, L. Robles, and J. W. Holaday, Life. Sci., 37, 497 (1985).

EFFECT OF ETHANOL ON NEUROPEPTIDE, ACTH, AND CORTICOSTERONE CONCENTRATIONS IN IMMOBILIZATION STRESS

R. Yu. Yukhananov, V. V. Rozhanets, and A. I. Maiskii

UDC 613.863-07:612.129:[577.175.82+577.175.325+577.175.53].014.46:615.31:547.262

KEY WORDS: rats; brain; adrenals; Met-enkephalin; Leuenkephalin; ACTH; β-endorphin; corticosterone; immobilization stress.

Ethanol consumption is largely dependent on the character of response of animals to stress [4]. The widespread use of alcohol, it is suggested, is due to its stress-protective action, to its ability to abolish emotional strain [2, 4, 7]. However, animal experiments have shown that ethanol consumption in animals rejecting ethanol under free choice conditions initially increases in response to stress, whereas conversely, animals more sensitive to stress consume significantly less ethanol than those resistant to stress [4, 12]. To elucidate the details of the action of ethanol during stress we studied the effect of ethanol on plasma concentrations of corticosterone, ACTH, and β-endorphin, used as quantitative parameters of the level of response to stress [10, 11]. Considering that the level of ethanol consumption and the formation of dependence to it may be controlled by the endogenous opiate system and delta sleep-inducing peptide (DSIP) [3, 5, 7, 8], we also determined concentrations of enkephalins and DSIP in different parts of the brain of animals exposed to stress and receiving ethanol.

EXPERIMENTAL METHOD

Experiments were carried out on male laboratory albino rats weighing 200-250 g, kept on a standard diet with the natural alternation of light and darkness (November-December). Before the experiments the animals were divided into three groups: 1) intact rats kept

Laboratory for the Search for and Study of Substances for Prevention and Treatment of Drug Addictions, Moscow.

(Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 108, No. 10, pp. 455-457, October, 1989. Original article submitted February 2, 1989.

0007-4888/89/0010-1448 $12.50