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Serotonin-Dependent Suppression of the Immune Response via κ-Opiate Receptors

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Previously we demonstrated that the Δ opiate receptors are involved in immunomodulation and interact with the dopamine receptors [8]. At the same time, a few data have emerged on the immunomodulative role of κ-type receptors that exist in such structures of the brain as the hypothalamus [16], pituitary gland [10], and striatum [14], whose participation in the immune response has already been shown. Intercommunication between the enkephalinergic system and both the serotonin- [15] and dopaminergic [13] neurotransmitter systems has been observed precisely in these structures.

The aim of the present investigation was to establish the role and the possible mechanism of action of the κ opiate receptors in immunomodulation and to clarify their relationship with the receptors of one of the mentioned brain systems.

MATERIALS AND METHODS

Experiments were carried out on 162 male mice weighing 20-22 g. Rimorphine - decapeptide (1-10) amide was injected i.p. in saline 30 min before immunization in doses of 1, 10, and 100 μg/kg (rimorphine - decapeptide (1-10) amide was synthesized and kindly placed at our disposal by Dr. O.S.Papsuevich, Riga); the specific blocker of the postsynaptic dopamine receptors haloperidol (Gedeon Richter, Hungary) was injected in a dose of 2 mg/kg 2 h before antigen administration. Cyproheptadine (Serva, Germany), a specific blocker of postsynaptic serotonin S-2 receptors was administered in a dose of 30 mg/kg in distilled water 30 min before immunization. Combined injections of the drugs were performed with an interval of 10 min. Control mice were treated with a solvent according to the same scheme and in the same volume. The immunomodulative effect of rimorphine was recorded at the peak of the immune response as the number of plaque-forming cells (PFC) on the 4th day of the experiment after administration of sheep erythrocytes (SE) in a dose of 5×10^8 [7] and as the number of rosette-forming cells (RFC) in the spleen of each mouse on the 5th day after SE administration in a dose of 5×10^6 [2]. The involvement of the pituitary gland in the effect of rimorphine on immunogenesis was studied in mice with a transected hypophyseal peduncle 10 days before the experiment. The operation was performed under nembutal via the auricular route. The accuracy of cutting the hypophyseal peduncle was assessed visually after decapitation.

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TABLE 1. Central Immunosuppressive Effect of Rimorphine Amide Obtained in CBA Mice on the 5th Day of Experiment after SE Immunization ($M \pm m$, $n = 10$)

Experimental conditions	Dose (mg/kg)	PFC per 10^6 cells	RFC per 10^3 cells
Saline (control)		55.7±2.6	12.1±0.9
Rimorphine amide	1	21.0±1.4*	6.0±0.9*
	10	30.±3.8*	4.0±0.8*
	100	34.0±2.9*	3.6±0.7*
Transection of hypophyseal peduncle		–	13.2±1.1
Operation + rimorphine amide	100	–	13.2±0.9

Note. Asterisk denotes $p<0.05$ in comparison with control.

Data were processed statistically using the Student t test. Differences were reliable at $p \leq 0.05$.

RESULTS

Rimorphine is a C-terminal tridecapeptide of dinorphine 17 [12] and the latter is an endogenous ligand of the κ opiate receptors [5]. Activation of these receptors by one-trial administration of rimorphine amide resulted in a significant (twofold and even more) dose-dependent suppression of immunogenesis (Table 1). The maximal suppressive effect per number of PFC appears when the opioid is used in its minimal dose, while with an increase of the dose the effect is attenuated. At the same time, inhibition of rosette formation takes place along with an increase of the dose. Since the total number of RFC, including IgM and IgG RFC, was determined, it may be assumed that the IgM-producing cells of the PFC population are more sensitive to rimorphine amide than the immune response realized by IgG. These findings are in agreement with the data on inhibition of the IgM-population under conditions of chronic i.p. administration of enkephalins in mice, namely, leu-enkephalin (2 and 10 mg/kg) [11], which belongs, together with rimorphine, to the prodinorphine family.

Radioreceptor assays have revealed a large number of κ-binding sites in the mammalian hypothalamus [16] and pituitary gland [10]. In turn, the hypothalamohypophyseal regulation of immune reactions is well known [6]. Since κ receptors have also been revealed on immunocompetent cells [4], it was necessary to clarify the mechanisms (central or peripheral) that realize the inhibitory effect of rimorphine amide. Experiments performed on mice with destroyed communication between the pituitary and hypothalamus attested to the central effect of opioid immunogenesis. Operated animals treated with rimorphine amide exhibit no decrease of the number of RFC, below the control level. The operation itself does not affect the magnitude of the immune reaction (Table 1).

It is known that serotonin, its precursor, and the substances which enhance the metabolism and release of the amine have an inhibitory effect on the immune response [1]. Conversely, administration of serotonin antagonists stimulates immunogenesis [3]. We established that the administration of rimorphine amide for a cyproheptadine blockade of the serotonin receptors produced no immunosuppression; rather, immunostimulation was observed. The number of RFC is 18.8±0.6 versus 12.1±0.9 in the control. This suggests a serotonin dependence, the effect being mediated by activation of the S-2 postsynaptic serotonin receptors. The obtained interaction between the opiate κ receptors and serotonin is probably determined by the morphofunctional relations of the enkephalin- and serotoninergic systems in such brain structures as n. raphe, the striatum, and the hypothalamus [15].

There are some data on the interaction between the κ receptors and dopamine receptors. The expression of the latter is demonstrated on the striatonigral neurons, which also contain dinorphine [9]. However, there are contradictions in recent reports on the role of the dopaminergic mechanism in the rimorphine effect, particularly on behavior. As for immunomodulation, the present experiments, performed under conditions of dopamine receptor blocking by haloperidol followed by administration of rimorphine amide demonstrated that the suppression of the RFC number was preserved (and not prevented as may be expected under the dopamine-dependent effect): 7.8±0.8 in comparison with 8.4±1.1 for injection of rimorphine alone. As has been shown for the immune response, the inhibitory effect of rimorphine amide is ultimately realized via serotoninergic activity, which is reciprocally enhanced in response to the switching off of the dopaminergic system [1].

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Antimutagenic Effect of Adaptation to Stress

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Mutagenesis and, particularly, chromosome mutations play an important role as suppliers of the "raw material for evolution" [3], but at the same time they cause genetic defects found in one tenth of the human population and form the proven or putative basis for thousands of hereditary diseases [15]. This is in conformity with the following data: mutations often arise in the sex cells [2]; in many widespread diseases they are recessive, i.e., do not manifest themselves in the first generation [14]; newly synthesized chemical compounds, which now number in the 3-4 millions, frequently become potential mutagens [11]. Thus, induced mutagenesis harbors multiple risks for the health and lives of the present and future human generations. In response to this threat, antimutagenic influences are now being extensively studied, especially in the context of pharmacological protection of the genome [1,7,21]. In an evaluation of the data on antimutagenic protection the following two facts engage the attention: first, the huge and ever-growing presence of chemical and physical mutagens in the human environment has not restrained progress, population growth, or life-span elongation in highly developed countries. In other words, the actual harm wreaked by mutagenesis is less then its potential harm. Second, among the substances successfully employed for antimutagenic protection an important role is allocated to such factors naturally occurring in the living organism as purine nucleotides [20], vitamins, amino acids, and antioxidants [6]. All these facts suggest that the organism possesses an antimutagenic self-defense system, whose efficiency varies depending on the presence or absence of stable adaptation to a variety of environmental factors. However, the effect of adaptation to particular environmental factors on the resistance of animals and man to mutagens has not yet been studied.

The aim of the present study was to investigate the effect of preliminary adaptation to repeated short-term stress factors or periodic hypoxia on chromosome aberrations in nuclei of the bone marrow stem cells, induced by dioxidine, a well-known chemical mutagen.

MATERIALS AND METHODS

Experiments were performed on C57Bl male mice weighing 18-20 g (Svetlye Gory nursery, Russian

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