was induced by lectins. Indirect proof of this point of view is given by the B-cell immunity, observed by the writers previously [1, 8], resulting from combined administration of B-mitogens (LPS) and CP. It is to be hoped that selective damage to individual T-cell subpopulations may be observed by the use of a similar principle, by choosing mitogens with a more selective action in combination with CP.

LITERATURE CITED

1. T. K. Kondrat'eva, L. N. Fontalin, N. V. Mikheeva, and V. Holan, Byull. Éksp. Biol. Med., No. 10, 483 (1987).
2. L. N. Fontalin, T. K. Kondrat'eva, and N. V. Mikheeva, Byull. Éksp. Biol. Med., No. 7, 75 (1988).
3. D. Berd, H. C. Maguire, and M. J. Mastrangelo, Immune Modulation Agents and Their Mechanisms, ed. by R. L. Fenichel, New York (1984), pp. 39-61.
4. A. Cooke and S. Marshall-Clarke, Strategies of Immune Regulation, ed. by E. Sercarz, New York (1980), pp. 373-374.
5. T. R. Cupps, L. C. Edgar, and A. S. Fauci, J. Immunol., 128, 2453 (1982).
6. R. W. Dutton, J. Exp. Med., 138, 1496 (1973).
7. S. M. Fineman, F. B. Mudawwar, and R. S. Geha, Cell Immunol., 45, 120 (1979).
8. L. N. Fontalin et al., Folia Biol. (in press).
9. J. C. D. Hengst and R. A. Kempf, Clin. Immunol. Allergy, 4, 199 (1984).
10. I. Hilgert, H. Krištofova, V Horejšsi, et al., Transplant. Proc., 15, 578 (1983).
11. K. R. McIntosh, M. Segre, and D. Segre, Immunopharmacology, 4, 279 (1982).
12. J. H. Playfair and E. Purves, Immunology, 21, 113 (1971).
13. M. Segre, E. Tomel, and D. Segre, Cell Immunol., 91, 443 (1985).

ROLE OF THE DOPAMINERGIC SYSTEM IN THE STIMULATING EFFECT OF MURAMYL DIPEPTIDE ON THE IMMUNE RESPONSE

E. L. Al'perina, Z. Zidek, G. V. Idova, and L. V. Devoino

UDC 615.275.4.015.46:612.017.1

KEY WORDS: muramyl dipeptide; dopaminergic system; pituitary gland; immune response.

The action of biologically active peptides on immune resistance of the body is currently under intensive study. These compounds include the mycobacterial peptidoglycan muramyl dipeptide (MDP). Besides its adjuvant properties, MDP can also activate macrophages [14] and helper T cells [12], and in high doses, it can include suppressor T cells [11]. MDP may also have an influence not only on the immune system, but also on the CNS, as is shown by the pyrogenic and somnogenic effects of this compound [7, 8].

Despite the extensive study of the biological activity of MDP the mechanism of its stimulating action and the role of the CNS in this process are not yet clear. The aim of the present investigation was to study this problem.

EXPERIMENTAL METHOD

Experiments were carried out on 140 male CBA mice weighing 23 g and aged 3-4 months. The mice were immunized with a suspension of sheep's red blood cells (SRBC) in a single dose of $5 \cdot 10^6$ cells. The magnitude of the immune response was determined by counting the number of rosette-forming cells (RFC) on the 5th day after immunization [4]. MDP (N-acetyl-muramyl-L-alanyl-D-isoglutamine; from Spofa, Czechoslovakia) was injected intraperitoneally together with the antigen in a dose of 1 or 5 mg/kg, and haloperidol (Gedeon Richter, Hungary) was injected intraperitoneally in a dose of 1 mg/kg twice a day for 2 days. The first injection was given 30 min before immunization.

Laboratory of Mechanisms of Neurochemical Modulation, Institute of Physiology, Siberian Branch, Academy of Medical Sciences of the USSR, Novosibirsk. Institute of Pharmacology, Czechoslovak Academy of Sciences, Prague.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. A. Matyukhin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 106, No. 8, pp. 198-200, August, 1988. Original article submitted October 27, 1987.

0007-4888/88/0008-1141$12.50

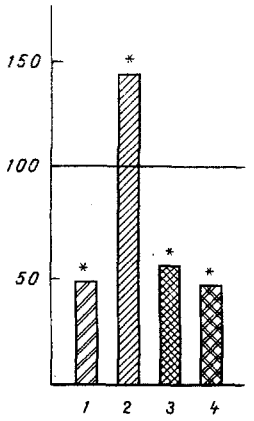

Fig. 1

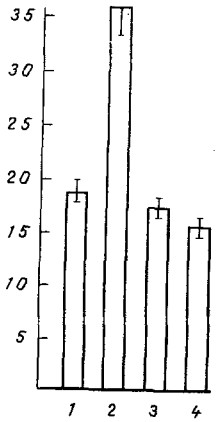

Fig. 2

Fig. 1. Number of RFC on 5th day of immune responses of CBA6 mice immunized with SRBC in a dose of $5 \cdot 10^6$ (control) and receiving haloperidol in a dose of 1 mg/kg twice a day. 1) First injection given 30 min before immunization; 2) MDP injected in a single dose of 1 mg/kg simultaneously with immunization; 3) MDP injected in a single dose of 5 mg/kg simultaneously with immunization; 4) haloperidol + MDP in a dose of 1 mg/kg. Horizontal line indicates control. Here and in Fig. 2: ordinate, number of RFC (in % relative to 10^3 cells).

Fig. 2. Stimulation of immune response by injection of MDP is prevented by division of the pituitary stalk. 1) Control: immunization with SRBC ($5 \cdot 10^6$) + 0.2 ml physiological saline; 2) injection of a single dose of 1 mg/kg MDP simultaneously with immunization; 3) division of pituitary stalk; 4) injection of MDP into mice after division of pituitary stalk.

To determine the role of the pituitary gland in the mechanism of the modulating action of MDP on the immune response experiments were carried out in which MDP was injected into animals after preliminary division of the pituitary stalk. The operation was performed by a transauricular approach under pentobarbital anesthesia (50 mg/kg). The accuracy of destruction of the pituitary stalk was determined visually after decapitation of the animals.

The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Injection of MDP in a dose of 1 mg/kg simultaneously with immunization caused a significant increase in the number of RFC compared with the control. When the dose of MDP was increased to 5 mg/kg the opposite effect was observed: depression of the immune response (Fig. 1). The ability of MDP and its synthetic analogs to induce both stimulation and inhibition of immune reactions, in the opinion of some workers, is due to its effect of different cell populations, depending on the conditions under which the preparation was used: the time and method of administration and the dose given. For instance, in low doses MDP increases helper T-cell activity [12], whereas large doses of MDP activate suppressor T cells [6, 11].

The study of the neuropharmacological activity of MDP has shown that, like many other preparations of bacterial origin, MDP promotes the formation of circulating endogenous pyrogens both in vivo and in vitro [16]. MDP likewise is a factor prolonging the phase of slow-wave sleep [8]. Macrophages activated by MDP also evoke a somnogenic effect [10].

There is evidence that a pyrogenic dose of MDP leads to an increase in serotonin turnover in the hypothalamus and midbrain [12]. However, the possibility cannot be ruled out that other neurochemical systems of the brain are involved in the action of MDP on the CNS.

Previously, in a study of the modulating effect of the dopaminergic system on immune responses, the writers showed that this system participates in the activation of immunogenesis [2, 3], helper T-cell function being enhanced in the bone marrow [5].

Taking the above facts into account it can be postulated that stimulation of rosette formation under the influence of MDP is mediated through activation of the dopaminergic system. Accordingly, experiments were carried out in which the animals were given injections of haloperidol, a specific blocker of dopaminergic receptors, 30 min before immunization and injection of MDP.

In doses acting on the postsynaptic dopamine receptor (more than 0.5 mg/kg) haloperidol is known to depress immune responses — to reduce the number of rosette-forming [2] and plaque-forming cells [3], and also to promote longer survival of a skin graft than in the control [15].

Preliminary injection of haloperidol completely prevented stimulation of rosette formation induced by a low dose (1 mg/kg) of MDP (Fig. 1). The number of RFC in the mice of this group did not exceed the level of rosette formation in animals receiving haloperidol alone. It can be concluded from these results that stimulation of the immune response by MDP is dopamine-dependent.

Evidence has now been obtained to show that the immunomodulating effect of the dopaminergic system is central and is realized through the hypothalamohypophyseal complex [1]. Since the absence of an immunostimulating action of MDP against the background of dopamine receptor blockade points to a role of the dopaminergic system in this effect, it can be tentatively suggested that enhancement of the immune response by MDP will be realized through the hypothalamus and pituitary. Injection of MDP (1 mg/kg) into animals with a divided pituitary stalk confirmed this hypothesis. By itself, division of the pituitary stalk had no effect on the level of the immune response compared with that in mice undergoing a mock operation (Fig. 2). When such animals were given an injection of MDP, the response of rosette formation was not stimulated: the number of RFC found in them was the same as in the control.

Division of the pituitary stalk thus prevents stimulation of the immune response evoked by MDP, evidence that the pituitary gland is involved in the mechanism of the immunostimulating effect of MDP on immunogenesis.

LITERATURE CITED

1. E. L. Al'perina, G. V. Idova, and L. V. Devoino, Fiziol. Zh. SSSR, 71, No. 11, 1428 (1980).
2. L. V. Devoino and E. L. Al'perina, Farmakol. Toksikol., No. 5, 590 (1980).
3. L. V. Devoino and R. Yu. Il'yuchenok, Monoaminergic Systems in Regulation of the Immune Response [in Russian], Novosibirsk (1983).
4. G. V. Idova, M. A. Cheido, and L. V. Devoino, Zh. Mikrobiol., No. 2, 57 (1976).
5. G. V. Idova, E. L. Al'perina, and L. V. Devoino, Immunologiya, No. 6, 75 (1985).
6. E. N. Stepanova, K. P. Kashkin, M. N. Kitaeva, et al.,Immunologiya, No. 3, 37 (1985).
7. A. Adam and E. Lederes, Med. Res. Rev., 4, 111 (1984).
8. L. Chedid, Meth. Find. Exp. Clin. Pharmacol., 8, 101 (1986).
9. J. M. Krueger, J. R. Pappenheimer, and M. J. Karnovsky, J. Biol. Chem., 257, 1664 (1982).
10. J. M. Krueger, J. Walter, C. A. Dinarello, et al., Am. J. Physiol., 246, 994 (1984).
11. C. Leclerc, E. Bourgeois, and L. Cheddid, Eur. J. Immunol., 12, 249 (1982).
12. I. Löwy, C. Bena, and L. Cheddid, Cell. Immunol., 29, 195 (1977).
13. K. Masek, Fed. Proc., 45, 2549 (1986).
14. J. J. Oppenheim, A. Togawa, L. Cheddid, et al., Cell Immunol., 51, 71 (1980).
15. W. Pierpaoli and G. J. M. Maestroni, J. Immunol., 120, 1600 (1978).
16. G. Rivaen, K. Masek, M. Parant, et al., J. Exp. Med., 152, 869 (1980).