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EFFECT OF INTERLEUKIN 1 ON ADRENAL FUNCTION IN MICE

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The functions of the immune and endocrine systems are known to be closely interconnected. There is abundant experimental evidence of the influence of the endocrine glands on lymphoid cells and macrophages [1, 3, 4, 6]. Meanwhile, investigations have shown that the plasma glucocorticoid level rises in animals of various species during the development of an immune response [3, 4, 6]. However, the nature of the signal from the activated immune system to the adrenals is not yet known. It has been found [10] that macrophages, which perform an important function in the formation and regulation of the immune response, produce a spectrum of biologically active substances, including interleukin 1 (IL-1) and prostaglandin E_2 (PGE_2), which play an essential role in the regulation of immune reactions [13]. There is also evidence that IL-1 acts on the hypothalamus [7] and that this effect is mediated by PGE_2.

The aim of this investigation was to study the effect of factors of macrophagal nature, secreted during antigen processing, on adrenal function.

EXPERIMENTAL METHOD

Male (CBA × C57Bl)F_1 mice aged 2-3 months, obtained from the Stolbovaya Nursery, Academy of Medical Sciences of the USSR, were used in all the experiments. The animals were given intravenous injections of purified supernatants of macrophages, containing IL-1, in a volume of 0.2 ml. Mice of the control group received injections of the same volume of physiological saline. Adrenal function was judged from the corticosterone level in plasma from peripheral blood. The corticosterone concentration was determined by competitive protein binding with modifications [2]. IL-1 was isolated from supernatant of peritoneal macrophages, activated by lipopolysaccharide (LPS, 25 μg/ml) in vitro in (CBA × C57Bl)F_1 mice. The collected supernatant was dialyzed, concentrated by means of an Amicon membrane (RM-10; from LKB, Sweden), and applied to a "Toyoperl 50F" column. Fractions containing material with mol. wt. of 10-20, 20-30, 30-40, and 40-60 kilodaltons were dialyzed against medium 199, filtered through a filter with pore diameter of 0.2 μ (Millipore), frozen at −20°C, and kept until use. IL-1 was tested on a mouse thymocyte culture by the method in [11].

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EXPERIMENTAL RESULTS

Intravenous injection of 0.2 ml of IL-1 into mice caused their corticosterone level to rise compared with the control. The maximal response of the adrenals was observed after 2 h, and thereafter the hormone level returned to its initial values. Injection of LPS, which stimulates production of IL-1 and PGE_2 by macrophages both in vitro and in vivo [11], also caused a considerable increase in the plasma corticosterone concentration of the experimental animals. In this case, however, the response lasted longer. The maximal response of the adrenals was found 2-3 h after injection of LPS, and control values were restored 6 h later. Injection of physiological saline did not affect the plasma level of the hormone, except after 3 h, when the corticosterone concentration was depressed. This was evidently connected with circadian changes in the blood glucocorticoid level of the experimental animals.

The next stage of the investigation was to study the dose dependence of IL-1 and the plasma corticosterone level.

The results are evidence of dose-dependent activation of adrenal function in response to injection of IL-1.

To study the mechanism of action of IL-1 on adrenal function, we investigated the effect of this factor on the plasma corticosterone level of mice after preliminary administration of indomethacin, an inhibitor of PGE_2 synthesis. We know [7] that the immunomodulating action of IL-1 is mediated through PGE, synthesized in the brain. The hormonal effect of IL-1 was abolished by preliminary injection of indomethacin. Apparently the affect of IL-1, on the functional activity of the adrenal gland, like its immunomodulating action, is connected with the stimulation of the synthesis and secretion of prostaglandins.

Thus, in the process of the formation of the humoral immune response of a macrophage, a factor is secreted which increases the functional activity of the adrenal gland. An analogous rise in the level of glucorticoids was noted in rat experiments [5] in their response to the introduction of a supernatant of spleen cells which contained IL-1, IL-2, and inhibition factor of the migration of macrophages, and, in clinical experiments [8], in cancer patients who were given lymphocytes from a culture of lymphoid cells. It has been suggested that lymphokines may exert their influence on adrenal function indirectly through macrophages, inducing release of IL-1 [8].

The secretion of IL-1 by activated macrophages has been shown to be inhibited by glucocorticoids [13]. Elevation of the blood corticosterone level caused by injection of IL-1 is probably a stage in the negative feedback mechanism, and in this way glucocorticoids take part in immunoregulation.

The question of what are the concrete mechanism of the effect of IL-1 on adrenal function requires further study. The monokine may perhaps pass through the blood–brain barrier, inducing stimulation of PGE_2 synthesis by cells of the hypothalamus, and thereby activating the hypothalamo–hypophyseoadrenal system. IL-1 may also induce synthesis of PGE_2 by peripheral blood monocytes [9], and in turn, this acts on adrenal function.

The investigation thus showed that IL-1, secreted by macrophages in the course of the humoral immune response, induces increased adrenal function. This effect is evidently mediated through a biologically active compound such as PGE_2.

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