Normalization of the Immune Response in Old Stressed Mice by Apomorphine

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UDC 612.017.1.053.9].06:
615.243.5:547.837.6

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol.116, № 11, pp. 532-534, November, 1993. Original article submitted June 3, 1993.

Key Words; *dopaminergic system; immune respons; aging; stress*

That the immune function changes in aging is well known both in man and in animals of various species. A decrease of immunological reactivity to heterologous antigens and lowering of the tolerance to homologous antigens [13] have also been observed, mainly due to quantitative and qualitative changes in the T-cell component of immunity, namely, in altered of relations between T helpers ($SD4^+$) and T suppressors ($SD8^+$). The number of $SD4^+$ T cells in lymphoid organs is half as many in 27-month-old mice as it is in 2-month old animals [1].

The basis for such changes in the immune system may be thought to be disturbances in mechanisms of neuroimmune modulation [6]. On the one hand, a decrease of indexes of the dopaminergic system activity has been observed in aging, namely, lowering of the dopamine turnover in the brain [10], and of dopamine receptor sensitivity, a decrease of density of the D1 and D2 receptors, and a drop of the dopamine content in the substantia nigra [15], which reportedly is involved in the immunomodulatory processes [1]. On the other hand, it is well known that the activatory role of the dopaminergic system in immunomodulation is accompanied by an increase of the number of T cells with helper function in the bone marrow [1]. On this basis it may be logically assumed that a neurochemical mechanism can enhance immune function, and we attempted to show this in the present study. An increase of dopaminergic activity was achieved in old mice in health and under stress conditions, when a decrease in dopaminergic system activity [2] and in immunoreactivity [8] is characteristic.

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MATERIALS AND METHODS

Experiments were carried out on 70 C57Bl/6 mice. Old animals of this line are often used in tests, since they rarely develop tumours in the course of life [7] (the average lifetime is 2.5 years). Two age groups were used, animals aged 2-3 months and 24-27 months. Each age group comprised four series with 5-10 mice in each series : the first series included the control animals (saline); the mice of the second series were injected with apomorphine 3.5 h before immunization; the stressed animals of the third series received saline, and the fourth series consisted of stressed mice treated with apomorphine 30 min before stress (3.5 h before immunization).

The animals were fixed on their backs with tight elastic bandages during 3 h (from 9 h to 12 h) to produce immobilization stress. After this the mice were immediately immunized i.v. with sheep erythrocytes (SE) in a dose of 5×10^8. Apomorphine was administered in a dose of 1 mg/kg, at which it acts as an agonist of the postsynaptic dopamine

0007-4888/93/0011-1421$12.50

TABLE 1. Effect of Apomorphine on Immune Response in Immobilization–Stressed (3 h) Young (2–3 months) and Old (24–27 months) C57Bl/6 Mice ($M \pm m$)

Age of mice	Number of RFC on 5th day after immunization with SE			
	control	stress	apomorphine	apomorphine+stress
2–3 months	18.7±1.0 (n=9)	10.8±0.6* (n=9)	31.2±1.5* (n=9)	16.5±1.4 (n=9)
24–27 months	8.6±0.8 (n=11)	4.7±0.4* (n=9)	21.3±1.7* (n=11)	15.7±1.0* (n=7)

Note. Apomorphine was administered in a dose of 1 mg/kg 30 min prior stress; n: number of animals; asterisk means differences reliable (p<0.001) in comparison with the corresponding control.

receptors [4]. The immune response was tested in animals on the 5th day postimmunization and expressed as the number of rosette-forming cells (RFC) [3].

RESULTS

The results obtained demonstrated that the immune response dropped more than 2-fold in old mice, which is consistent with the data on a decline of immunological reactivity in aging [13].

Apomorphine activation (1 mg/kg) of the postsynaptic dopamine receptors [4] resulted in a marked increase of the number RFC in old animals on the 5th day postimmunization: 21.3±1.7 vs. 8.6 ±0.7 in the control, or 247.7% . Apomorphine also boosted the immune reaction in young animals, as reported previously [1], but to a lesser degree (166.8%).

The immunostimulatory action of apomorphine has been shown to be mediated through the hypothalamo-hypophyseal system and manifests itself only in the presence of the thymus [1]. In aging the thymus becomes involuted and T-cell function decreases. A single administration of apomorphine to old animals, despite hypoplasia of their thymus, resulted in immunostimulation, just as in young animals. It may be assumed that the activation of the dopamine system in old animals altered of hypophyseal hormone production. Administration of luteinizing releasing hormone [12] or implantation of GH_3 epithelial cells of the pituitary gland, which produce growth hormone and prolactin [9], causes regeneration of thymus cells, restores their morphology, and prevents the decline of immunity in old animals.

The effect of stress in old animals has been described ambiguously [8]. We found that sensitivity to stress in old animals was the same as that in young mice.

Immunologic reactivity in old stressed animals was markedly lowered. Measured at the peak of reaction (on the 5th day after immunization), it was nearly twofold lower than in young mice (Table 1).

Apomorphine prevented the immunosuppressive effect of stress in young animals, and their immune reaction reached the control level. Old animals treated with apomorphine demonstrated nearly a twofold (compared to the control) increase of the immune response after stress (while in young mice this parameter only reached the control level), which approached the magnitude of the immune response in young nonstressed animals (Table 1).

Changes in dopamine neurotransmission, a decrease of the dopamine content, and a lower density of D1 and D2 receptors [10,15] have been demonstrated in the course of aging. It is interesting to note that in old animals a change in the sensitivity of the dopamine receptors to their activation by apomorphine has been described [14]. Apomorphine administration in a dose that activates the postsynaptic dopamine receptors produces stereotypic activity which is more pronounced in old animals. In our experiments apomorphine induced a more pronounced (as compared to the age-matched control) increase of the immune response in old animals than in young mice not only under stress but under normal conditions as well.

The administration of the catecholamine precursor DOPA which markedly raises the dopamine level in the brain and intensifies the immunologic reactivity [1], is known to change the life span in mice [5].

Thus, the data obtained on normalization of immune response by apomorphine in stressed young animals allow us to assume that the decline of immunity in aging and in stress are largely related to inpaired of psychoneuroimmunomodulation due to changes in the neurochemical status of the brain. A decrease of dopaminergic activity may change the interaction among the serotonin-, dopamine-, and GABA-ergic systems in immunomodulation with the dominance of just one, for example, the serotoninergic system [1, 3]. Apomorphine activation of the dopaminergic system restores the neurochemical pattern of interaction.

This study was performed with the financial support of the Russian fund of basic research (project code 93-04-22067).

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ONCOLOGY

Inhibition of the Development of Experimental Tumors of the Cervix and Vagina by Tinctures from Biomass of Cultured Ginseng Cells and Its Germanium-Selective Stocks

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UDC 618.1-006-092:615.015.89

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol.116, № 11, pp. 534-536, November, 1993
Original article submitted June 9, 1993

Key Words: *bioginseng; carcinogenesis of cervix and vagina*

Natural phytoadaptogens are promising candidates for remedies of prophylaxis and treatment of cancer [7]. Preparations of ginseng root have been shown to exhibit an antitumor effect both in experimental animals with transplanted tumors and in clinical practice [3,7]. In addition, ginseng root extract produces an anticarcinogenic action on the growth of lung adenoma induced by different chemical carcinogens in mice [16]. Epidemiological observations have shown that in persons regu-

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0007-4888/93/0011-1423$12.50