

ACTION OF RESERPINE ON ANTIBODY FORMATION IN HYPOPHYSECTOMIZED ANIMALS

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Administration of reserpine to intact rabbits causes delay in the appearance of circulating antibodies after primary immunization with bovine serum albumin and also depresses the primary and secondary immune responses. This effect is not found in hypophysectomized animals or after destruction of the pituitary stalk.

The inhibitory action of reserpine, a drug modifying the concentration of biogenic amines in the tissues on immune reactions has been demonstrated [4,12]. However, the mechanism of this effect remains unexplained. Giving regard to the important role of the hypothalamus - pituitary system in the regulation of immune responses [2,7,8], the present investigation was carried out to study the effect of reserpine on humoral antibody formation in hypophysectomized animals.

EXPERIMENTAL METHOD

Experiments were carried out on 46 male chinchilla rabbits weighing from 2 to 3 kg. The animals were immunized with crystalline bovine serum albumin in a dose of 5 mg/kg by a single intramuscular injection. The animals were reimmunized on the 40th day with the same dose of antigen. Blood was taken before immunization, on the 4th, 7th, 10th, 14th, 21st, 28th, and 40th days after primary immunization, and on the 2nd, 4th, 7th, and 10th days after reimmunization. Antibodies were determined by Boyden's method [10].

Reserpine was given by mouth in a dose of 2 mg/kg daily for 8 days starting three days before primary immunization.

Hypophysectomy was carried out electrolytically under intravenous nembutal anesthesia. The electrodes were inserted by means of a stereotaxic apparatus, using the atlas of Sawyer, Everett, and Green [17]. At the end of the experiment, control macroscopic and microscopic examinations were made. Hypophysectomized animals and animals with destruction of the pituitary stalk, in which the pituitary was either uninjured or showed a varied degree of degeneration, were included in the analysis.

The time from operation until the beginning of reserpine treatment varied from 10 to 15 days. Since the reserpine lowered the body temperature by 3-5°, during treatment with this drug the rabbits were kept at a temperature of 25°.

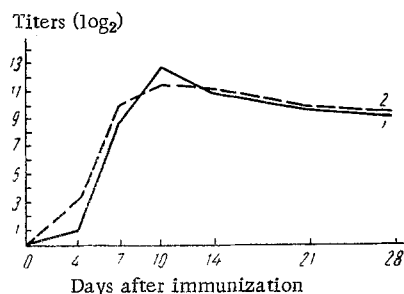


Fig. 1. Dynamics of humoral antibody formation in hypophysectomized animals. 1) Control animals; 2) hypophysectomized animals.

EXPERIMENTAL RESULTS

In the experiments of series I, the effect of hypophysectomy on the formation of humoral antibodies was studied. The experimental results illustrated in Fig. 1 show that hypophysectomy alone has no significant effect on this process. This agrees with data obtained by other investigators [13,14].

In the next series of experiments, the effect of reserpine on antibody formation was compared in animals with an intact pituitary and in hypophysectomized animals. The antibody titers in the hypophysectomized animals and animals with destruction of the pituitary stalk, when treated with reserpine, were similar.

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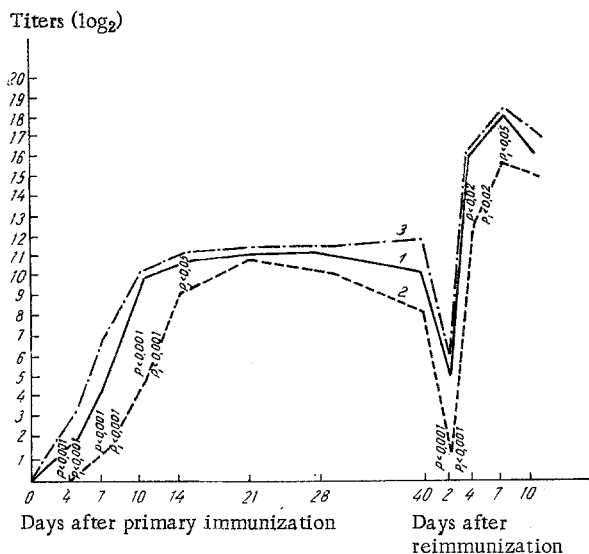


Fig. 2. Effect of destruction of the pituitary on humoral antibody synthesis during treatment of animals with reserpine. 1) Control animals; 2) animals with intact brain receiving reserpine by mouth in a daily dose of 2 mg/kg for 8 days, starting on the 3rd day before primary immunization; 3) animals with destroyed pituitary, treated with reserpine in the same dose for the same time. Re-immunization on 40th day; P denotes significance of difference between 1 and 2; P₁, significance of difference between 2 and 3.

Because of the similar action of reserpine and of tryptophan metabolites (5-hydroxytryptophan and serotonin) on immunogenesis, it can be concluded that this effect of reserpine on immune responses took place through a change in the serotonin level [5]. It may be considered that reserpine, by preventing the binding of this biogenic amine by the tissues, leads to the creation of a constant and higher than normal level of free serotonin. This confirms the earlier hypothesis [11,12,16,17]. Disturbance of serotonin deposition evidently blocks one of the pathways of its inactivation, and monoamine oxidase possibly cannot completely destroy the fresh amounts of serotonin newly synthesized and liberated from the depots. If monoamine oxidase is blocked, but the mechanism of serotonin deposition left intact, the effect of inhibition of antibody formation is produced as before. Probably the inhibitory factor in the action of reserpine on humoral antibody formation is free serotonin.

Reserpine also affects catecholamine metabolism. However, the inhibitory effect cannot be due to this property of reserpine, because 3,4-dihydroxyphenylalanine and adrenomimetic substances (in contrast to serotonin) stimulate the process of antibody formation [5].

There are data in the literature to show the participation of hypothalamic structures in the regulation of immunogenesis [1,3,8,9,15]. The fact that the inhibitory effect of reserpine is not exhibited, not only in hypophysectomized animals, but also in animals in which only the pituitary stalk is divided, suggests that the hypothalamus-pituitary system is concerned in the realization of this action.

It may be postulated that hypothalamic structures participating in the mechanism of inhibition of immunogenesis are sensitive to serotonin.

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Accordingly, they were subsequently combined into a single group - animals with destruction of the pituitary.

Analysis of the results of the experiments on rabbits with an intact pituitary showed that administration of reserpine prolongs the latent period of the primary immune response (Fig. 2). Whereas in the control animals antibodies appeared on the 4th day, in animals treated with reserpine no antibodies were found at this time, and only in one of 8 animals had they appeared by the 7th day. The intensity of the immune response in animals of this series was much reduced later still, on the 10th day after primary immunization and the 2nd, 4th, and 7th days after reimmunization (Fig. 2). Despite the much lower intensity of antibody formation after reimmunization in the rabbits receiving reserpine, the character of the secondary immune response was unchanged.

After hypophysectomy or destruction of the connection between the hypothalamus and pituitary (destruction of the pituitary stalk), reserpine treatment produced no such inhibition of the immune response (Fig. 2). The character and magnitude of both primary and secondary immune responses in these animals (in contrast to rabbits with an intact brain) were essentially indistinguishable from those in the control series.

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