Hormonal synergism and antagonism in tissue reactions

D. C. 615.361:616.091

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Hormonal Synergism and Antagonism in Tissue Reactions

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Mesenchymal structures are important participants in tissue response to various injurious agents. The tissue reaction itself is determined by autonomous factors, their mechanism is still poorly understood. Hormones play an important role in regulating the quantity and quality of the proliferating tissues, thus representing an integral link in the chain of events between the injurious agent and the reactor.

The *stimulating* effect of the *anterior pituitary* is best demonstrated in hypophysectomized animals, in which actively proliferating granulation tissue accumulating around turpentine abscesses is observed in white rats (1). In such animals the quantity and the quality of granulation tissue is by far inferior to normal controls. The fibroblasts are flat and small, the collagen fibers sparse and in some areas practically no granulation tissue is seen at all adjacent to the leukocytic layer. *Growth hormone* of the anterior pituitary injected to such animals reestablishes granulation tissue formation. If injected in larger doses it causes proliferation beyond normal, giant fibroblasts appear and the granulation tissue layer is considerably thicker than in the control animal. Growth hormone injected to intact animals also produces a stimulatory effect. However a certain optimal level of growth hormone can be observed in normal animals, beyond which no stimulation takes place: growth hormone injected to normal animals in larger doses actually inhibits granulation tissue formation. This is most likely due to contamination of the growth hormone preparation by inhibiting factors (ACTH), which become apparent if the bulk of injected material is increased. Growth hormone fails to exhibit its stimulatory effect if injected to adrenalectomized animals, indicating that its action is dependent upon adrenal steroid. Recently the suggestion has been made (2), that the

[1] The work was aided by a grant (RG 2522) from the U.S. Public Health Service to the Rheumatoid Arthritis Research Group of Michael Reese Hospital (*S. Soskin*, Chairman).

pituitary growth hormone stimulates desoxycorticosterone production and thus produces its effects upon fibroblastic proliferation (vide infra).

The effect of the *thyrotropic hormone* of the anterior pituitary has not been tested directly. The fact that this hormone has a stimulatory effect upon granulation tissue can be assumed from experiments in which hypophysectomized animals, which show ordinarily an inhibition of granulation tissue formation, are injected with thyroxin (1). Such animals exhibit a fair granulation tissue response indicating that at least one factor responsible for failure of granulation tissue development in hypophysectomized animals is the loss of thyroid function. Thyroidectomized animals produce granulation tissue, slightly inferior to the normal ones and exhibiting changes in the ground substance resembling myxedema. Such changes can be abolished with thyroxin. Thyroid hormone injected to intact animals has no demonstrable effect upon granulation tissue formation.

Another very powerful stimulant of granulation tissue is *desoxycorticosterone* (3), which had been shown to produce also other proliferative changes in mesenchymal structures (4). Under the influence of this hormone the quantity of granulation tissue accumulating around turpentine abscesses is enormously increased. The quality of the tissue however differs from the normal in that the fibroblasts assume a stellate or polygonal appearance, the ground substance is glassy and the fiber formation is inhibited. Such an effect can only be observed, however, if the animals are pretreated with the hormone for many days prior to the injection of turpentine. In contradistinction to growth hormone, no stimulating effect of desoxycorticosterone can be observed if the hormone is injected only while the turpentine abscess is developing. The significance of this observation remains unexplained. The action of desoxycorticosterone upon wound healing has been studied more recently and its stimulation of granulation tissue has been confirmed (5). It was shown however, that the actual wound healing is not improved under the influence of this hormone. The question whether desoxycorticosterone is active in hypophysectomized animals is under our investigation. Desoxycorticosterone has no local effect, such as can be observed with cortisone (*vide infra*), because it exhibits no effect in the immediate surrounding of the turpentine abscess, if mixed with the turpentine injected (6).

It appears appropriate to point out the differences between the action of growth hormone of the anterior pituitary and of the desoxycorticosterone upon granulation tissue, both hormones exhibiting a stimulating effect. First there is a definite qualitative difference in the granulation

tissue produced by the hormones. Under growth hormone influence, the granulation tissue is activated and although giant cells appear, the overall picture of the tissue does not appear abnormal. Under the influence of desoxycorticosterone the granulation tissue appears pathologic. Second, there is the time element involved, in that growth hormone produces its effect while granulation tissue is forming and without pretreatment. Desoxycorticosterone must be administered long before and during the injury has been placed, to produce effects. Objections therefore may be raised against the assumption that growth hormone acts by desoxycorticosterone stimulation (2) and additional investigations have to be performed to clarify this important point. In perfusion experiments of the isolated adrenal gland, it has been shown that growth hormone has a stimulating effect upon steroid hormone output however, this has been attributed to contamination with ACTH (7).

Among the *inhibitors* of granulation tissue formation *Cortisone* plays a paramount role, as has been found independently in different laboratories (1, 8, 9). The fibroblasts of granulation tissue under the action of cortisone appear small, rounded, and diminished in number. The ground substance is possibly altered, as observed by simple staining techniques, although chemical studies and better fixation methods are being employed to study the changes in this element. Changes of fiber structure and fiber growth are indicated by experimental work and clinical observations. The study of a case of scleroderma treated with cortisone revealed that the cohesion of collagen fibers in this condition is altered, and the thick fiber bundles are broken up into thinner ones and also assume a more normal, wavy appearance under the influence of the hormone (10). Similar observations were made on cutaneous collagen of experimental animals (11). In order to study fiber growth, the observation was utilized that cortisone inhibits growth of experimental animals in general and the tail in particular. The tendon fibers, if examined under the electrone microscope, look very much like collagen fibers and consist of fibrils of certain widths and are subdivided in band-like, axial repeating periods of a rather constant length. Tail tendon fibrils of young rats were examined and their widths and lengths of the axial periods were measured on electron micrograms. Several of the young animals were permitted to grow until their body weights and their tail length approximately trebled. The same measurements were taken on electron microscopic pictures of these fibrils and it was found that many of the fibrils had become considerably wider, but the axial period lengths remained the same. This finding was interpreted as meaning that the fibril grows longitudinally by apposition of new axial repeating

periods of equal length, rather than by elongation of the periods. The width increases by actual increase of the diameter of the fibril. Another group of young animals received daily cortisone injections for the same period of time as the previous group. Cortisone inhibited growth in these animals and their body and tail lengths remained approximately at the level of the young control animals. Electron microscopical examination of fibrils in these animals revealed that again the axial repeating periods measured the same as in the previous group. The widths were found to be the same as in the grown-up animals. It was concluded, therefore, that cortisone inhibits apposition of new axial repeating periods, but does not interfere with the transverse growth of the fibril (12). No correlation between tendon and collagen fibrils has been made as yet.

Cortisone seems to exhibit its effect upon granulation tissue locally (11, 13), and therefore does not act by indirect means or by its catabolic effect upon the proteins in general. Intact innervation or hyperemia is unnecessary for the cortisone to take effect (13). The hormone seems to exert its greatest influence in the early stages of inflammation (14) and cannot dissolve existing granulation tissue (15). The inhibitory effect of cortisone can be counteracted by desoxycorticosterone but not by small doses of growth hormone. Large doses of the latter seem to be able to counteract the action of cortisone and produce proliferation, in spite of its activity (6). This may indicate that cortisone counteracts growth hormone locally. Thyroxin has no effect upon the inhibitory influence of cortisone (6). The methods to study antagonists of cortisone have been facilitated by the observation (13) that cortisone, if mixed with the turpentine and injected into one area of the experimental animal, produces local inhibitory effects. Turpentine alone, placed into the contralateral area of the same animal simultaneously, will produce normal granulation tissue. The effects of various hormones, injected systematically to such animals, can be studied both on the cortisone and the control side. Thus the antagonistic action of desoxycorticosterone and growth hormone, mentioned before, could be ascertained.

We have no knowledge about the mechanisms operating in the action of cortisone upon granulation tissue. There is no correlation between its effects upon the general metabolism, vasomotor phenomena, about the controversial role of ascorbic acid, membrane permeability, etc., on the one hand, and the inhibitory effect upon granulation tissue on the other. Very recently it has been shown that cortisone may not produce any inhibition at all in wounds, healing per primam (16). That fair granulation tissue formation occurs in absence of the adrenals, has been shown before (3). ACTH induces similar changes as cortisone (1).

Inhibition of granulation tissue occurs also under the influence of *testosterone* and in particular *estradiol* (3). Granulation tissue developing in such animals resembles the one observed in hypophysectomized animals. The mode of action of these hormones, however, differs considerably from the cortisone. Sex hormones do not exhibit any local effect, the inhibition is systemic and occurs wherever granulation tissue is forming, no matter where the hormones were injected (6). Injection of small amounts of growth hormone as a maintenance dose will completely abolish the sex hormone effect and actually produce strong proliferation of granulation tissue (1). This would suggest that sex hormones act by inhibiting the discharge and/or production of growth hormone in the anterior pituitary gland.

Methyl androstenediol acts very much like testosterone and produces the same systemic, inhibitory effect upon granulation tissue (6).

Thus it becomes evident that mesenchymal or inflammatory reactions are stimulated or inhibited by hormonal interaction and depend on a hormonal balance. If we realize that the mesenchyma is a target organ of hormones, their physiologic, pathologic and especially pharmacologic effects become better understandable. This statement deserves emphasis before this group, since allergic phenomena are basically mesenchymal reactions.

The following table *summarizes* the effects of various hormones upon granulation tissue and its elements:

	General effect	Fibroblasts	Collagen fibers	Ground substance
Ant. pituitary Growth hormone	Stimulation	Large, of normal contour	Thick	?
Thyroxin	Stimulation in deficient animals	Normal	Normal	Abolishes myxedema
Desoxycorticosterone	Stimulation	Large, polygonal or stellate	Diminished	Altered
Cortisone	Inhibition	Small	Inhibition of longitudinal growth	Altered
Estrogen	Inhibition	Small, flat	Thin	Altered (?)
Testosterone	Inhibition	Small	Thin	Altered (?)
Methyl androstenediol	Inhibition	Small	?	?

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