

Medical Endocrinology / Introduction 5

Medical Endocrinology

Hormone Interactions

The responsiveness of a target cell to a hormone depends on

- (1) the hormone's concentration,
- (2) the abundance of the target cell's hormone receptors, and
- (3) influences exerted by other hormones.

A target cell responds more vigorously when the level of a hormone rises
or

when it has more receptors (up-regulation).

In addition, the actions of some hormones on target cells require a
simultaneous or recent exposure to a second hormone.

In such cases, the second hormone is said to have a ***Permissive Effect***.

For example, epinephrine alone only weakly stimulates lipolysis (the breakdown of triglycerides), but when small amounts of thyroid hormones (T3 and T4) are present, the same amount of epinephrine stimulates lipolysis much more powerfully.

Sometimes the permissive hormone increases the number of receptors for the other hormone, and sometimes it promotes the synthesis of an enzyme required for the expression of the other hormone's effects.

When the effect of two hormones acting together is greater or more extensive than the effect of each hormone acting alone, the two hormones are said to have a ***Synergistic Effect***. For example, normal development of oocytes in the ovaries requires both follicle-stimulating hormone from the anterior pituitary and estrogens from the ovaries. Neither hormone alone is sufficient.

When one hormone opposes the actions of another hormone, the two hormones are said to have ***Antagonistic Effects***. An example of an antagonistic pair of hormones is insulin, which promotes synthesis of

glycogen by liver cells, and glucagon, which stimulates breakdown of glycogen in the liver.

PERMISSIVE EFFECTS-One H. can not exert its effects fully unless a 2nd H. is present & the action of 1st hormone enhances response to 2nd hormone eg. (Up-regulation of progesterone receptor in response to estrogen)& (The maturation of the reproductive system is under the control of GnRH from hypothalamus ; Gonadotropins from adenohypophysis & steroid H. from the gonads. However; if thyroid H. are not present in sufficient amounts 'maturation of the reproductive system is delayed .Because T.H. by itself can not stimulate maturation of the reproductive system).

T.H. is considered to have a PERMISSIVE EFFECT on sexual maturation:

-T.H. alone : No development of the reproductive system.

-Reproductive H. alone :Delayed development of the reproductive system .

- *Reproductive H. +T.H.: Normal development of the reproductive system.*

SYNERGISTIC EFFECTS-The combined effect of 2 H. is greater than the sum of the effects of the 2 H.taken individually (Eg.

-Epinephrin elevates blood glucose 5mg/dl blood

-Glucagone elevates blood glucose 10mg/dl blood

Epinephrin+ Glucagoneelevates blood glucose 22mg/dl blood.(

So both hormones must act simultaneously to function effectively (eg. FSH & testosterone for sperm production)

ANTAGONISTIC EFFECTS -2 hormones have opposite effects (work against each other ,one diminishing the effectiveness of the other) eg.

Insulin & glucagon (glucagon & growth H. ,both of which raise the conc.

Of glucose in the blood ,are ANTAGONISTIC to insulin , which lowers

the conc. Of glucose in the blood (One H. may decreases No. of receptors

for opposing H.((Eg. G.H. decreases No. of insulin receptors providing part of its ANTAGONISTIC EFFECTS on blood glucose conc.)).

Hormone ANTAGONISTIC & Cancer:

Tamoxifen is a drug used for the treatment of Breast Cancer when the cancer cells have estrogen receptors & are stimulated by endogenous estrogen. Tamoxifen acts as an ANTAGONIST by competing with estradiol for binding to estrogen receptors .Once Tamoxifen binds it block estradiols action.

Transport and Metabolism of Hormones

Once a hormone is released into the bloodstream it may circulate freely, or it may be bound to a carrier protein. In general, catecholamines, peptides, and proteins circulate in free form whereas steroids and thyroid hormones are bound to transport proteins. Plasma proteins such as albumin and

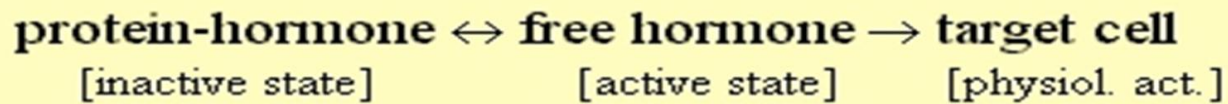
prealbumin have the capacity to nonselectively transport a variety of low molecular weight hormones.

These proteins have a very high capacity to weakly associate with many types of compounds, such as steroid hormones, free fatty acids, and calcium.

The binding is said to be nonspecific and the equilibrium constant for dissociation is relatively high. In contrast, there are specific transport proteins for several hormones. These are globulins produced in the liver that have saturable, high-affinity binding sites for the hormones they carry. These proteins include thyroxine-binding globulin (TBG), testosterone-binding globulin (TeBG), and cortisol-binding globulin (CBG).

Binding of hormones to carrier proteins has important consequences:

- (1) it prevents small hormone molecules from passing out in the urine because the carriers are too large to be filtered by the glomerulus;
- 2) it slows liver metabolism of the hormone to an inactive form;
- (3) it acts as a reservoir;
- 4) it keeps the hormone in an inactive state until the target organ is reached.



An equilibrium is established between carrier-hormone complex and free hormone in serum. As free hormone enters the target cell, the equilibrium shifts to the right and a new equilibrium is established by dissociation of the complex to restore free hormone concentration. In this way, the complexed hormone acts as a reservoir and maintains the hormone in an inactive state.

In general, changes in the plasma levels of binding proteins are rapidly followed by adjustments in the secretion rate of the corresponding hormone, so that the fraction of hormone readily available for tissue delivery remains constant and endocrine function thus remains normal. One well-known example of this is the increase in CBG concentration that occurs during pregnancy as a consequence of estradiol stimulation. While the total plasma cortisol rises as a result of the increased CBG levels, the cortisol available to the tissues remains normal.

As the concentration of CBG increases, there is a temporary shortage in the cortisol available to target tissues as more is bound to CBG. This results in a temporary increase in ACTH by activation of feedback mechanisms and increased cortisol secretion to bring the total plasma concentration of cortisol to a higher level and return tissue delivery of cortisol to normal. Thus, in the steady state with intact control mechanisms, alterations in hormone-binding proteins do not affect endocrine status.

The metabolic clearance rate (MCR) of a hormone defines quantitatively its removal from plasma. Under steady-state conditions the MCR represents the volume of plasma cleared of the hormone per unit of time; usually the units employed are milliliters per minute. Suppose a radioactive hormone is infused into the bloodstream until a constant level is reached. The infusion is then stopped, the disappearance rate of the labeled hormone from the plasma can be determined, and the plasma half-life of the hormone calculated.

The plasma half-life of a hormone is inversely related to its MCR metabolic clearance rate, i.e., a long half-life indicates a slow clearance rate.

Usually, the larger molecules have the longer half-life. Of course, small hormone molecules that form complexes with serum proteins would not follow this rule. Such hormones would have much a half-life much longer than expected based on its size since the carrier proteins protects it from metabolism.

Thyroid hormones and steroid hormones are good examples. Thyroid hormones are small molecules of modified amino acids with a half-life of 7 days for thyroxin and 8-24 hours for triiodothyronine. Thyroxin is more tightly bound to TBG than triiodothyronine. Steroid hormones such as cortisol which is transported tightly bound to CBG (transcortin, as the human serum protein is called) has a half-life of about 90 minutes whereas aldosterone and angiotensin II which circulate free in serum have half-lives of about 15 minutes and 1-3 minutes, respectively. The bulk of hormone clearance is done by the liver and the kidneys. This process includes degradation by a variety of enzymatic mechanisms such as hydrolysis, oxidation, hydroxylation, methylation, decarboxylation,

sulfation, and glucuronidation. In general only a small fraction ($<1\%$) of any hormone is normally excreted intact in the urine or feces.

The interaction of hormones with their target tissues apparently is followed by intracellular degradation of the hormone. In the case of protein hormones and catecholamines, degradation occurs after their binding to membrane receptors, internalization of the hormone-receptor complex, and the dissociation of this complex into its two components, which occurs in lysosomes.

THANK YOU

Prof. Dr. Sa'ad Merza Alaraji