

ORGANIZATION OF THE TALK

- General overview of endocrine systems: What functions do they serve?
- Influence of alcohol on endocrine systems: General mechanisms.
- The hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes.

ENDOCRINOLOGY AND THE PRINCIPLE OF HOMEOSTASIS

An essential aspect of mammalian organisms is that their cells must communicate with each other. They do so via nerve impulses and blood-borne signals. Endocrinology is concerned with the study of these blood-borne, chemical messengers (hormones), substances secreted by cells of endocrine glands and tissues, that regulate the activity of other cells in the body.

Role of hormones:

For the body to function properly, its various parts and organs must communicate with each other in order to:

1. Ensure that a constant internal environment (i.e., homeostasis) is maintained.
2. Enable the organism to respond appropriately to any changes in their internal or external environment.

The capacity of specialized tissues to function in this integrated fashion is made possible by two control mechanisms which are functionally linked:

1. The nervous system, which transmits electrochemical signals as two-way traffic between the brain and peripheral tissues, or between tissues in reflex circuits. Can be viewed as a wired system.
2. The endocrine system, which releases chemical mediators called hormones into the circulation and/or to adjacent tissues. Can be viewed as a wireless system.

Endocrinology has been defined as the branch of biological science that concerns itself with the actions of hormones and the organs in which the hormones are formed.

ENDOCRINE GLANDS

Endocrine glands (ductless glands) are specialized organs that manufacture hormones and secrete them directly into the blood stream. This is in contrast to exocrine glands such as salivary glands, which release their products into ducts leading into the lumen of other organs (such as the intestine).

Main endocrine glands

pituitary gland (hypophysis)
adrenals
thyroid
parathyroid
gonads (testes and ovaries)
pineal
pancreas
gastrointestinal tract

Hormones

ACTH, TSH, LH, FSH, GH, PRL
corticosteroids
thyroxine (T4), triiodothyronine (T3)
parathyroid hormone
testosterone, estrogen, progesterone
melatonin
insulin, glucagon, somatostatin, etc.
gastrin, cholecystokinin, motilin, etc.

FUNCTION OF HORMONES

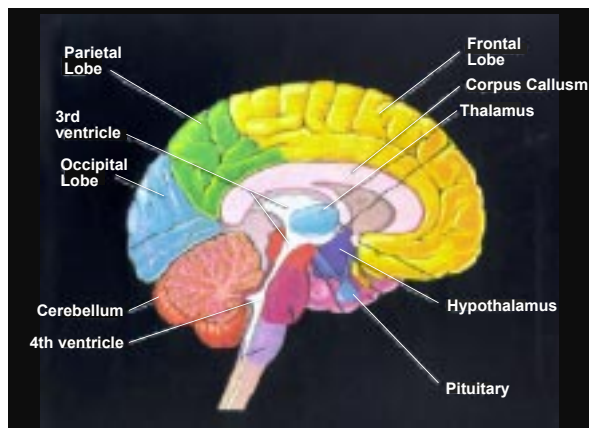
- Reproduction
- Growth and development
- Maintenance of internal environment (electrolytic content of body fluids, blood pressure and heart rate, acid-base balance, temperature, etc.)
- Energy production, utilization and storage

CHEMICAL NATURE OF HORMONES

- Peptides and amino acid derivatives
 - Glycoproteins (TSH, LH, FSH)
 - Peptides (ACTH)
 - Sugarless proteins (insulin)
- Derivatives of single amino acids (catecholamines, serotonin, histamine)

THE HYPOTHALAMUS

Slide 1 illustrates a sagittal view of the human brain. The hypothalamus is the basal part of the diencephalon lying below the thalamus, as its name implies. It forms the walls and lower part of the third ventricle of the brain. The endocrine hypothalamus is connected to and influenced by the rest of the central nervous system by synaptic contacts from other neuronal elements. Information flows from other brain centers and is relayed to the hypothalamus through pathways that manufacture neurotransmitters such as catecholamines, serotonin, etc. This is how information from the periphery is coded and conveyed to the hypothalamus, allowing this structure to mount appropriate endocrine responses aimed at restoring homeostasis.



Slide 1

THE HYPOTHALAMIC-PITUITARY AXIS

Type

HYPOTHALAMIC HORMONES

Corticotropin-releasing factor (CRF)
 Gonadotropin-releasing hormone (GnRH)
 Growth hormone releasing hormone (GHRH)
 Somatotropin release inhibiting hormone (Somatostatin)
 TSH-releasing hormone (TRH)

Major Role

↑ ACTH
 ↑ LH (FSH)
 ↑ GH
 ↓ GH
 ↑ TSH

ANTERIOR PITUITARY HORMONES

Adrenocorticotropin (ACTH)
 LH, FSH (gonadotropins)
 Prolactin
 Growth hormone
 Thyroid stimulating hormone (TSH)

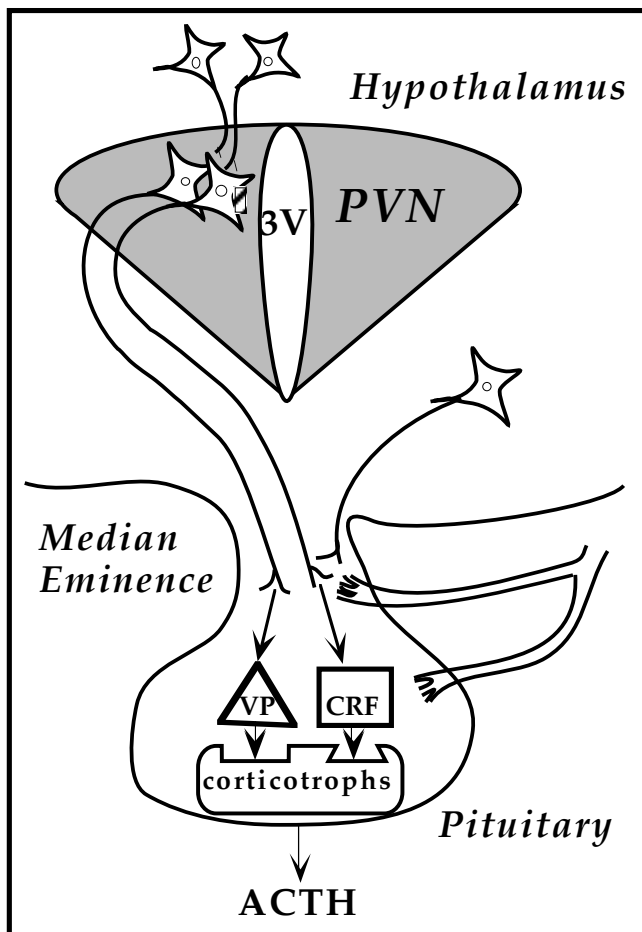
↑ adrenal steroidogenesis
 ↑ gonadal steroidogenesis
 ↑ milk synthesis (corpus luteum)
 controls metabolic processes
 ↑ thyroid hormones synthesis

INFLUENCE OF ALCOHOL ON ENDOCRINE SYSTEMS: GENERAL MECHANISMS

Alcohol could act by influencing:

- Hormone synthesis, storage and release
- Hormone transport:
 - For water-soluble molecules, transport in plasma without specific transport mechanisms
 - For more insoluble hormones: carrier mechanisms (transport proteins; because only free, unbound hormones enter cells, these proteins act as reservoirs)
- Hormone regulation by feedback mechanisms
- Hormone mechanisms of action: Interaction with receptors, effect on second messengers

THE HYPOTHALAMIC-PITUITARY AXIS

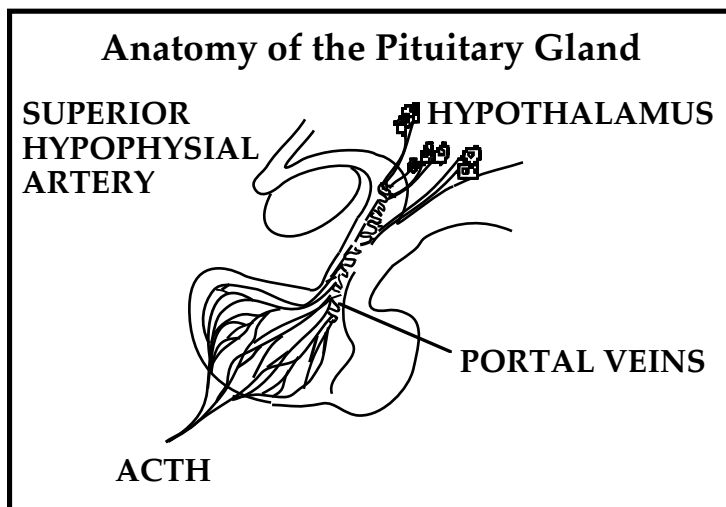


Slides 2 and 3:

Neurons of the hypothalamus that synthesize CRF and vasopressin are found in an area called the paraventricular nucleus (PVN). These cell bodies send axons to the median eminence, where peptides are released from the nerve terminals and are transported through vessels of the portal system. When they reach the anterior pituitary, these peptides act on their respective receptors, thereby stimulating ACTH secretion.

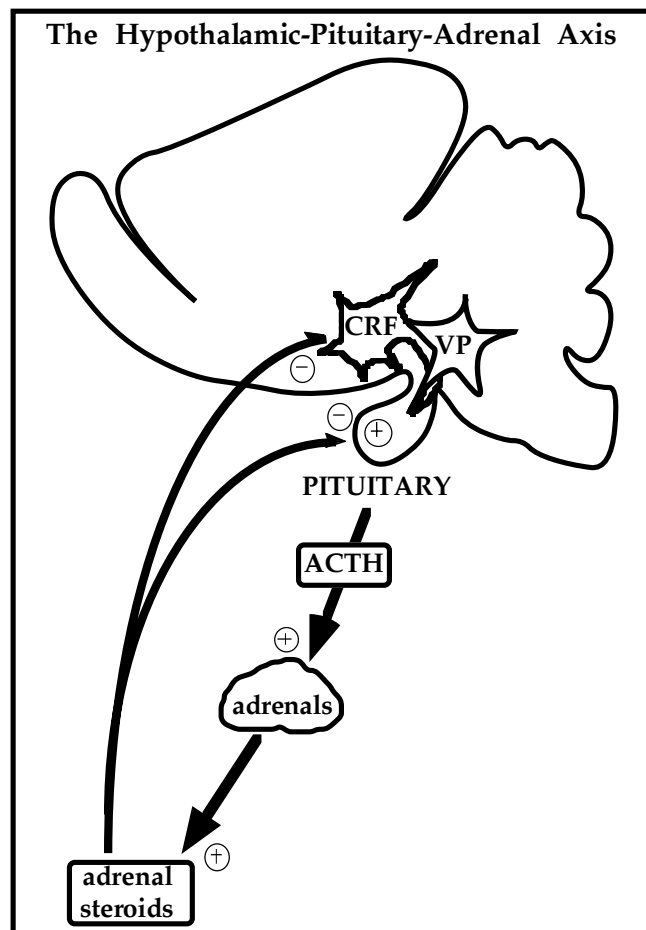
Slide 2

THE HYPOTHALAMIC-PITUITARY AXIS

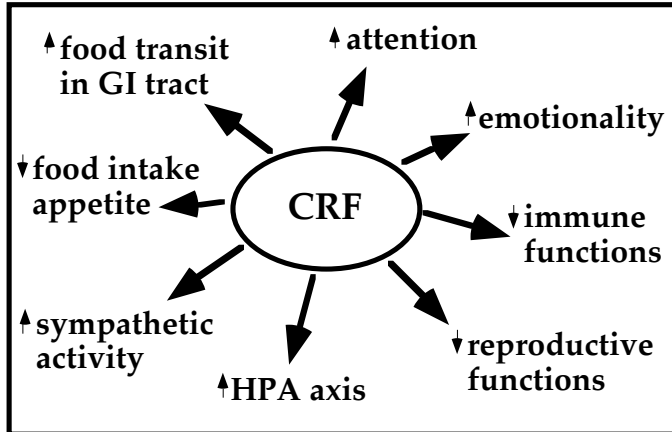


Slide 3

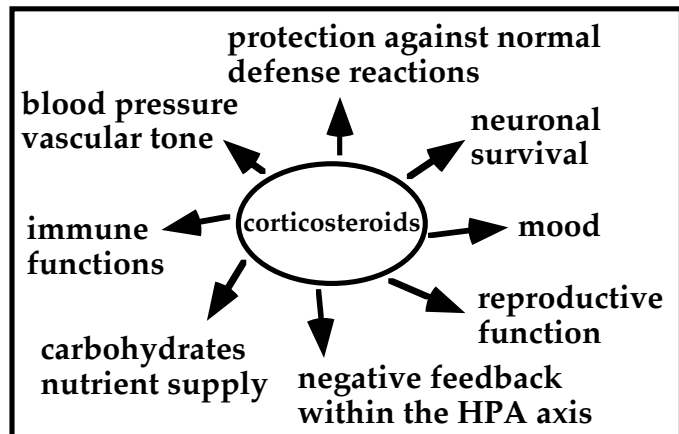
Slide 4: Following its release into the general circulation, ACTH acts on the cortex of the adrenal glands, which manufacture and secrete glucocorticoids (corticosterone in rodents and cortisol in humans). These glucocorticoids exert a classical negative feedback influence on the pituitary, where they inhibit the effect of CRF and VP, and on the PVN, where they inhibit the synthesis of CRF. Thus after a stimulus stimulates CRF and ACTH release, the production of glucocorticoids will eventually terminate this release, thereby ensuring the maintenance of homeostasis.



IMPORTANCE OF CRF AND GLUCOCORTICOIDS FOR HOMEOSTASIS



Slide 5

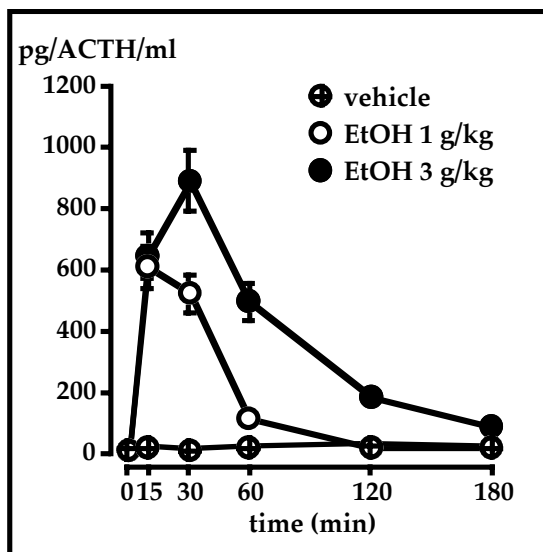


Slide 6

Both CRF and steroids produced by the adrenal gland (glucocorticoids) exert a plethora of effects within the body. The most important effects are illustrated on **Slides 5 and 6**. These wide-ranging effects underscore the importance of understanding how the HPA axis functions, what effects various stimuli exert on it, and the mechanisms through which these effects are exerted.

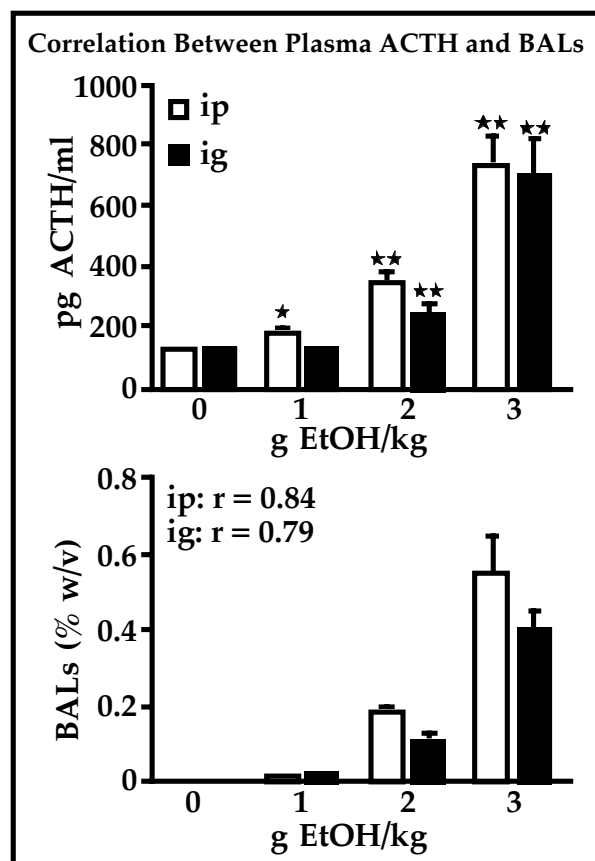
EFFECT OF ALCOHOL ON THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

These studies were done to investigate the effect of alcohol on ACTH release, and the relationship between the amount of alcohol injected and this hormone response. They were also done to determine possible differences between the effect of intraperitoneal (ip) and intragastric (ig) injections.



Slide 7 illustrates the time course of the ACTH response to the ip injection of two different doses of alcohol to intact male rats. This response was dose-dependent in that the larger alcohol dose induced the larger release of ACTH. It was also time-dependent in that the ACTH response was longest in response to the larger dose of alcohol. Each point represents the mean \pm SEM of 5-6 animals. **, $P < 0.01$ versus vehicle (bottom line).

Slide 8 illustrates the relationship between ACTH release and blood alcohol levels (BALs) following the ip or ig injection of alcohol. ACTH data represent cumulative hormone release over a 60 min time period. BALs data illustrate peak values for each dose. Each bar represents the mean \pm SEM of 5-6 animals. *, $P < 0.05$ and **, $P < 0.01$ versus vehicle ("0" alcohol).

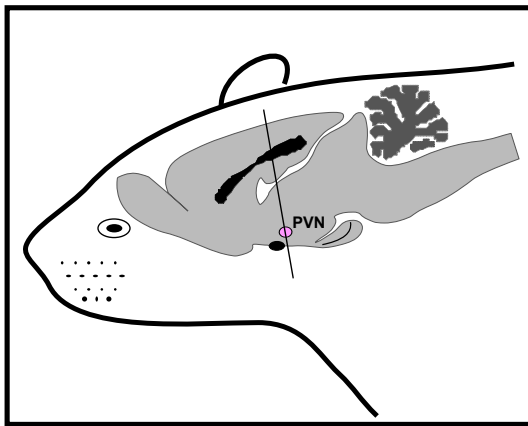


Alcohol could act at the level of:

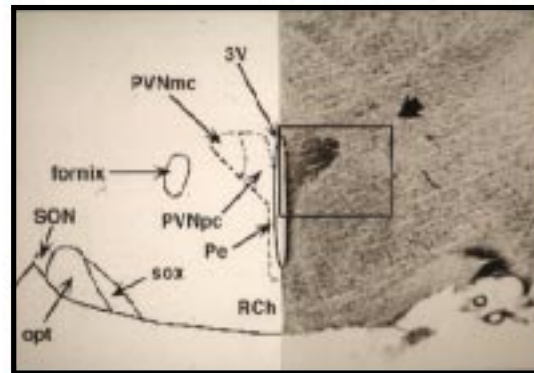
- PVN afferents
- PVN itself (secretagogues synthesis and release; responsiveness to neurotransmitters)
- Median eminence (secretagogues release, effect of neurotransmitters)
- Pituitary (receptors, second messengers, intracellular molecular mechanisms)
- Adrenals (including events related to steroid feedback)

• **Hypothalamus: Alcohol stimulates CRF synthesis.**

These experiments were done to investigate the PVN neuronal response to the ip injection of alcohol (3 g/kg).



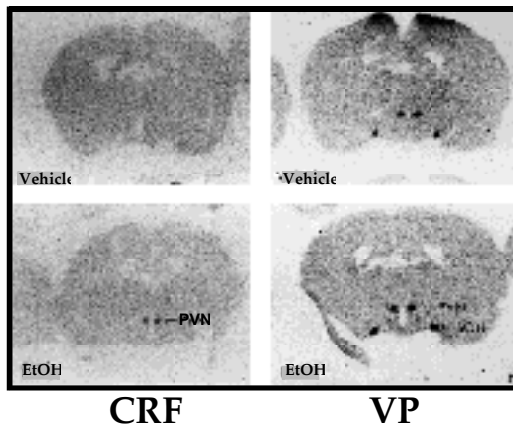
Slide 9



Slide 10

Slide 9 depicts a rat brain and the site along which the brain was cut. This cut is called coronal, and indicates that it was made along longitudinal section passing through the brain at right angles to the median plane.

Slide 10 illustrates pictures of a coronal section of the rat PVN. The left side illustrates a cartoon of this nucleus while the right side shows a section of this nucleus stained to show landmark anatomical features. The third ventricle (3V) is in the middle and the PVN is situated on each side, in the shape of the wings of a butterfly. Several areas of the PVN are also illustrated, including the parvocellular (pc) portion, which contains CRF and VP neurons with terminals in the median eminence, and the magnocellular (MC) portion, which contains VP but no CRF neurons.



Slide 11 illustrates the ability of alcohol to stimulate CRF and VP synthesis, as shown by increases in CRF and VP heteronuclear RNA levels in neurons of the PVN. Peak CRF and VP responses, which are illustrated here, were measured 20 and 5 min after alcohol treatment.

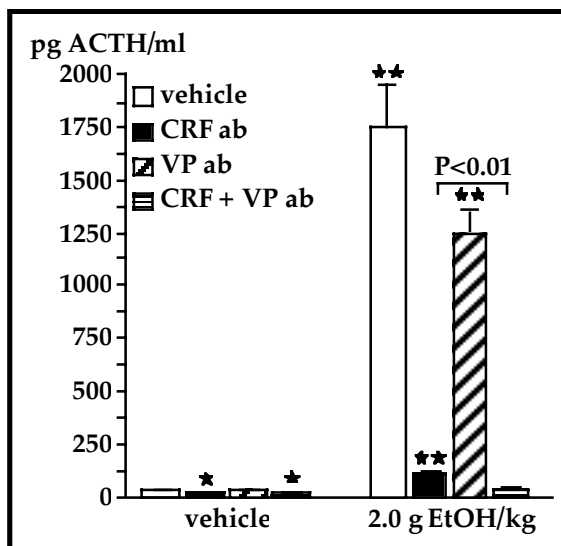
- **Adrenals:**

At present, there is no convincing evidence that alcohol alters ACTH receptors and/or corticosteroid synthesis release through a direct influence on the adrenals.

- **Role of CRF and VP in modulating the ACTH response to alcohol.**

If alcohol induces the release of CRF and VP, it is reasonable to ask whether these peptides modulate the ACTH response to alcohol. To test this hypothesis, one can measure plasma ACTH levels in rats injected with antibodies that immunoneutralize endogenous CRF and VP, or with antagonists to their receptors.

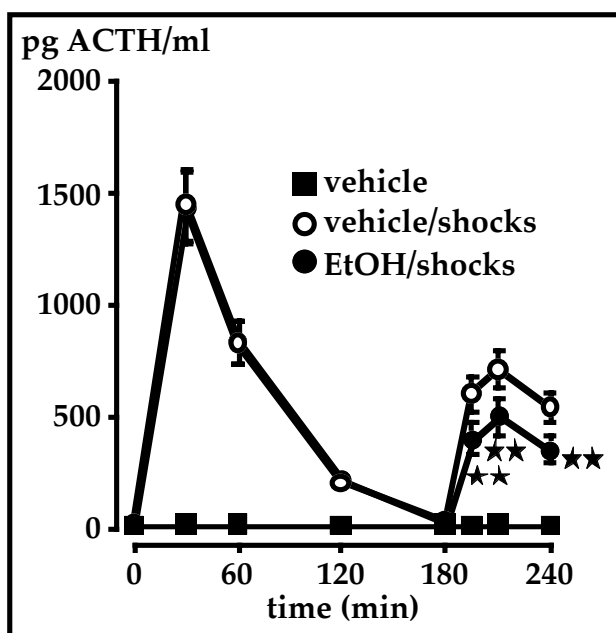
In **Slide 12**, groups of rats administered alcohol were previously (-1 h) injected with antibodies (ab) against CRF or VP. These studies indicate that removal of endogenous CRF reduced the ACTH response by >85% while removal of endogenous VP produced a significant, but less potent effect. Removal of both peptides totally abolished the ACTH response. We conclude from these data that endogenous CRF is a central mediator of the ACTH response to alcohol while VP only partially mediates it.



Slide 12. Each bar represents the mean \pm SEM of 5-7 animals. *, $P < 0.05$ and **, $P < 0.01$ vs. corresponding vehicle.

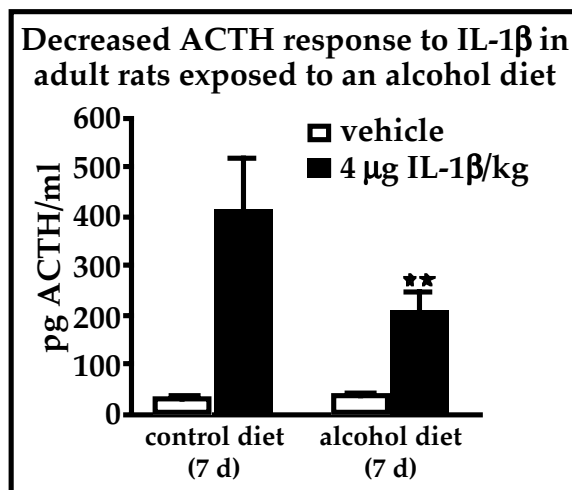
- **Effect of prior exposure to alcohol.**

In general, exposure to a stimulus alters the ability of the HPA axis to subsequently respond to this same stimulus or different stimuli. Accordingly, prior exposure to alcohol modifies the response of the HPA axis to subsequent challenges. Because of the multi-faceted influence of the hormones of the HPA axis (CRF, POMC, adrenal steroids), alcohol-induced changes in this axis have far-reaching consequences for the health of the organism.



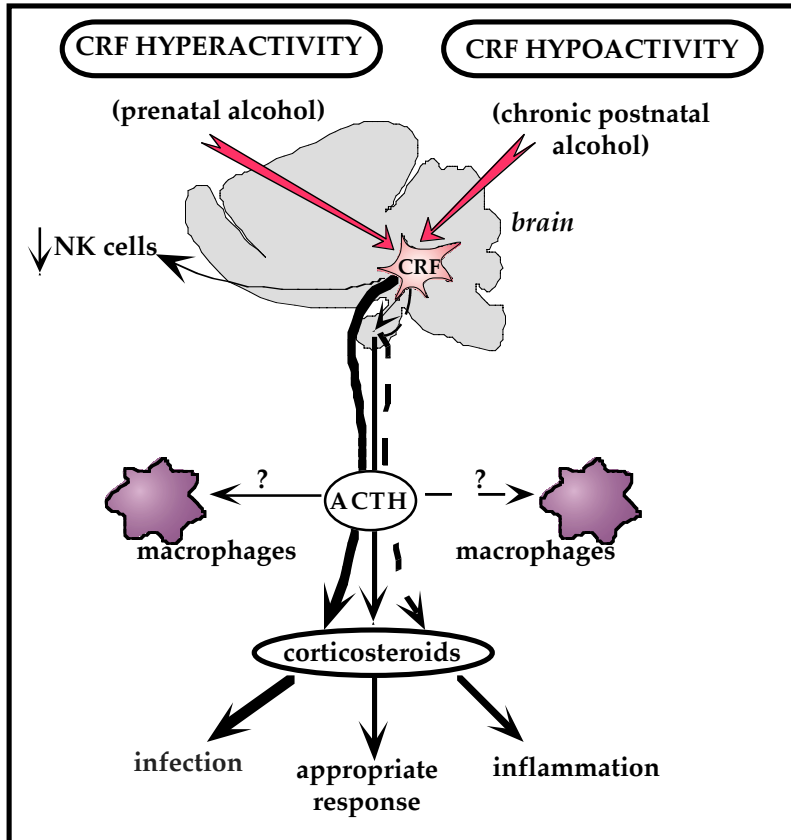
In **Slide 13**, rats were injected with the vehicle or alcohol (1.8 g/kg, ip) 3 h prior to being exposed to a neurogenic stressor (mild electrofootshocks). Alcohol-pretreated rats showed a significantly lower ACTH response to shocks. Each point represents the mean \pm SEM of 6 rats. **, $P < 0.01$ vs. prior treatment with vehicle.

In **Slide 14**, rats were fed an alcohol diet for 7 days, then were injected with The pro-inflammatory cytokine Interleukin-1b (IL-1b). Here again, Animals previously exposed to alcohol exhibited a significantly blunted ACTH response to this immune signal. Each bar represents the mean \pm SEM of 5-6 rats. **, $P < 0.01$ vs. control diet.



- **Long-term consequences of alcohol exposure.**

We have seen earlier that CRF and glucocorticoids have widespread effects. Here we illustrate in cartoon form a few of the consequences of an hypoactive (right panel) or hyperactive (left panel) HPA axis. This can result from, respectively, prolonged postnatal treatment with alcohol (right panel) or exposure to alcohol during embryonic development (left panel).



Slide 15

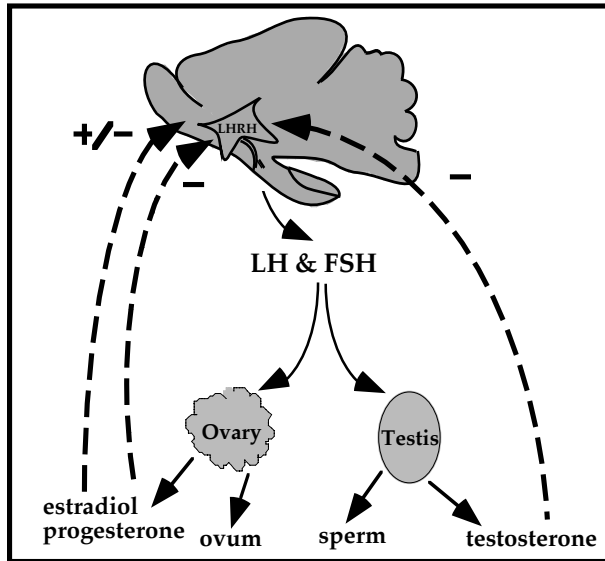
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Rivier. Alcohol stimulates ACTH secretion in the rat: Mechanisms of action and interactions with other stimuli. Alcoholism: Clin Exper Res. 20: 240-254, 1996.

Rivier and Lee. Acute alcohol administration stimulates the activity of hypothalamic neurons that express corticotropin-releasing factor and vasopressin. Brain Res 726:1-10, 1996.

THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS



Slide 16

Neurons of the hypothalamus synthesize luteinizing hormone-releasing hormone (LHRH). These cell bodies send axons to the median eminence, where LHRH is released from the nerve terminals and is transported through vessels of the portal system. Upon reaching the anterior pituitary, LHRH stimulates the release of LH, and to a lesser degree FSH. Both gonadotropins are released into the general circulation and reach the gonads

The gonads (testes and ovaries) have two major functions: steroid production (male: **testosterone**; female: **estrogen** and **progesterone**) and gamete production (male: sperm; female: ova). These functions are controlled by LH and FSH.

In males, it is primarily LH that stimulates testosterone production by Leydig cells, while both LH and FSH participate in the spermatogenesis process that takes place in the Sertoli cells-seminiferous tubules complex. In females, LH and FSH participate in the synthesis and release of estrogen and progesterone by granulosa cells and cells of the corpus luteum in the ovary, and stimulate the growth of the ovarian follicles and the release of ova.

Steroids (testosterone, estrogen and progesterone) influence LHRH and gonadotropin production through both a positive and a negative feedback, which maintains appropriate levels of all the reproductive hormones.

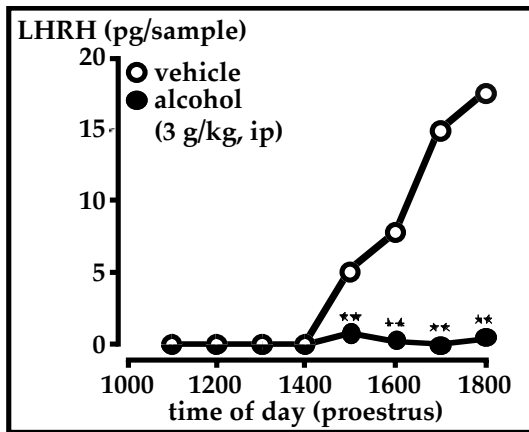
EFFECT OF ALCOHOL ON THE MALE REPRODUCTIVE SYSTEM

Alcohol is known to inhibit some aspects of the reproductive system. As in the case of the HPA axis, this effect could be exerted on:

- The hypothalamus (LHRH synthesis)
- The median eminence (LHRH release from nerve terminals)
- The pituitary (blockade of LH/FSH release)
- The gonads (blockade of steroid synthesis/release)

Hypothalamus:

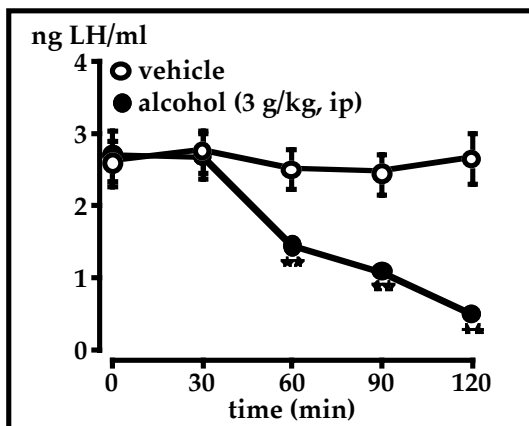
Alcohol inhibits LHRH synthesis/release. This is illustrated in **Slide 17**, which shows that the proestrous release of LHRH in female rats were totally blocked by alcohol injected at 8:00 am and 12:00 pm. LHRH was measured with a microdialysis probe placed in the median eminence.



Slide 17. Each point represents the mean \pm SEM of 4-5 rats. **, $P < 0.01$ vs. vehicle.

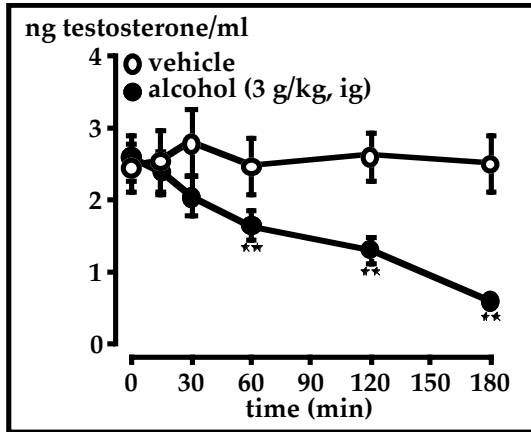
Pituitary:

Alcohol decreases plasma LH levels. This is illustrated in studies carried out in castrated rats, chosen as a model because they have elevated baseline LH concentrations.



Slide 18. Each point represents the mean \pm SEM of 4-5 rats. **, $P < 0.01$ vs. vehicle.

As most investigators have failed to detect effects of alcohol on LHRH receptors, the effect of alcohol on LH release is probably primarily due to blunted LHRH secretion.



Slide 19. Each point represents the mean \pm SEM of 5 rats. **, $P < 0.01$ vs. vehicle.

Testes:

Alcohol also significantly decreases testosterone release, as illustrated in **Slide 19**. There are probably several causes for this decline. First, it is undoubtedly due at least in part to reduced LH levels. In addition, alcohol may be able to alter the number and types of sugar molecules present in the LH molecule, which decreases its biological activity on the testes. Alcohol also acts directly on steroidogenic pathway in the testis, thereby inhibiting the synthesis/release of this steroid. This may be due to the altered production of intratesticular compounds that influence steroidogenesis and/or to inhibition of the steroidogenic enzymes necessary for testosterone production.

Collectively, these results indicate that alcohol can inhibit the activity of the HPG axis through several distinct mechanisms.

References.

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MA Emanuele and VN Emanuele. Alcohol's effects on male reproduction. *Alcohol health and Research World* 22: 195-201, 1998.