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PHARMACOLOGY

300 LEVEL

PHA 304- ENDOCRINE AND REPRODUCTIVE SYSTEM PHARMACOLOGY

**PHARMACOLOGY OF THE PITUITARY GLAND**

 The pituitary gland comprises three different structures arising from two different embryological precursors. The anterior pituitary and the intermediate lobe are derived from the endoderm of the buccal cavity, while the posterior pituitary is derived from neural ectoderm. The anterior and posterior lobes receive independent neuronal input from the hypothalamus, with which they have an intimate functional relationship.

 **THE ANTERIOR PITUITARY GLAND**

 The anterior pituitary gland (adenohypophysis) secretes a number of hormones crucial for normal physiological function. Within this tissue are specialised cells such as corticotrophs, lactotrophs (mammotrophs), somatotrophs, thyrotrophs and gonadotrophs, which secrete hormones that regulate different endocrine organs of the body. Interpersed among these are other cell types, including folliculostellate cells, which exert a nurturing and regulatory influence on the hormone-secreting endocrine cells.

 Secretion from the anterior pituitary is largely regulated by the release from the hypothalamus (hypothalamic hormones) that reach the pituitary through the bloodstream. The blood supply to the hypothalamus divides to form a meshwork of capillaries, the primary plexus, which drains into the hypophyseal portal vessels. These pass through the pituitary stalk to feed a secondary plexus of capillaries in the anterior pituitary. Peptidergic neurons in the hypothalamus secrete a variety of releasing or inhibitory hormones directly into the capillaries of the primary capillary plexus. Most of these regulate the secretion of hormones from the anterior lobe, although the melanocyte-stimulating hormones (MSHs) are secreted mainly from the intermediate lobe.

 The release of stimulatory hormones is regulated by negative feedback pathways between the hormones of the hypothalamus, the anterior pituitary and the peripheral endocrine glands. In long negative feedback pathways, hormones secreted from the peripheral glands exert regulatory actions on both the hypothalamus and the anterior pituitary. Anterior pituitary hormones acting directly on the hypothalamus comprise the short negative feedback pathway.

 The peptidergic neurons in the hypothalamus are themselves influenced by other centres within the central nervous system (CNS) mediated through neural pathways that release dopamine, noradrenaline, 5- hydroxytryptamine and the opioid peptides (which are particularly abundant in the hypothalamus). Hypothalamic control of the anterior pituitary is also exerted through the tuberohypophyseal dopaminergic pathway, the neurons of which lie in close apposition to the primary capillary plexus. Dopamine secreted directly into the hypophyseal portal circulation reaches the anterior pituitary in the blood.

HYPOTHALAMIC HORMONES

 The secretion of anterior pituitary hormones is primarily regulated by the hormones (releasing factors) that originate in the hypothalamus. These hypothalamic hormones are; somatostatin, gonadotropin-releasing hormone (GnRH), growth hormone releasing factor (GHRF), thyrotropin-releasing hormone (TRH), corticotrophin-releasing factor (CRF). Somatostatin and gonadotropin- releasing hormone are used therapeutically, the others being used mainly for diagnostic tests or as research tools. Some of these factors also function as neurotransmitters or neuromodulators elsewhere in the CNS.

 SOMATOSTATIN

 Somatostatin is a peptide of 14 amino acid residues. It inhibits the release of growth hormone and thyroid- stimulating hormone (TSH, thyrotropin) from the anterior pituitary, and insulin and glucagon from the pancreas. It also decreases the release of most gastrointestinal hormones, and reduces gastric acid and pancreatic secretion.

**Octreotide** is a long-acting analogue of somatostatin. It is used for the treatment of carcinoid and other hormone-secreting tumours. It also has a place in the therapy of acromegaly (a condition in which there is oversecretion of growth hormone in an adult). It also constricts splanchnic blood vessels, and is used to treat bleeding oesophageal varices. Octreotide is generally given subcutaneously. The peak action is at 2 h, and the suppressant effect lasts for up to 8 h.

 Unwanted effects include pain at the injection site and gastrointestinal disturbances. Gallstones and postprandial hyperglycaemia have also been reported, and acute hepatitis or pancreatitis has occurred in a few cases.

**Lanreotide** and **pasireotide** have similar effects. Lanreotide is also used in the treatment of thyroid tumors, while pasireotide, which is a particularly potent analogue, is used in the treatment of Cushing’s syndrome when surgery is inappropriate or has been ineffective.

 GONADOTROPHIN-RELEASING HORMONE

 Gonadotropin- (or luteinising hormone-) releasing hormone is a decapeptide that releases both follicle-stimulating hormone and luteinising hormone from gonadotrophs. Gonadotropin and its analogues (**gonadorelin, buserelin**, **goserelin**, **leuprorelin**, **nafarelin** and **triptorelin**) are used mainly in the treatment of infertility and some hormone-dependent tumours.

 GROWTH HORMONE-RELEASING FACTOR (SOMATORELIN)

 Growth hormone-releasing factor (GHRF) is a peptide with 44 amino acid residues. An analogue, **sermorelin**, may be used as a diagnostic test for growth hormone secretion. Given intravenously, subcutaneously or intranasally, it causes secretion of growth hormone within minutes and peak concentrations in 1 h. The action is selective for the somatotrophs in the anterior pituitary, and no other pituitary hormones are affected. Unwanted effects are rare.

 THYROTROPHIN-RELEASING HORMONE

 Thyrotrophin-releasing hormone (TRH) from the hypoth- alamus releases TSH from the thyrotrophs. **Protirelin** is a synthetic TRH that has been used for the diagnosis of thyroid disorders. Given intravenously in normal subjects, it causes an increase in plasma TSH concentration, whereas in patients with hyperthyroidism there is a blunted response because the raised blood thyroxine concentration has a negative feedback effect on the anterior pituitary. The opposite occurs with hypothyroidism, where there is an intrinsic defect in the thyroid itself.

 CORTICOTROPHIN-RELEASING FACTOR

 Corticotrophin-releasing factor (CRF) is a peptide that releases adrenocorticotropic hormones (ACTH, corticotrophin) and β-endorphin from corticotrophs in the anterior pituitary gland. CRF acts synergistically with antidiuretic hormone (ADH; arginine-vasopressin), and both its action and release are inhibited by glucocorticoids. Synthetic preparations have been used to test the ability of the pituitary to secrete ACTH, and to assess whether ACTH deficiency is caused by a pituitary or a hypothalamic defect. It has also been used to evaluate hypothalamic pituitary function after therapy for Cushing’s syndrome.

**HORMONES SECRETED BY THE HYPOTHALAMUS AND THE ANTERIOR PITUITARY AND RELATED DRUGS**

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| **Hypothalamic factor or hormone**  | **Effect on anterior pituitary**  | **Main effects of anterior pituitary hormone**  |
| Corticotrophin-releasing factor (CRF)  | Releases adrenocorticotrophic hormone (ACTH, corticotrophin) *Analogue*: tetracosactide  | Stimulates secretion of adrenal cortical hormones (mainly glucocorticoids); maintains integrity of adrenal cortex  |
| Thyrotrophin-releasing hormone (TRH)  *Analogue*: protirelin  | Releases thyroid-stimulating hormone (TSH; thyrotrophin)  | Stimulates synthesis and secretion of thyroid hormones; maintains integrity of thyroid gland. |
| Growth hormone-releasing factor (GHRF, somatorelin)  *Analogue*: sermorelin  | Releases growth hormone (GH; somatotrophin) *Analogue*: somatropin  | Regulates growth, partly directly, partly through by releasing somatomedins from the liver and elsewhere; increases protein synthesis, increases blood glucose, stimulates lipolysis  |
| Growth hormone release-inhibiting factor (somatostatin)  *Analogues*: octreotide, lanreotide  | Inhibits the release of GH  | Prevents effects above as well as TSH release  |
| Gonadotropin (or luteinising hormone)-releasing hormone (GnRH) *Analogues*: ‘gonadorelin analogues’ – buserelin, goserelin, leuprorelin, naferelin, triptorelin  | Releases follicle-stimulating hormone  | Stimulates the growth of the ovum and the Graafian follicle (female) and gametogenesis (male); with LH, stimulates the secretion of oestrogen throughout the menstrual cycle and progesterone in the second half  |
| Releases luteinising hormone (LH) or interstitial cell- stimulating hormone  | Stimulates ovulation and the development of the corpus luteum; with FSH, stimulates secretion of oestrogen and progesterone in the menstrual cycle; in male, regulates testosterone secretion  |
| Prolactin-releasing factor (PRF)  | Releases prolactin  | Together with other hormones, prolactin promotes development of mammary tissue during pregnancy; stimulates milk production in the postpartum period  |
| Prolactin release-inhibiting factor (probably dopamine)  | Inhibits the release of prolactin | Prevents effects above  |
| Melanocyte-stimulating hormone (MSH)-releasing factor  | Releases α-, β- and γ-MSH  | Promotes formation of melanin, which causes darkening of skin; MSH is anti-inflammatory and helps to regulate appetite/feeding  |
| MSH release-inhibiting factor  | Inhibits the release of α-, β- and γ-MSH  | Prevents effects above  |

ANTERIOR PITUITARY HORMONES

 Anterior pituitary hormones are classified into three different groups based on their structural features. Growth hormone (GH) and prolactin (PRL) belong to the somatotropic family, which in humans also includes placental lactogen. The glycoprotein hormones; thyroid-stimulating hormone (TSH, also called thyrotropin), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) share a common α-subunit but have different β-subunits that determine their distinct biological activities. Placenta-derived human chorionic gonadotropin (hCG) also is a member of the glycoprotein hormone family. Corticotropin (adrenocorticotropic hormone; ACTH) and α-melanocyte-stimulating hormone (α-MSH) are part of a family of peptides derived from proopiomelanocortin (POMC) by proteolytic processing.

GROWTH HORMONE (SOMATOTROPHIN)

 Growth hormone is secreted by the somatotroph cells and is the most abundant pituitary hormone. Secretion is high in the new-born, decreasing at 4 years to an intermediate level, which is then maintained until after puberty, after which there is a further decline. Recombinant human growth hormone, **somatropin**, is available for treating growth defects and other developmental problems.

**Regulation of Secretion**

 Secretion of growth hormone is regulated by the action of hypothalamic GHRF and modulated by somatostatin. A different peptide releaser of growth hormone (‘ghrelin’) is released from the stomach and pancreas and is implicated in the control of appetite and of body weight (Ch. 32). One of the mediators of growth hormone action, insulin-like growth factor (IGF)-1, which is released from the liver, has an inhibitory effect on growth hormone secretion by stimulating somatostatin release from the hypothalamus.

 As with other anterior pituitary secretions, growth hormone release is pulsatile, and its plasma concentration may fluctuate 10- to 100-fold. These surges occur repeatedly during the day and night, and reflect the dynamics of hypothalamic control. Deep sleep is a potent stimulus to growth hormone secretion, particularly in children.

**Actions**

 The main effect of growth hormone (and its analogues) is to stimulate normal growth. To do so, it acts in conjunction with other hormones secreted from the thyroid, the gonads and the adrenal cortex. It stimulates hepatic production of the IGFs – also termed somatomedins – which mediate most of its anabolic actions. IGF-1 (the principal mediator) mediates many of these anabolic effects and stimulates the uptake of amino acids and protein synthesis by skeletal muscle and the cartilage at the epiphyses of long bones, thus influencing bone growth. Receptors for IGF-1 exist on many other cell types, including liver cells and fat cells.

**Disorders of Production and Clinical Use**

 Deficiency of growth hormone (or failure of its action) results in pituitary dwarfism. In this condition, which may result from lack of GHRF or a lack of IGF generation or action, the normal proportions of the body are maintained. Growth hormone is used therapeutically in these patients (often children) as well as those suffering from the short stature associated with the chromosomal disorder known as Turner’s syndrome. It may also be used to correct short stature caused by chronic renal insufficiency in children.

 Humans are insensitive to growth hormone of other species, so human growth hormone (hGH) must be used clinically. This used to be obtained from human cadavers, but this led to the spread of Creutzfeldt–Jakob disease, a prion-mediated neurodegenerative disorder. hGH is now prepared by recombinant DNA technology (somatropin), which avoids this risk. Satisfactory linear growth can be achieved by giving somatropin subcutaneously, six to seven times per week, and therapy is most successful when started early.

 hGH is also used illicitly by athletes to increase muscle mass. The large doses used have serious side effects, causing abnormal bone growth and cardiomegaly. It has also been tested as a means of combating the bodily changes in senescence; clinical trials have shown increases in body mass, but no functional improvement.

 Human recombinant IGF-1 (**mecasermin**) is also available for the treatment of growth failure in children who lack adequate amounts of this hormone.

 An excessive production of growth hormone in children results in gigantism. An excessive production in adults, which is usually the result of a benign pituitary tumour, results in acromegaly, in which there is enlargement mainly of the jaw and of the hands and feet. The dopamine agonist **bromocriptine** and octreotide may mitigate the condition. Another useful agent is **pegvisomant**, a modified analogue of growth hormone prepared by recombinant technology that is a highly selective antagonist of growth hormone actions.

PROLACTIN

 Prolactin is secreted from the anterior pituitary gland by lactotroph (mammotroph) cells. These are abundant in the gland and increase in number during pregnancy, probably under the influence of oestrogen.

**Regulation of Secretion**

 Prolactin secretion is under tonic inhibitory control by dopamine (acting on D2 receptors on the lactotrophs) released from the hypothalamus. The main stimulus for release is suckling; in rats, both the smell and the sounds of hungry pups are also effective triggers. Neural reflexes from the breast may stimulate the secretion from the hypothalamus of prolactin-releasing factor(s), possible candidates for which include TRH and oxytocin. Oestrogens increase both prolactin secretion and the proliferation of lactotrophs through release, from a subset of lactotrophs, of the neuropeptide galanin. Dopamine antagonists (used mainly as antipsychotic drugs) are potent stimulants of prolactin release, whereas agonists such as **bromocriptine** suppress prolactin release. Bromocriptine is also used in Parkinson’s disease.

**Actions**

 The prolactin receptor is a single transmembrane domain receptor related to the cytokine receptors. Several different isoforms and splice variants are known. These are found not only in the mammary gland but are widely distributed throughout the body, including the brain, ovary, heart, lungs and immune system. The main function of prolactin in women is the control of milk production. At parturition the prolactin concentration rises and lactation is initiated. Maintenance of lactation depends on suckling which causes a 10- to 100-fold increase in blood hormone levels within 30 min.

 Together with other hormones, prolactin is responsible for the proliferation and differentiation of mammary tissue during pregnancy. It also inhibits gonadotrophin release and/or the response of the ovaries to these trophic hormones. This is one of the reasons why ovulation does not usually occur during breastfeeding, and is believed to constitute a natural contraceptive mechanism.

**Modification of Prolactin Secretion**

 Prolactin itself is not used clinically. Bromocriptine, a dopamine receptor agonist, is used to decrease excessive prolactin secretion (hyperprolactinaemia). It is well absorbed orally, and peak concentrations occur after 2 h.

 Unwanted reactions include nausea and vomiting. Dizziness, constipation and postural hypotension may also occur. Cabergoline and quinagolide are similar.

ADRENOCORTICOTROPHIC HORMONE

 Adrenocorticotrophic hormone (ACTH, corticotrophin) is the anterior pituitary secretion that controls the synthesis and release of the glucocorticoids of the adrenal cortex. It is a 39-residue peptide derived from the precursor pro-opiomelanocortin (POMC) by sequential proteolytic processing. Failure of ACTH action because of defects in its receptor or intracellular signalling pathways can lead to severe glucocorticoid deficiency.

 Adrenocorticotrophic hormone itself is not often used in therapy today, because its action is less predictable than that of the corticosteroids and it may provoke antibody formation. Tetracosactide (tetracosactrin), a synthetic polypeptide that consists of the first 24 N-terminal residues of human ACTH, has the same drawbacks but is now widely used in its stead for assessing the competency of the adrenal cortex.

 The concentration of ACTH in the blood is reduced by glucocorticoids, forming the basis of the dexamethasonesuppression test.

**Actions**

Acting through MC2 receptors, tetracosactide and ACTH have two actions on the adrenal cortex:

• Stimulation of the synthesis and release of glucocorticoids. This action occurs within minutes of injection, and the ensuing biological actions are those of the steroids released.

• A trophic action on adrenal cortical cells, and regulation of the levels of key mitochondrial steroidogenic enzymes. The loss of this effect accounts for the adrenal atrophy that results from chronic glucocorticoid administration, which suppresses ACTH secretion.

The main use of tetracosactide is in the diagnosis of adrenal cortical insufficiency. The drug is given intramuscularly or intravenously, and the concentration of hydrocortisone in the plasma is measured by radioimmunoassay.

MELANOCYTE-STIMULATING HORMONE (MSH)

 α-, β- and γ-MSH are peptide hormones with structural similarity to ACTH and are derived from the same precursor. Together, these peptides are referred to as melanocortins, because their first recognised action was to stimulate the production of melanin by specialised skin cells called melanocytes. As such, they play an important part in deter- mining hair coloration, skin colour and reaction to ultra- violet light.

 Melanocyte-stimulating hormone acts on melanocortin receptors, of which five (MC1–5) have been cloned. These are G protein-coupled receptors (GPCRs) that activate cyclic adenosine monophosphate (cAMP) synthesis. Melanin formation is controlled by the MC1 receptor. Excessive α-MSH production can provoke abnormal proliferation of melanocytes and may predispose to melanoma.

**POSTERIOR PITUITARY GLAND**

 The posterior pituitary gland (neurohypophysis) consists largely of the terminals of nerve cells that lie in the supraoptic and paraventricular nuclei of the hypothalamus. Their axons form the hypothalamic-hypophyseal tract, and the fibres terminate in dilated nerve endings in close association with capillaries in the posterior pituitary gland. Peptides, synthesised in the hypothalamic nuclei, pass down these axons into the posterior pituitary, where they are stored and eventually secreted into the bloodstream.

 The two main hormones of the posterior pituitary are oxytocin (which contracts the smooth muscle of the uterus) and vasopressin (antidiuretic hormone ADH). They are highly homologous cyclic nonapeptides. Several analogues have been synthesised that vary in their antidiuretic, vasopressor and oxytocic (uterine stimulant) properties.

OXYTOCIN

 The neurohypophyseal hormone oxytocin (an octapeptide) regulates myometrial activity, causing uterine con- traction. Oxytocin release is stimulated by cervical dilatation, and by suckling􏰛 its role in parturition is incompletely understood but the fact that an antagonist (atosiban) is effective in delaying the onset of labour implicates it in the physiology of parturition.

 Oestrogen induces oxytocin receptor synthesis and, consequently, the uterus at term is highly sensitive to this hormone. Given by slow intravenous infusion to induce labour, oxytocin causes regular coordinated contractions that travel from fundus to cervix. Both amplitude and frequency of these contractions are related to dose, the uterus relaxing completely between contractions during low-dose infusion. Larger doses further increase the frequency of the contractions, and there is incomplete relaxation between them. Still higher doses cause sustained contractions that interfere with blood flow through the placenta and cause fetal distress or death.

 Oxytocin contracts myoepithelial cells in the mammary gland, which causes milk ejection. It also has a vasodilator action. A weak antidiuretic action can result in water retention, which can be problematic in patients with cardiac or renal disease, or with pre-eclampsia. Oxytocin and oxytocin receptors are also found in the brain, particularly in the limbic system, and are believed to play a role in mating and parenting behaviour. Oxytocin can be given by intravenous injection or intra- muscularly, but is most often given by intravenous infusion. It is inactivated in the liver and kidneys, and by circulating placental oxytocinase.

**Action**

 In the human myometrium, oxytocin acts *via* specific GPCRs, coupled to Gq and G11, to activate the PLCβ-IP3-Ca2+ pathway and enhance activation of voltage-sensitive Ca2+ channels. Oxytocin also increases local prostaglandin production, which further stimulates uterine contractions.

**Clinical Uses**

 Oxytocin is used to induce or augment labour when the uterine muscle is not functioning adequately. It can also be used to treat postpartum haemorrhage.

 􏰎Unwanted effects of oxytocin include dose-related hypotension, due to vasodilatation, with associated reflex tachycardia. Its antidiuretic hormone-like effect on water excretion by the kidney causes water retention and, unless water intake is curtailed, consequent hyponatraemia.

VASOPRESSIN OR ANTIDIURETIC HORMONE (ADH)

 **Regulation of Secretion and Physiological Role**

 Vasopressin released from the posterior pituitary has a crucial role in the control of the water content of the body through its action on the cells of the distal part of the nephron and the collecting tubules in the kidney. The hypothalamic nuclei that control fluid balance lie close to the nuclei that synthesise and secrete vasopressin.  􏰋

 One of the main stimuli for vasopressin release is an increase in plasma osmolarity (which produces a sensation of thirst). A decrease in circulating blood volume (hypovolaemia) is another, and here the stimuli arise from stretch receptors in the cardiovascular system or from angiotensin release. Diabetes insipidusis a condition in which large volumes of dilute urine are produced because vasopressin secretion is reduced or absent, or because of a reduced sensitivity of the kidney to the hormone.

**Vasopressin Receptors**

 There are three classes of receptor: V1A, V1B and V2. All are GPCRs. V2 receptors stimulate adenylyl cyclase, which mediates the main physiological actions of vasopressin in the kidney, whereas the V1A and V1B receptors are coupled to the phospholipase C/inositol trisphosphate system.

 The receptor for oxytocin (OT receptor) is also a GPCR, which primarily signals through phospholipase C stimulation but has a secondary action on adenylyl cyclase. Vasopressin is a partial agonist at OT but its effects are limited by the distribution of the receptor, which, as might be inferred from its classic action on the pregnant uterus, is high in the myometrium, endometrium, mammary gland and ovary. The central actions of oxytocin (and vasopressin) have also attracted attention as they are apparently involved in `pair bonding’ and the other psychosocial interactions.

**Actions**

 Renal Actions

 Vasopressin binds to V2 receptors in the basolateral membrane of the cells of the distal tubule and collecting ducts of the nephron. Its main effect in the collecting duct is to increase the rate of insertion of water channels (aquapor- ins) into the lumenal membrane, thus increasing the permeability of the membrane to water. It also activates urea transporters and transiently increases Na+ absorption, particularly in the distal tubule. Several drugs affect the action of vasopressin. Non- steroidal anti-inflammatory drugs and carbamazepine increase, andlithium, colchine and vinca alkaloids decrease, vasopressin effects. The effects of the last two agents are secondary to their action on the microtubules required for translocation of water channels. The antagonists demeclocyclineand tolvaptan counteract the action of vasopressin on the V2 receptor in renal tubules and can be used to treat patients with water retention combined with urinary salt loss (and thus hyponatraemia) caused by excessive secretion of the hormone. This syndrome of inappropriate ADH secretion (‘SIADH’) is associated with lung or other malignancies or head injury. Specific V2 receptor antagonists are also being investigated in the treatment of heart failure.

Other Non-Renal Actions

 Vasopressin causes contraction of smooth muscle, particularly in the cardiovascular system, by acting on V1A receptors. The affinity of vasopressin for these receptors is lower than that for V2 receptors, and smooth muscle effects are seen only with doses larger than those affecting the kidney. Vasopressin also stimulates blood platelet aggregation and mobilisation of coagulation factors. When released into the pituitary portal circulation it promotes the release of ACTH from the anterior pituitary by an action on V1B receptors. In the CNS, vasopressin, like oxytocin, is believed to have a role in emotional and social behaviour.

**Pharmacokinetic Action**

 Vasopressin, as well as various peptide analogues, is used clinically either for the treatment of diabetes insipidus or as a vasoconstrictor. Several analogues have been developed to (a) increase the duration of action and (b) shift the relative potency between the V1 and V2 receptors.

The main substances used are:

􏰻 -Vasopressin itself; short duration of action, weak selectivity for V2 receptors, given by subcutaneous or intramuscular injection, or by intravenous infusion.

 -Desmopressin; increased duration of action, V2- selective and therefore fewer vasopressor effects, can be given by several routes including nasal spray.􏰛

 - Terlipressin; increased duration of action, low but protracted vasopressor action and minimal antidiuretic properties.

 - Felypressin; a short-acting vasoconstrictor that is injected with local anaesthetics such as prilocaine to prolong their action.

Vasopressin itself is rapidly eliminated, with a plasma half-life less than 10 min and a short duration of action. Metabolism is by tissue peptidases, and 33% is removed by the kidney. Desmopressin is less subject to degradation by peptidases, and its plasma half-life is 75 min.

**Unwanted Effects**

 There are few unwanted effects and they are mainly cardiovascular in nature: intravenous vasopressin may cause spasm of the coronary arteries with resultant angina, but this risk can be minimised if the antidiuretic peptides are administered intranasally.

**REFRENCES:** Rang & Dale`s pharmacology

 Goodman & Gilman Pharmacology