

Review

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Interaction of Vasopressin with Hormones of the Hypothalamo-Pituitary-Adrenal Axis: Significance for Therapeutic Strategies in Cardiovascular and Metabolic Diseases

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Review

Interaction of Vasopressin with Hormones of the Hypothalamo-Pituitary-Adrenal Axis: Significance for Therapeutic Strategies in Cardiovascular and Metabolic Diseases

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Abstract: A multiple number of studies provide evidence that vasopressin (AVP) and steroid hormones are frequently secreted together and closely cooperate in the regulation of blood pressure, metabolism, water-electrolyte balance, and behavior, securing thereby survival and comfort of life. Vasopressin interacts with hormones of the hypothalamo-pituitary-adrenal axis (HPA) at several levels through regulation of release of corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone ACTH, and multiple steroid hormones, as well as through interactions with steroids in the target organs. The interactions are facilitated by positive and negative feedbacks occurring between specific components of the HPA axis with engagement of other regulatory molecules. Altogether AVP and HPA cooperate closely as a coordinated functional AVP-HPA system. It has been shown that cooperation between AVP and steroid hormones may be affected by the cellular stress combined with hypoxia, and by metabolic, cardiovascular and respiratory disorders, neurogenic stress and inflammation. Growing evidence indicates that central and peripheral interactions of AVP and steroid hormones are reprogrammed in cardiovascular diseases and that the rearrangements play either beneficial or harmful effects. The present review highlights specific mechanisms of interactions of AVP and steroids at cellular and systemic levels and analyses consequences of inappropriate cooperation between various components of the AVP-HPA system for the regulation of the cardiovascular system and energy balance in cardiovascular and metabolic diseases.

Keywords: AVP; CRH; ACTH; glucocorticoids; mineralocorticoids; androgens; estrogens; hypertension; cardiac failure; stress

1. Introduction

The first experimental studies showing close functional relationship between vasopressin and steroid hormones were published over 60 years ago. In 1960 Hilton et al., reported that arterial perfusion of the adrenal glands with arginine vasopressin (AVP) or lysine vasopressin (LVP) potently stimulates release of cortisol [1]. Subsequently it has been found that in many instances vasopressin and steroid hormones are secreted together and closely cooperate in regulation of blood pressure, metabolism, water-electrolyte balance and behavior in a manner securing survival and comfort of life. It has been also shown that the cellular stress combined with hypoxia, disturbances of metabolism, cardiovascular and respiratory disorders, neurogenic stress and inflammation may disorganize cooperation between AVP and steroid hormones. Under homeostatic, unstressed conditions both steroid hormones and vasopressin are released in characteristic diurnal rhythms. Expression of AVP mRNA in the suprachiasmatic nucleus shows distinct endogenous circadian rhythm. The diurnal rhythm of secretion is also typical for adrenocorticotrophic hormone (ACTH) and glucocorticoids. Interestingly, it appears that the responsiveness of AVP synthesis to steroids also manifests circadian rhythmicity [2]. Vasopressin interacts with the hypothalamo-pituitary-adrenal

axis (HPA) at various levels, i.e. in the hypothalamic nuclei, affecting release of corticotropin-releasing hormone (CRH), in the pituitary gland, enhancing ACTH release and in the adrenal glands modulating release or action of multiple steroid hormones. The interactions are facilitated by positive and negative feedbacks occurring between specific components of the HPA system with engagement of other neurotransmitter and neuropeptide pathways.

Vasopressin and CRH are synthesized mainly in the hypothalamic nuclei, however both these peptides can be also produced in other regions of the brain. In the hypothalamus vasopressin and CRH are released partly by the same cells of the paraventricular nucleus (PVN). Immunostaining studies showed that virtually all parvocellular CRH neurons in the PVN are stained positively for vasopressin [3] and are co-packaged in neurosecretory vesicles of the hypothalamic-pituitary axons in the median eminence [4]. and the hypophyseal-portal circulation [5-7]. There is also evidence that vasopressin may be necessary for appropriate action of glucocorticoids, as it has been shown that the maximal binding capacities for corticosterone and dexamethasone in the hippocampus and the anterior pituitary are significantly lower in homozygous diabetes insipidus (HDI) rats that do not synthesize vasopressin than in their nondiabetic counterparts. Importantly the difference could be eliminated by AVP treatment [8]. On the other hand, glucocorticoids were found to exert negative effect on release and action of vasopressin. For instance corticosterone was found to inhibit release of AVP from the explants containing supraoptic nucleus (SON) and sending projections to the neural lobe of the pituitary [9]. Experiments on Sprague Dawley rats have shown that release of AVP from the hypothalamic slices encompassing PVN and SON neurons could be inhibited by corticosterone, cortisol, testosterone and 17-beta estradiol in a dose-dependent manner, whereas dexamethasone, aldosterone and progesterone were not effective in these experiments [10]. Chronic application of dexamethasone, which is an agonist of corticosterone, significantly decreased plasma corticosterone and ACTH concentrations and elicited differential changes in expressions of CRH, ACTH and AVP in several brain regions, including the cortex, the hippocampus, the hypothalamus and the cerebellum [11]. There is also evidence that vasopressin exerts weak stimulatory effect on secretion of aldosterone from the glomerulosa cells of the adrenal medulla [12].

It is highly probable that some steroid hormones can modulate vasopressin action through actions exerted at the level of AVP receptors. For instance experiments on rats have shown that adrenalectomy, which eliminates the main source of circulating steroid hormones, reduces vasopressin V1a receptors (V1aR) in the hippocampus, the dorsolateral septum and the bed nucleus of the stria terminalis (BNST). Moreover, effects of adrenalectomy on V1aR in the hippocampus, and the BNST can be reduced by treatment with corticosterone and aldosterone [13-15]. At the same time it should be noted that glucocorticoids may act in opposite way on expression of V1b vasopressin receptors (V1bR), because administration of dexamethasone was found to increase V1bR mRNA in the pituitary, whereas adrenalectomy reduced V1bR mRNA. The latter effect could be reversed by administration of dexamethasone [16].

It appears that negative feedback between glucocorticoids and vasopressin arises in early life. In the rat applications of dexamethasone and aldosterone to fetal hypothalamic cells cultures have been found to inhibit release of CRH, AVP and oxytocin through mechanisms involving activation of protein kinase A (PKA) and protein kinase C (PKC) [17]. In addition, administration of cortisol to the medium bathing the hypothalamic neurons of the fetal sheep significantly inhibited potassium-induced secretion of AVP [18]. There is also evidence that secretion of several steroid hormones is sex-dependent [19-20].

It is possible that during chronic stress glucocorticoids and mineralocorticoids may act in opposite way on AVP release. Hence, expressions of CRH hnRNA and AVP hnRNA in parvocellular neurons of PVN is significantly elevated in rats exposed to the forced swim stress and the increase is abolished by administration of dexamethasone [21]. On the other hand, application of eplerenone, which is a mineralocorticoid receptor antagonist, alleviated anxiety-like behavior and reduced vasopressin and corticosterone concentrations in the posterior pituitary [22].

Thus far there are still multiple gaps in understanding mutual interactions between vasopressin and steroid hormones in health and cardiovascular diseases. Therefore, the principal aim of the

present review is to analyze the cooperation of vasopressin and steroid hormones at the cellular and systematic levels in context of their influence on cardiovascular regulation, tissue metabolism and oxygenation. Specifically we discuss positive and negative consequences of interactions of AVP and steroid hormones in development of hypertension and heart failure.

2. Interactions of the Hypothalamo-Pituitary-Adrenal System with Vasopressin at the Cellular Level

2.1. Genomic and Nongenomic Actions of Steroid Hormones

Multiple studies show that steroid hormones exert rapid as well as delayed cellular effects, that are mediated by specific types of non-genomic and genomic receptors located either in the cellular membrane or intracellularly [23-26]. Receptors of specific steroids are encoded by different genes and their activation may result either in stimulatory or in inhibitory effects, depending on the cell type. The final action of the specific steroid is determined by dose of the hormone, type of stimulated receptors, number of receptors, and presence of specific enzymatic pathways in the targeted cell. In the cardiovascular system stimulation of steroid receptors causes a wide range of actions that may be either beneficial or detrimental.

In the individual cell steroid ligand cooperates with local transcription factors and other regulatory compounds [27-28]. Essential role in binding to receptors and mobilization of posttranslational modifications play coactivators, which are involved in integration of cellular processes and adjustment of cellular responses to current needs. Especially important role is attributed to Steroid Receptor Coactivators (SRC, namely SRC1, SRC2, SRC3), which are known as Nuclear Receptor Coactivators (NCOAS), and to Coactivator Binding Inhibitors (CBIs) [29-30].

Mineralocorticoid receptors (MR, MCR), glucocorticoid receptors (GR), estrogen receptors (ER, ESR), androgen receptors (AR) and progesterone receptors (PGR) belong to a subfamily 3 of nuclear receptors possessing the ligand binding domain (LBD), the DNA-binding domain (DBD) and the N-terminal domain (NTD). In the inactive state the receptors are present in the cytoplasm in a multiprotein chaperon complex, which contains the ligand-binding cleft identifying and binding the ligand. Binding elicits conformational transformations within the complex that permit subcellular trafficking of the ligand to the target within the cell and its interaction with DNA [31-32].

Glucocorticoid and Mineralocorticoid Receptors. In humans function of glucocorticoid is served by cortisol, whereas in the rat it is attributed to corticosterone, which acts also as mineralocorticoid. Glucocorticoid and mineralocorticoid receptors are members of the nuclear receptor superfamily of transcription factors (TF) that modulate processes of transcription through direct binding to glucocorticoid response element (GRE) or mineralocorticoid response element (MRE) in the DNA. A DNA binding domain is in 96% identical in GR and MR. Initiation of specific transcriptional processes at particular promoter and enhancer regions warrants coordinated cellular responses to steroid hormones. The receptors possess also a C-terminal ligand-binding domain (CT-LBD) and an amino-terminus domain (NTD). GR is a 97 kDA protein encoded by *NR3C1/Nr3c1* gene (in humans located in chromosome 5) and cooperates with several co-regulators [32-34]. An amino-terminus contains AF-1 and AF-2 regions which interact with CT-LBD and can stimulate transcription in absence of a ligand [35-39].

It has been shown that GR and MR can bind as dimers or tetramers [40-41]. Binding of the ligand by MR or GR initiates a cascade of events enabling translocation of the ligand-bound receptor to the nucleus. In the nucleus the receptors bind to specific DNA sequences which are known as glucocorticoid response elements (GREs) and negative glucocorticoid response elements (nGREs) [42-43]. Regulation of GREs appears to play dominant role in cellular processes of neurons [23, 42]. Direct occupancy of nGRE results in repression of the target gene. Steroid receptor coactivators (SRCs) appear to participate in repression of CRH expression by GR in the hypothalamus. In the nucleus MR and GR can also interact with some other active proteins (MAZ- myc-associated zinc finger protein, AP-1 – activator protein 1, NF-κB – nuclear factor κB, and SRC-1/2/3) that operate as ligand-selective co-regulators. They can induce remodeling of gene conformation and may initiate

formation of transcription-initiation complexes. GRE-DNA interactions are modulated by chromatin configuration. In the cardiovascular system expression of MR is higher in males than in females [44].

Glucocorticoid receptors have been also identified in mitochondria where they regulate mitochondrial gene transcription. In neuronal mitochondria GRs interact with Bcl-2 protein and form GR/Bcl-2 complexes. Interestingly short time action exerted at low density intensifies formation of these complexes, whereas in high doses cortisol exert opposite effects [45]. Interaction of Bcl-2 with other regulatory factors determines specificity of actions of glucocorticoids in various organs [37, 46-47].

Glucocorticoids modulate also process of transcription indirectly by physical interaction (tethering), which does not require direct contact with DNA but engages activation of transcription factors. In various types of cells these factors may act either as co-activators or as co-repressors. Tissue-cell dependent expression of co-regulators causes specific tissue-cell action of steroid molecules [30, 37, 48-50]. It is likely that the protein-protein interactions mediate rapid effects of steroid hormones and play essential role in trans-repression of genes by glucocorticoids in hypoxia and inflammatory processes. For instance it has been found that they interact with hypoxia induced factors (HIFs) at the level of the promoter region of the inflammatory genes and can either enhance or inhibit activation of the HIF pathway [49, 51]. It has been postulated that during the inflammatory processes the co-activating function of steroids determines collagen synthesis, generation of reactive oxygen species and engagement of peroxisome proliferator-receptor gamma co-activator 1-alpha (PGC-1 α) as well as activation of p38 mitogen activated protein kinase (MAPK) and nicotinamide adenine dinucleotide phosphate oxidases (NOX) 2 and 4 [52, 53]. On the other hand, glucocorticoids can inhibit inflammation through repression of genes engaged in synthesis of pro-inflammatory proteins (AP-1, NF κ B) and through enhancement of expression of genes involved in generation of anti-inflammatory compounds [49, 54].

There is evidence for reciprocal interactions between glucocorticoid receptors pathways. For instance, it has been shown that GR can induce expression of genes that are promoting or inhibiting p38 MAP kinase pathway (MAPK) [53]. Furthermore, expression of GR and its responsiveness to glucocorticoids is regulated by microRNAs, whereas expression of microRNA is regulated by glucocorticoids [55].

Mineralocorticoid receptor is also known as nuclear receptor of subfamily 3, group C, member 2 (NR3C2). MRs bind mainly aldosterone, but they also show high affinity to cortisol and androgens. Regulatory importance of cortisol and aldosterone in specific cell type largely depends on availability of 11- β -hydroxysteroid dehydrogenase type 2 (11- β HSD2), which converts active cortisol into inactive cortisone. Opposite action is exerted by 11- β HSD1, which transforms cortisone into cortisol. Presence of these isoenzymes significantly determines sensitivity of specific organs and tissues to glucocorticoids and mineralocorticoids. Availability of 11 β -HSD2 in several regions of the brain causes that aldosterone has good access to brain MR receptors and can exert potent regulatory effects in spite that its concentration in plasma is hundreds of time lower than the concentration of cortisol [56-58]. In the heart cardiomyocytes and macrophages do not express 11- β HSD2 and both cortisol and aldosterone participate in MR stimulation. Moreover, in the heart aldosterone exerts some effects through cross-talk with cardiac G-protein-coupled receptors (GPCRs) [59]. Activated MR can form homodimers or can associate with GR and form heterodimers.

MRs are present in the kidney, heart and vessels where mineralocorticoids participate in the regulation of hypertrophy, fibrosis, inflammation, and apoptosis. Mineralocorticoids can act either directly on NR3C2 receptors or their action can be mediated by formation of other active molecules, such as interleukin-1 (IL-1), tumor necrosis factor α (TNF- α), cardiotrophin-1 (CT-1) and Toll-like receptor 4 (TLR-4). During inflammatory process the inflammatory cytokines (IL-1, IL-6, TNF- α) act synergistically with mineralocorticoids and can act jointly through inhibition of ACTH secretion in the hypothalamic-pituitary-adrenal axis [60]. In the rat mesangial cells aldosterone was found to stimulate NF- κ B and glucocorticoid-inducible protein kinase-1 (SGK1) activities. It elevates also promoter activities and protein expressions of intercellular adhesion molecule-1 (ICAM-1) and

connective tissue growth factor (CTGF). There is evidence that these factors are involved in aldosterone mediated mesangial fibrosis and inflammation [61].

In cardiomyocytes the genomic action of aldosterone mediated by MR participate in chronotropic and hypertrophic actions. It has been shown that aldosterone enhances expression of mRNA which is coding for the $\alpha 1H$ protein and the latter is a constituent of CaV3.2 channel, which is one of the two T channels of the cardiomyocytes [62,63]. Action of aldosterone on T channels is presumably indirect, because the gene *CACNA1h*, which is coding for the CaV3.2 T type channel does not possess mineralocorticoid response element (MRE). Increased formation of reactive oxygen species (ROS) and their involvement in the regulation of affinity of steroid hormones to MR receptors should be also taken into consideration [63-66]. In the cardiovascular system the genomic and non-genomic effects of aldosterone are also modified by angiotensin II (Ang II) [35].

In the brain MRs have been identified mainly in the hippocampus, septum and other limbic structures, whereas GRs are expressed in the septum, hippocampus, brain stem and the prefrontal cortex [46, 67-68]. Affinity of corticosterone to MR in neurons is 10-fold higher than to GR [68-69]. MRs are associated with cellular membrane and after activation are translocated with help of β -arrestin to the cells where they can exert their actions through non-genomic GPCR processes [25,59].

Androgen, Estrogen and Progesterone. Both in males and females androgens are synthesized in the adrenal glands (mainly in the *zona fascicularis* and the *zona reticularis*), in the brain (mainly in the hippocampus), and in the liver [70]. In males testosterone is produced chiefly by Leydig cells of the testis, while in females testosterone and its metabolites are produced primarily in the adrenals and ovaries. Cells of the adrenal cortex synthesize also dehydroepiandrosterone (DHEA), androstenedione, androstendione, androstenediol and 11- β -hydroxyandrostenedione. Testosterone can be converted to dihydrotestosterone by 5 α -reductase (aromatase), while deoxycorticosterone is converted into dihydrodeoxycorticosterone. Both DHEA and testosterone are able to stimulate androgen receptors, however DHEA has significantly greater androgenic activity than testosterone. The aromatase producing dihydrotestosterone is also involved in formation of estradiol, which is engaged in stimulation of estrogen receptors. The gene, which is encoding aromatase (*CYP19A1*) is located on chromosome 15, and has been identified in lungs, vessels and multiple brain regions [71, 72]. The process of aromatization of testosterone to estradiol occurs in several peripheral tissues and in the brain [70].

The main steps of synthesis of progesterone include conversion of cholesterol into pregnenolone by cholesterol side-chain cleavage enzyme (P450_{scc}) belonging to cytochrome p-450 superfamily, and conversion of pregnenolone into progesterone by the 3 β -hydroxy-steroid dehydrogenase (3 β -HSD). In the brain progesterone is also converted to neuroactive steroids, specifically to 5 α -dihydroprogesterone (5- α -DHPROG) and tetrahydroprogesterone (3 α -5 α -THPROG) [73].

Androgens, estrogens and progesterone interact with receptors in the brain, heart and vessels and participate in the regulation of the cardiovascular system by means of classic genomic and non-classic pathways [74-77]. Androgen receptors were identified in cells of the reproductive system, bones, vessels and brain [78-79]. In the brain ARs are present in the cortex, midbrain, brain stem and spinal cord. Specifically, high density of AR immunoreactivity was found in the olfactory bulb, the nucleus accumbens, the medial amygdala, the bed nucleus of the lamina terminalis, the medial preoptic area, the septum, the mesencephalic periaqueductal gray (PAG), the dorsal raphe nucleus, the substantia nigra, the area postrema, the dorsal motor vagus nucleus, and in the preganglionic cells of the autonomic nervous system [78, 80].

Androgen signaling engages several molecular pathways. The primary androgen receptor is a nuclear transcription factor that is activated mainly by testosterone and dihydrotestosterone. Non-stimulated ARs are present mainly in cytoplasm and are associated with heat shock proteins (HSPs). Binding of androgen with ARs allows dissociation of the receptor from chaperone proteins and translocation of the complex androgen-AR to the nucleus where it binds to androgen-response element (ARE) and regulates gene transcription. Androgens regulate also rapid non-genomic processes, engaging G-protein coupled receptor family C (GPRC6A), zinc transporter ZIP9 membrane-receptor and oxoeicosanoid receptor (OXER). In consequence through activation of the

genomic-dependent and non-genomic dependent signaling pathways androgens initiate transcription processes and activate canonical pathways associated with activation of ionotropic receptors, G-protein coupled receptors activating phospholipase C, calcium transporters, and endothelial nitric oxide synthase (eNOS). Testosterone can also stimulate membrane ARs, which are binding to Src and activating MAPK pathway. Transactivation of membrane ARs by other ligands has been also reported [81-84]. Most likely activation of the rapid non-genomic processes is essential for fast actions of androgens, such as cell migration, mitosis and inflammatory processes [85].

Estrogens easily penetrate through cellular membrane and majority of their molecules is localized within the nucleus [84, 86]. In cells they regulate long-lasting processes by means of nuclear receptors and rapid non-genomic processes. Nuclear estrogen receptors ESR1 (ER α) and ESR2 (ER β) are codified by *ESR1* and *ESR2* genes. *ESR1* is located on chromosome 6 (6q25.1) and *ESR2* on chromosome 14 (14q23.2). Both receptors act as transcription factors which mediate transcriptional activity of estrogens with reference to specific genes. In absence of the ligand ESRs are associated with heat shock protein and do not express transcriptional activity. After activation by the ligand ESRs interact with estrogen response element (ERE) and operate either as the monomers or as the dimers (ESR1-ESR1; ESR2-ESR2 or ESR1-ESR2). In the nucleus estrogens enhance transcription of specific target genes [77, 87- 88] Estrogens can also modulate expression of other genes acting indirectly *via* activation of PI3K/Akt and MAPK/ERK pathways as well as through inhibition of JNK pathway [89].

Multiple essential actions of estrogens, such as inhibition of ROS production, regulation of mitochondrial ATP level and formation of mitochondrial structural conglomerations occur in mitochondria [90-91]. Estrogens interact also with membrane-associated G-protein-coupled receptor (GPER, named as GPR30), which is encoded on chromosome 7 (7p22.3), and which is found in the endoplasmic nucleus, Golgi apparatus and cellular membrane. GPERs are involved in rapid non-genomic actions of estrogens, that are mediated by extracellularly activated kinase (ERK), cyclic adenosine monophosphate (cAMP) and Ca²⁺. With regard to the cardiovascular system it is essential to note that stimulation of estrogen receptors results in activation of several rapid and long-lasting cellular processes which are essential for function of the heart and vessels. Functionally effective ESRs are present in the cardiac and vascular smooth muscle cells, and modulate function of the perivascular unit [92-93]. GPERs, ER α , ER β and GPER1 are widely represented in most cell types of the cardiovascular system and in the adipose tissue [89, 94-95]. These processes of stimulation of ERs involve activation of phosphoinositide 3-kinase-serin/threonine-specific kinase B (PI3K/Akt /eNOS) and mitogen-activated protein kinase MAPK/e/NOS pathways, that are engaged in production of NO and play essential role in vasodilation. Moreover, it has been shown that in the cardiomyocytes estrogens regulate activity of calcium handling proteins, including L-type Ca²⁺ channel (LTCC), ryanodine channel (RYR), sarcoplasmic reticulum Ca²⁺ ATPase and sodium – calcium exchanger. Thus, it has been suggested that complex reciprocal interactions between activation of estrogen receptors and calcium signaling pathways may play essential role in the regulation of cardiomyocytes activities [76, 96]. Furthermore, it has been reported that estrogens exert an antioxidant action and regulate cell contractility through effects exerted on calcium-dependent signaling pathways operating in cardiac mitochondria and sarcoplasmic/endoplasmic reticulum, where they modulate Ca²⁺-ATPase 2a (SERCA2a) activity and function of calcium ion channels [76, 97-100]. Altogether it is likely that in the heart deficiency of estrogens may result in disturbances of calcium homeostasis. Recently attention has been drawn to essential role of estrogens in the regulation of mitochondrial bioenergetics in human subjects [101]. It has been also reported that interaction of ER α with peroxisome proliferator-activator receptors (PPARs) causes repression of transactivation of the PPAR in the heart and vessels [89].

It is likely that estrogens may also influence function of the cardiovascular system through actions exerted in the brain as their receptors are widely expressed in multiple brain regions involved in the cardiovascular regulation, such as the frontal cortex, and sensorimotor cortex, the thalamus, the hypothalamus, the amygdala, the ventral tegmental area, the hippocampus, the dorsal raphe nucleus and the cerebellum [75, 102]. Finally, it should be noted that activation of ER α and GPER1

plays significant role in modulation of immune processes that are mobilized in cardiovascular diseases [77, 87, 103].

Action of progesterone (P4) is mediated through the genomic signaling engaging two subtypes of nuclear receptors (PGR α , PGR β) and through non-genomic G-protein associated membrane-progesterin receptors (mPRs). Some actions of P4 can be also exerted by GRs [104-107]

Neurosteroids. Some steroids, which are known as neurosteroids, have been identified in the nervous system and act preferably on neuronal membrane receptors. Among them are steroid sulfates, such as DHEAS which is a product of sulfation of DHEA [108]. It is suggested that neurosteroids play significant role in modulation of action of other steroids and classical neurotransmitters. Their action is not a subject of discussion of the present survey [see 109, 110 for further review of this topic].

2.2. Genomic and Non-Genomic Effects of Vasopressin

Vasopressin, which is a principal vasopressin peptide in mammals, is synthesized mainly in neurons of the hypothalamic supraoptic, paraventricular and supraoptic nuclei. Majority of axons of these neurons reach the posterior pituitary where AVP is released to the blood and can be distributed to peripheral organs. Some of the axons reach the median eminence and release AVP into the hypophyseal portal system and the anterior pituitary, where vasopressin contributes to regulation of ACTH. Vasopressin expressing cells have been also identified in the brain regions engaged in the regulation of blood pressure, metabolism, pain, stress and anxiety. Among them are neurons of the brain cortex, olfactory bulb, BNST, dorsomedial hypothalamic nucleus, nucleus of the diagonal band of Broca (DBB), circumventricular organs (CVO), brain stem, and spinal cord [111-113]. In addition AVP mRNA has been detected in the heart and vessels and in the pancreatic tissue [114-115].

Vasopressin gene is located in chromosome 20 and consists of three exons (A, B, and C). The exon A codes for a signal peptide, vasopressin peptide (Cys-Tyr-phe-Gln-Asn-Cys-Pro-Arg-Gly-NH₂), a three amino-acid spacer, and the first nine (NH₂ terminal) aminoacids of neurophysin (NP). Exon B codes for mid-portion of NP, whereas exon C codes for terminal portion of NP, a cleavage site, and the COOH-terminal glycopeptide (GP, known as copeptin). Copeptin consists of 39 aminoacids and is released from neurons in equimolar quantities with AVP [116-117]. Because copeptin molecule is more stable than vasopressin molecule, measurements of GP concentration are frequently used as a marker of AVP level. Measurements of GP level have been included into ESC guidelines on the myocardial infarction and as a biomarker of inflammation [118-120].

Expression of vasopressin gene is influenced by changes of body fluid osmolality and blood volume, as well as by constituents of the hypothalamo-hypophyseal-adrenal axis, pain, cytokines and inflammation factors, especially those associated with COVID-19 [116, 121-125]. Vasopressin gene expression and AVP mRNA abundance are enhanced by chronic osmotic stimulation and are decreased in hypoosmolality. Osmotically-induced increase of AVP mRNA and release of AVP by neurons of the hypothalamo-neurohypophyseal axis are potentiated by administration of lipopolysaccharide and this is associated with enhanced release of IL-1 β and IL-6 in the posterior pituitary [126]. Expression of AVP gene in the hypothalamus is potentiated by IL-1 and IL-2. Moreover, IL-1 β stimulates release of CRH, AVP, and α -MSH [127-128].

It has been shown that hypoosmolality induces GRs expression and that this is related with corticosterone negative feedback on AVP transcription. The above data support the hypothesis that AVP gene is directly inhibited by glucocorticoids and that the induction of GR in the hypothalamic cells suppresses AVP expression during prolonged hypoosmolality. [116]. However, it should be noted that during prolonged increase of corticosteroids concentration, such as takes place during autoimmune inflammation, vasopressin neurons can escape from glucocorticoids inhibition, presumably due to increased engagement of inflammatory cytokines [129].

Osmotic stimulation induces rapid upregulation of CRH in vasopressinergic neurons of the hypothalamic magnocellular nuclei [130]. There is evidence for coordinated regulation of AVP and CRH genes by glucocorticoids. It has been shown that adrenalectomy causes enhancement of CRH

and AVP immunoreactivity in the hypothalamus and elevated CRH immunoreactivity in the cerebral cortex, the amygdala and the BNST. Since the stimulatory effect of adrenalectomy on expression of AVP and CRH in the hypothalamus could be reduced by administration of dexamethasone, it was concluded that glucocorticoids produced in the adrenal glands play primarily inhibitory role in regulation of AVP and CRH secretion [131]. The PVN neurons express glucocorticoids receptors and glucocorticoids reduce AVP gene expression in parvocellular neurosecretory neurons of the PVN [132]. AVP gene and CRH gene possess cAMP response elements (CRE), that are activated by intracellular cAMP and AP1 and AP2 transcription factors can be repressed by glucocorticoids. In the PVN neurons expression of CRH and AVP genes is regulated by nGRE and serum response element (SRE) [117,133-134]. Vasopressin neurons express also MRs and there is evidence that aldosterone and corticosterone increase ENaC Na^+ - leak current through an action exerted at the promoter region of the γ ENaC gene [135]. The magnocellular neurosecretory neurons of the PVN and SON, as well as of other brain regions express 11- β HSD2, and this increases their sensitivity for aldosterone [57, 136].

It appears that during restraint stress the inhibitory effect of glucocorticoids on CRH and AVP mRNA expressions in the PVN neurons can be modulated by concomitant release of testosterone [137]. During chronic stress glutamergic, gamma-aminobutyric acid (GABA) and noradrenergic terminals exert a number of convergent actions that jointly regulate activity of CRF and AVP neurons of the PVN [138]. Growing evidence indicates that androgens play essential role in the regulation of neurons expressing CRH, AVP, dopamine and serotonin during stress-related behavior [139].

Vasopressin receptors. Arginine vasopressin stimulates two subtypes of V1 receptors (V1R), known as V1aR and V1bR, and one type of V2 receptors (V2R). The AVP receptors belong to a family of G-protein coupled receptors, which includes also receptors for other essential cardiovascular regulators, such as β -agonists, Ang II, endothelin, glucagon-like peptide 1 (GLP-1) and CRH. In high concentrations AVP interacts also with oxytocin receptors [113, 140-143]. AVPR1a gene has been mapped to the 12q14.2 locus and AVPR1b to the 1q32.1 locus. AVPR2 gene is located on the long arm of the X-chromosome (Xq28). Mutation of V2R gene is inherited in an X-linked manner and results in congenital nephrogenic diabetes insipidus, which is characterized by strong polydipsia and polyuria [144-145]. It has been shown that vasopressin receptors can act as homodimers and as heterodimers and it is likely that the dimerization influences effectiveness of stimulation of the target cells. Specifically formation of V1aR and OTR, and V1bR and corticotropin-releasing hormone receptor (CRHR) heterodimers has been well documented [146-147]. Expression of vasopressin receptors is regulated by corticosteroids [148]

Vasopressin V1aR mRNA and protein have been detected in multiple organs and tissues, including heart and vessels and their expression is altered in pathological processes [117, 142, 149]. In the cardiac ventricular sarcolemma vasopressin was found to open K_{ATP} channels through action exerted on V1R [150]. AVP was also found to reduce Ca^{2+} influx through L-type Ca^{2+} channels, and this effect can be abolished by blockade of V1aR [151]. There is evidence that stimulation of cardiac V1aR decreases cardiac beta receptors responsiveness [152].

In vitro experiments on H9c2 rat ventricle cardiomyocytes exposed to hypoxia revealed that AVP acting on V1aR in a V1aR/GRK2/ β -arrestin1/ERK1/2- dependent manner, enhances cell survival. It has been suggested that during heart failure, when levels of circulating AVP are elevated, inhibition of G protein-coupled receptor kinase 2 (GRK2) can potentially exacerbate negative V1aR-mediated effects by preventing receptor desensitization and augmenting $\text{G}_{\alpha\text{q}}$ protein-dependent signaling [153-154]. In the heart stimulation of V1aR is also engaged in generation of pro-inflammatory cytokines and in development of inflammation and fibrosis. AVP increases IL-6 mRNA and protein levels in cardiac fibroblasts and this effect requires activation of G protein-coupled receptor kinase 2 (GRK2) and NF- κB [155]. In addition it has been shown that endotoxemia induced by lipopolysaccharide and concomitant increase of IL-1 β , TNF- α and interferon gamma causes downregulation of V1aR gene expression in the heart, vessels, liver and lungs, as well as reduction of responsiveness of vascular smooth muscle cells. It is likely that diminished responsiveness of V1aR

to vasopressin accounts for their inadequate stimulation during circulatory shock that can occur during endotoxemia [156].

Growing number of studies provide evidence for interaction of AVP with corticosteroids in other organs whose proper action is necessary for appropriate regulation of the cardiovascular functions, such as the brain and the gastrointestinal system. Administration of corticosterone was found to decrease expression of V1aR in the brain lateral septum and the hippocampus [148]. Stimulation of V1aR in cortical astrocytes was found to exert a neuroprotective action and this effect was associated with activation of the nuclear transcription factor cAMP response element-binding protein (CREB) and with prominent decrease of IL-1 β and TNF- α gene expressions [150]. Vasopressin plays also essential role in the regulation of the gut microbiome [151]. Enhanced stimulation of V1aR may participate in habituation of release of ACTH, corticosterone and testosterone to repeated stress in Sprague Dawley rats [157].

V1b receptor mRNA is expressed in the corticotropic cells of the brain, and in the anterior pituitary, the adrenal gland, the heart, the kidney, the thymus, the lung, the spleen, the pancreas, the uterus and in the white adipose tissue [158-160]. In the brain V1bR mRNA was detected in the olfactory bulb, the cortex, the hippocampus, the hypothalamus, the septum and the cerebellum, although its expression was lower than expression of V1aR mRNA [160]. In the pancreas stimulation of V1bR potentiates secretion of insulin from β cells where vasopressin can act synergistically with CRH [160]. Thus far there is no convincing evidence for presence of V2R in the heart and vessels and for their direct involvement in the regulation of cardiovascular functions by vasopressin. Nevertheless through stimulation of V2R in the kidneys and through regulation of urine concentration and body fluid natremia AVP may modulate effects of stimulation of V1R in the cardiovascular system [157- 161].

3. Role of the Hypothalamo-Pituitary- Adrenal System and Vasopressin in Regulation of Energy Balance and Water-Electrolyte Balance at Rest and during Neurogenic Stress

3.1. Regulation of Steroids Secretion

The synthesis of glucocorticoids in the adrenal cortex is regulated mainly by ACTH, which is released from the pituitary gland. Secretion of ACTH is closely regulated by CRH and AVP that are supplied principally by neurons of the PVN [163-164]. Glucocorticoids released from the adrenal cortex and ACTH secreted from the corticotropic cells of the pituitary gland are able to inhibit reciprocally secretion of CRH from the hypothalamic neurones [117, 133, 165] (Figure 1)

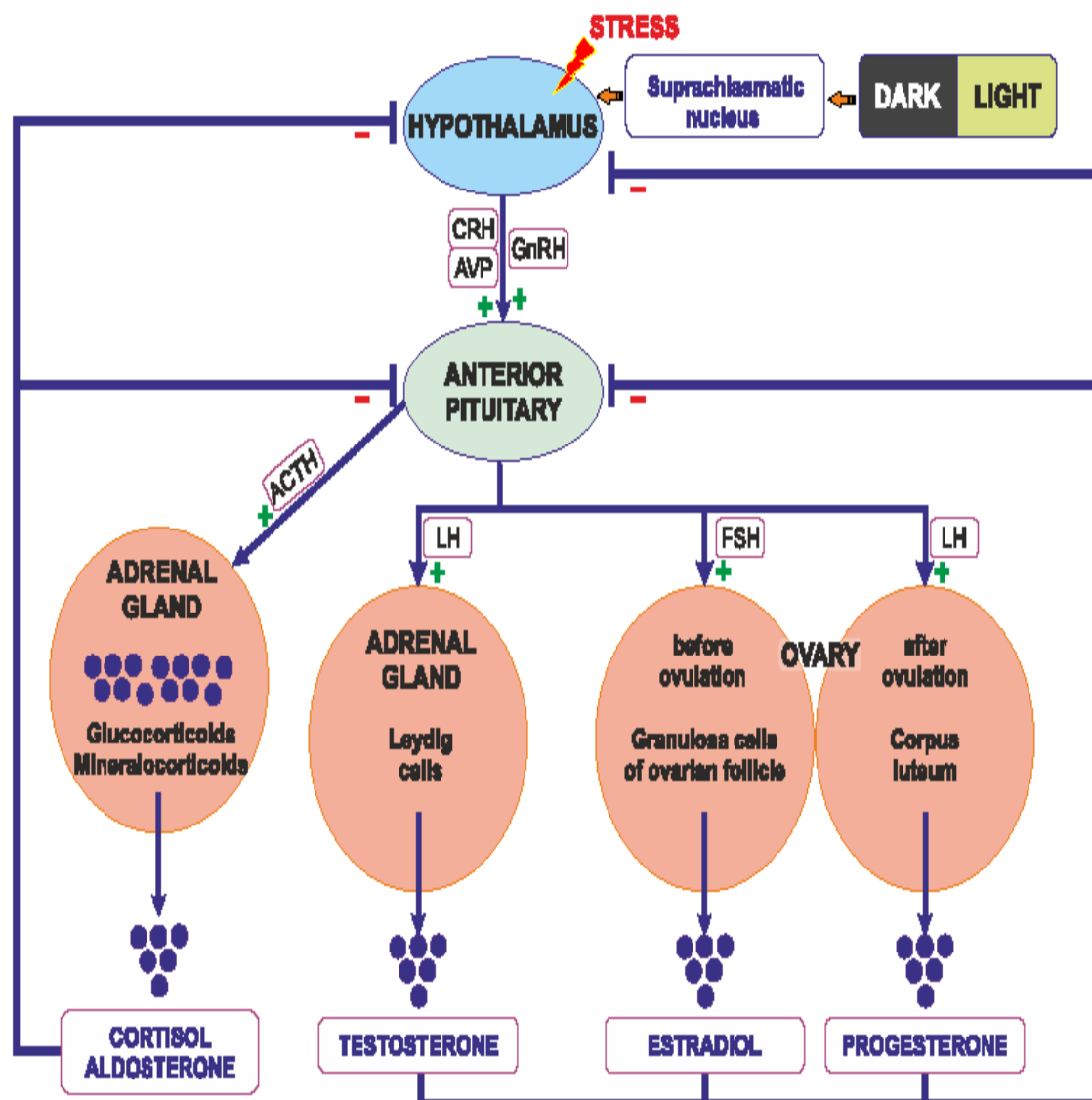


Figure 1. Regulation of secretion of hormones of the hypothalamo-pituitary-adrenal axis. ACTH – adrenocorticotrophic hormone, AVP – arginine vasopressin, CRH – corticotropine-releasing hormone, FSH - follicle-stimulating hormone GnRH – gonadotropine-releasing hormone, LH - luteinizing hormone. Other explanations in the text.

The secretion of glucocorticoids from the adrenal cortex is regulated by the circadian rhythm, however the daily rhythm of glucocorticoid release may be influenced by other factors, such as gender, aging, early life stress, inflammatory diseases, pregnancy and lactation [163,166]. ACTH binds on surface of cells of the fascicular layer of the adrenal cortex with the G protein-coupled melanocortin type 2 receptor (MC2R), which activates the 3',5'-cyclic AMP signaling cascade, enabling the penetration of cholesterol into the inner mitochondrial membrane. Cholesterol is converted by cytochrome P450 to pregnenolone, which is converted in several steps to progesterone, 11-deoxycortisol, and cortisol (the main glucocorticoid in humans), or corticosterone (the main glucocorticoid in rodents) (Figure 2) [163].

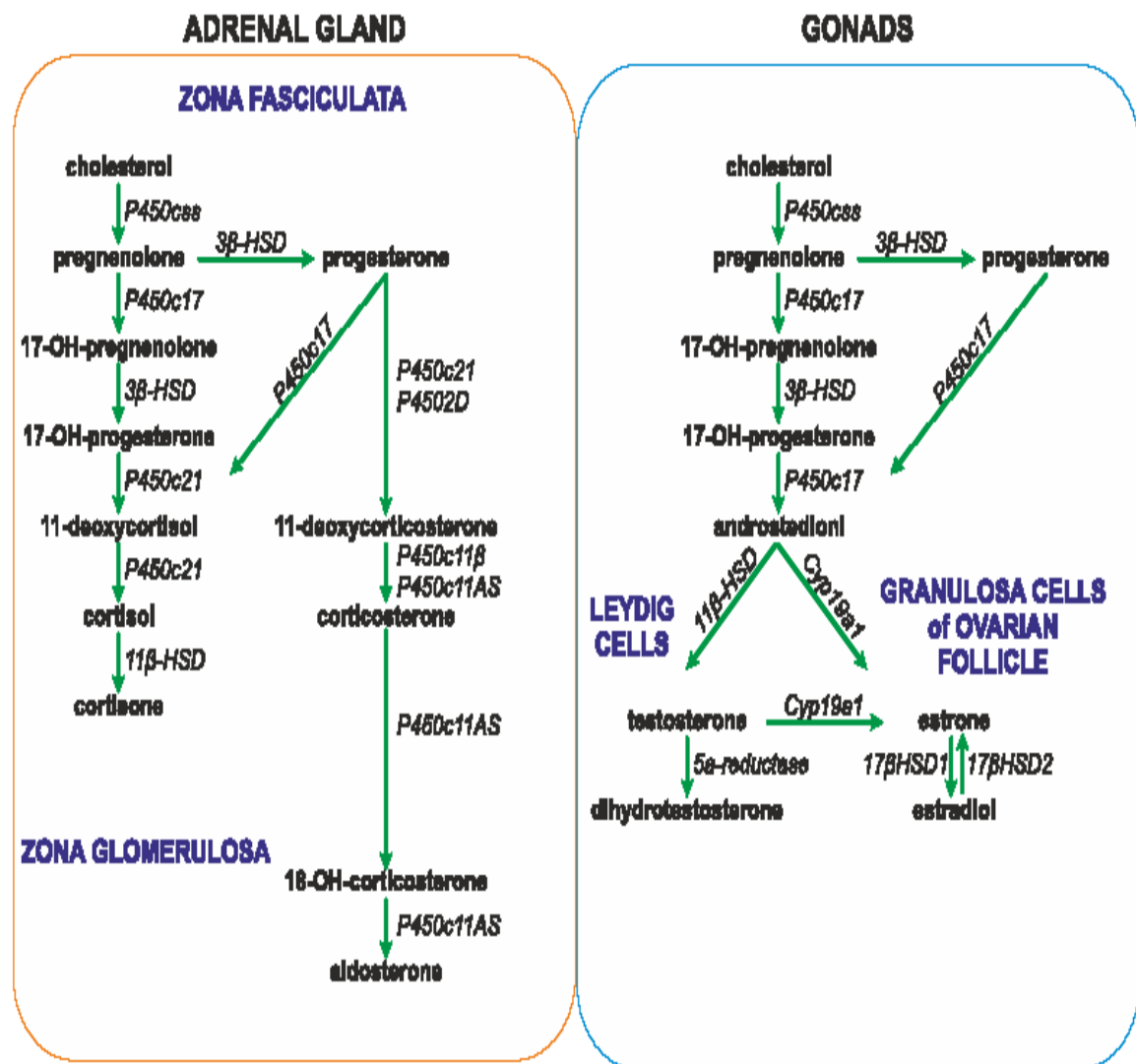


Figure 2. Steps of synthesis of steroid hormones in the adrenal glands and gonads. Other explanations in the text.

ACTH stimulates also synthesis of aldosterone in the glomerular layer of the adrenal cortex. Aldosterone is synthesized from cholesterol in the inner mitochondrial membrane with the participation of aldosterone synthase (CYP11B2), belonging to the cytochrome P450 (CYP) family. The process of synthesis includes the formation of pregnenolone and conversion of pregnenolone to 11-deoxycorticosterone (DOC) in the smooth endoplasmic reticulum (Figure 2). Further processing to aldosterone takes place again in the mitochondria [167, 168]. Synthesis of aldosterone in the adrenal cortex can be also stimulated by the renin-angiotensin system (RAS) and by extracellular potassium concentrations [167].

Androgens, as well as estrogen and progesterone, are released during activation of the HPA axis, which plays crucial role in the regulation of the ovarian cycle. The hypothalamic cells synthesize gonadotropin-releasing-hormone (GnRH), which stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. In the woman FSH stimulates follicular maturation and release of estrogen in the follicular phase, while LH triggers ovulation as well as release of progesterone from the corpus luteum (*ruptured follicle*) in the luteal phase. Estrogens released from the ovaries and acting through reciprocal inhibition are able to slow

down the activity of both the pituitary gland (synthesis and secretion of FSH and LH) and the hypothalamic neurons (synthesis and secretion of gonadotropin-releasing hormone), imposing thereby the menstrual cycle [169]. Estrogens are synthesized as a result of action of the aromatase, which is responsible for the aromatization of androgens into estrogens (Figure 2) [170]. The main site of aromatase expression in premenopausal women is located in the ovarian granulosa cells. In pregnant women it is also present in the placental syncytiotrophoblast. Both in men and in postmenopausal women, fibroblasts of adipose tissue and skin contribute to estrogen synthesis [171]. During the reproductive life women show characteristic periodicity of secretion of ovarian hormones, which corresponds to the monthly menstrual cycle. Namely, during the early follicular phase and menstruation, both estradiol (the main circulating estrogen in non-pregnant women of reproductive age) and progesterone levels are low. Estradiol concentration increases before the ovulation in the middle and late follicular phase, and decreases immediately after the ovulation. Subsequently, both estradiol and progesterone levels increase during the luteal phase until menstruation. Apart from the periovulatory phase, progesterone fluctuations correspond to estradiol fluctuations [169].

As already mentioned, androgens are synthesized mainly in the adult female ovaries and in the male testes. In addition, their synthesis is stimulated by ACTH in the reticular zone of the adrenal glands (mainly dehydroepiandrosterone sulfate, DHEA/-S; 4-androstenedione, A4 and 11 β -hydroxyandrostenedione). Androgens are metabolized in the liver and subsequently excreted by the kidneys [172]. In the man the dominant androgen is testosterone; its concentration is 15 times higher than in the woman [173,174] Testosterone synthesis in men takes place in Leydig cells of the testes (Figure 1). Activation of the Leydig cell LH receptors (LHR, G protein-coupled receptor) by LH initiates an intracellular signaling cascade, which involves stimulation of adenylate cyclase, increased production of cAMP, and the activation of adenosine-dependent kinase [175]. As a consequence of activation of cAMP-dependent intracellular signal transduction, cholesterol can be transferred to the mitochondria by the steroidogenic acute regulatory protein (STAR), the translocator protein (18 kDa; TSPO), and other transducosome proteins [176]. In the mitochondria of Leydig cells, cholesterol is converted to pregnenolone by the cytochrome P450 enzyme located on the matrix side of the inner mitochondrial membrane, which cleaves the C27 cholesterol side chain (CYP11A1). Subsequently, after transfer to the smooth endoplasmic reticulum, pregnenolone is metabolized to testosterone by 3 β -hydroxysteroid dehydrogenase (3 β -HSD; HSD3B), 17 α -hydroxylase/17,20 lyase (CYP17A1), and 17 β -hydroxysteroid dehydrogenase type 3 (17 β -HSD3, HSD17B) (Figure 2) [177-179].

3.2. Interaction of Steroids and AVP in Regulation of Energy Balance

Multiple studies indicate that both steroid hormones and vasopressin play an important role in regulation of energy balance. Glucocorticoids promote glucose production in the liver and reduce peripheral glucose uptake by muscle and adipose tissue. They also increase the breakdown of constituents of fat and muscle, providing thereby additional substrates for glucose and free fatty acids production [180].

Vasopressin is involved in regulation of food intake and energy balance *via* a wide range of central and peripheral actions exerted on cellular growth and proliferation, protein turnover, lipid metabolism, and glucose homeostasis [181]. For instance, endogenous nucleobindin-2 (NUCB2)/nesfatin-1 has been shown to regulate AVP and oxytocin in the PVN of male mice, and this was associated with resetting of fluid balance and food intake, and with an increase of body weight without the change of energy expenditure [182]. Experiments on mice showed that administration of AVP analogue (Ac3IV) twice a day for 22 days not only reduced energy consumption, body weight and fat content, but also decreased blood glucose concentration, increased insulin sensitivity and significantly improved glucose tolerance and glucose-induced insulin secretion. Moreover, it lowered total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides, and increased high density lipoprotein (HDL) cholesterol [183]. Several hormones affecting energy balance play significant role in regulation of AVP secretion. Ghrelin, an orexigenic hormone, has been shown to stimulate vasopressinergic neurons in the hypothalamic paraventricular nucleus and AVP secretion in a nutritional status-dependent manner in *in vivo* experiments. It also activated excitatory

GABAergic synaptic input via a retrograde neuron-glial circuit in the hypothalamic slices obtained from fasted rats [184]. On the other hand, i.c.v. administration of adiponectin significantly reduced basal plasma AVP concentrations in conscious rats in a dose-dependent manner, with the maximum effect achieved 10 min after administration [185].

Additionally, it appears that AVP may exert thermogenic functions, as exposure of brown adipose tissue (BAT) adipocytes to AVP was found to increase uncoupling protein-1 (UCP-1) protein expression, to induce a time- and dose-dependent increase in p38 MAP kinase phosphorylation, as well as to increase monocyte chemoattractant protein-1 (MCP-1) mRNA and IL-6 expressions. In contrast adiponectin mRNA expression was reduced [186]. Former studies have shown that acting in the adipose tissue on V1aR AVP may exert both lipolytic and antilipolytic effects [187-188]. Its action on lipid metabolism through V1bR is different. It has been shown that V1bR deficient mice have lower body weight and greater epididymal adipose tissue mass in comparison to wild-type mice. It is believed that AVP acting on V1bR receptors is able to influence lipid metabolism through modulation of insulin signaling. Currently it appears that stimulation of V1aRs results in the impairment of glucose tolerance and in the lipolytic action, whereas activation of V1bRs improves glucose tolerance and exerts an antilipolytic effect [189-190].

Elevated plasma copeptin (AVP substitute) concentrations have been demonstrated in patients with type 2 diabetes and with type 1 diabetes [191]. Moreover, recent studies indicate that higher concentrations of AVP or copeptin predispose to development of type 2 diabetes and metabolic syndrome and that consumption of larger amounts of water by people with high plasma copeptin concentrations results in reduction of fasting glucose or glucagon levels [192]. Studies on human populations revealed an association of polymorphisms of the gene encoding AVP with metabolic disorders. A significant relationship was found between high copeptin level and reduced insulin sensitivity as well as between AVP gene tagSNPs (CC genotype rs6084264, TT genotype rs2282018, C allele rs2770381 and CC genotype rs1410713) and the incidence of hyperglycemia [193]. Similarly, specific polymorphism of V1aR gene (T allele of rs1042615) has been associated with an increased incidence of type 2 diabetes in people who consume large amounts of fat or are overweight [194]. In another study the major A allele of rs35810727, a tagSNP of the V1bR, has been associated with an increased body mass index (BMI), and type 2 diabetes [195].

3.3. Interaction of AVP and Steroids in Regulation of Water-Electrolyte Balance

It has been well established that the vasopressin system plays pivotal role in the regulation of water and electrolyte balance and that lack of AVP results in excretion of large amounts of free water in the urine (polyuria) and in subsequent polydipsia [112, 196-197]. Release of AVP is regulated by a variety of internal and external cooperating factors, acting as anticipatory or consecutive signals [192, 198-199]. Regulation of water-electrolyte balance via AVP is a complex process in which the osmolality of the extracellular fluid (ECF), including plasma and cerebrospinal fluid, plays a key role. ECF tonicity is sensed by osmoreceptive neurons located mainly in the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT) which are able to sense the osmolality using aquaporin (AQP) receptor, and have direct connections with the PVN and SON [200-201]. Osmotically-induced shrinkage of osmoreceptive cells during dehydration causes activation of TRPV1 delta-N channels (a family of transient receptor potential cation channels) that sense mechanical stretch and allow the influx of cations into the cell [200, 202]. In addition activity of the brain osmoreceptors may be regulated by anticipatory signals—generated in receptors of the oropharyngeal region, esophagus or stomach, which participate in the regulation of fluid intake. Specifically, the information about the taste of water is transmitted centripetally by the tympanic cord belonging to the facial nerve, the information about the dry mouth is received *via* the trigeminal nerve and the information about the stretching of the esophagus and stomach and volume of water ingested are transmitted by the glossopharyngeal nerve and by the vagus nerve [203].

In the kidneys AVP regulates the activity of the aquaporin-2 (AQP2) water channel in the collecting duct and takes part in the process of urine concentration [204]. Moreover, it stimulates sodium reabsorption acting on the luminal sodium channel ENaC in the cortical and outer medullary

parts of the collecting tubules, and activates urea transporters UT-A1 and UT-A3 in the inner terminal medullary increasing urea reabsorption in the collecting tubules [205-206]. Additionally, at higher concentrations, AVP increases also sodium reabsorption through activation of Na-K-2Cl cotransporters (NKCC2) in the thick ascending limb of the nephron loop (Henle's loop) [207].

There is strong evidence that the regulation of water-electrolyte balance by vasopressin is significantly influenced by steroid hormones. Experimental studies have shown that glucocorticoids deficiency facilitates activation of V2 receptors in the renal collecting tubule [208]. It has been also shown that application of dexamethasone (a cortisol analogue) improves cardiac functions in rats with congestive heart failure elicited by coronary artery ligation, and this effect is associated with reduced expression of V2R and AQP2 and AQP3, and with reduced number of ENaC and Na-K-2Cl cotransporters 3 in the renal collecting tubule [209]. The effects of dexamethasone were abolished by the use of the glucocorticoid receptor inhibitor RU486 [209]. However, the clinical studies could not confirm significant involvement of glucocorticoids applied alone in fluid retention in critically ill patients and it has been postulated that effects of steroid hormones on water-electrolyte balance are mediated mainly by activation of mineralocorticoid receptors [210]. It is well known that mineralocorticoids have a significant impact on electrolyte balance, especially on sodium and potassium turnover as well as on clearance of free water [211-212]. Moreover, components of the renin-angiotensin-aldosterone system (RAAS), acting in the hypothalamus are able to stimulate vasopressin secretion, thirst, and sodium appetite [213].

Currently it appears that also gonadal steroids have a significant effect on the vasopressinergic system [214]. Experimental studies revealed that the antidiuretic function of AVP is more effective in male rats than in female rats [215]. Furthermore, its effect is more potent in females during the estrus when the level of circulating estrogen is lowest [215]. In addition, ovariectomy was found to increase the antidiuretic response to AVP to the level comparable to that observed in males, whereas estradiol substitution reduced the antidiuretic effect of AVP to the level observed in non-estrus females [215]. It appears that estrogens may also influence the hypothalamic vasopressinergic neurons acting both through ER α and ER β receptors. In this context presence of ER α on osmoreceptive neurons of the SFO and OVLT, which send projections to the SON has been demonstrated [216-218]. Moreover, both ER α and ER β have been detected in the kidney, where the expression of ER α is prevailing [219]. Interestingly, GPER is a newly discovered aldosterone receptor that is believed to mediate nongenomic aldosterone pathways. GPER activation by aldosterone mediates water and sodium retention in the body and contributes to vasoconstriction [220]. Recently it has been shown that production of aldosterone may be influenced by progesterone [221].

It should be noted that testosterone, in addition to estrogen, can directly inhibit AVP secretion [222]. However, it is frequently emphasized that the effect of testosterone, and action of some of its metabolites (α -androstane-3 β), on release of AVP may be mediated by ER β [219].

3.4. Interaction of AVP and Steroids in Neurogenic Stress

A number of studies provide evidence that neurogenically mediated stress causes joint stimulation of the vasopressin secreting neurons and CRH secreting neurons which suggests that a coordinated regulation of AVP and CRH release and action may play an important role in modulation of neurogenic stress. Moreover, it has been found that in chronic stress and depression the effects of CRH on ACTH release are strongly enhanced by vasopressin, which is produced in increasing amounts when the hypothalamic PVN and SON neurons are chronically activated [223-224]. It has been found that AVP is engaged in stress-induced tachycardia and baroreceptor reflex (BRR) desensitization [225]. Clinical studies have shown that healthy adults exposed to a social stress test respond with an increase in serum copeptin concentration [223]. Experiments on mice showed that chronic unpredictable stress (UCS) and ovariectomy influence AVP immunoreactivity in the lateral magnocellular and the medial magnocellular subdivisions of the PVN [226]. More recently it has been shown that during the chronic stress, hypothalamic activation of pituitary changes from the dominant CRH phenotype to the dominant AVP phenotype, however cortisol level remains elevated because its metabolism is reduced [227]. The role of vasopressin in the response to stress appears to

differ in female and male C57BL/6 mice. Namely, a six-week chronic variable stress (CVS) paradigm has been found to increase sociability in female mice and to decrease AVP mRNA in the PVN, whereas in male mice, CVS had no effect on social behavior or AVP expression [228]. Studies conducted on male Sprague Dawley rats subjected to a 4-week unpredictable chronic mild stress (UCMS) showed that injections of small interfering RNA (siRNA) directed against V1aR into the PVN prevent the increase in blood pressure and the elevation of renal sympathetic nerve activity (RSNA), whereas administration of scrambled RNA (scrRNA) into the PVN elicit an increase in blood pressure. The results suggested that V1aR signaling in the PVN contribute to generation of neuro-cardiovascular responses to stress [229]. In addition recent studies provided evidence that the rs10877969 polymorphism of V1aR gene is associated with elevation of symptoms of stress and acute pain [230]. Research performed by Komnenov et al. (2021) showed that rats subjected to UCMS have higher plasma AVP levels and greater abundance of V1aR and V1bR transcripts in the PVN. The rats manifested also higher resting MAP, heart rate, and RSNA and these effects could be eliminated by combined inhibition of V1aR and V1bR [231]

4. Altered Interactions of Vasopressin with the Hypothalamo-Pituitary-Adrenal System in Cardiovascular and Metabolic Diseases

4.1. Cardiovascular Diseases

Growing evidence indicates that central and peripheral interactions of steroid hormones and vasopressin are reprogrammed in hypertension and that the occurring modifications may initiate and/or potentiate cardiovascular complications. Pietranera et al. (2004) revealed that s.c. injections of deoxycorticosterone (DOC) acetate cause significantly greater increases of AVP and V1aR mRNA in the magnocellular divisions of the PVN in the spontaneously hypertensive (SHR) rats than in the control SHR rats receiving oil vehicle [232]. It is possible that AVP contributes to elevation of blood pressure in DOCA-induced hypertension through augmentation of the neurogenic component of vascular resistance. Studies conducted on DOC- treated and saline-treated rats revealed a significant increase in vascular resistance that was associated with amplification of the central sympathetic tone only in DOC-salt rats. These effects were intensified by vasopressin. Moreover, a reduction in vascular resistance was observed in DOC-salt rats treated with AVP antagonist (I-deaminopenicillamine, 4-valine, 8-D-arginine vasopressin, dPVDAVP) and in those who underwent lumbar sympathectomy [233]. Experiments on dogs maintained on normal salt diet showed that subcutaneous administration of DOC to dogs elicited an increase of blood pressure, that was accompanied by an increase of cardiac output, hypernatremia, and elevation of vasopressin concentration in plasma and in the cerebrospinal fluid (CSF) at early stage of hypertension [234].

Some evidence suggests that inappropriate interaction of steroid hormones and vasopressin may play a role in development of congestive heart failure. For instance, it has been reported that treatment of the sheep with paced-induced heart failure with urocortin 2 (Ucn2; group of peptides sharing structural similarities with CRH combined with canrenoic acid, which is an antagonist of mineralocorticoid receptor improved better hemodynamics than application of canrenoic acid alone. The combined treatment contributed also to reductions of PRA, Ang II and AVP concentrations, as well as to improvement of the kidneys functions [235].

4.2. Metabolic Diseases

Growing number of studies address a question whether interactions of AVP and steroids are altered in metabolic diseases. Clinical data, based on measurements of blood copeptin concentration, suggest that AVP may play a role in pathogenesis of the metabolic syndrome (MetS). In this line, obese men with elevated fat free mass and total fat mass show higher fasting glucose and insulin concentrations as well as enhanced pituitary response to combined CRH/AVP stimulation. The results suggest that joint stimulation of CRH and AVP, which is associated with excessive stimulation of ACTH release may promote development of body overweight, adiposity and hyperinsulinemia [236]. There is also evidence that obesity causes significant rearrangement of activation of the HPA

by the noradrenergic system. For instance noradrenergic transporter activity (NAT) assessed in positron emission tomography (PET) was found to correlate differently in obese and non-obese patients. In the non-obese patients, a positive correlation was found between orbitofrontal NAT and HPA axis activity, whereas in the obese patients the correlation was negative. The study suggested that in the obese patients regulation of HPA axis by the noradrenergic system activates mainly the hypothalamic neurons whereas in the non-obese subjects it engages more intensively the prefrontal-limbic cortex [237]. It has been also postulated that altered association of copeptin and insulin resistance is related to elevation of hepatic glycogenolysis, increased insulin, glucagon and ACTH secretions, and enhanced activation of 11β -HSD2 [238]. Links between specific steroid hormones and vasopressin in hypoglycemia are less evident. It has been reported that insulin-induced hypoglycemia increases secretion of cortisol, but it does not affect plasma AVP level [239]. In another study more drastic hypoglycemia (1.6 mmol/l), probably producing hypoglycemic stress, caused a rapid significant increase of serum copeptin concentration, which was positively correlated with ACTH and cortisol concentrations. Interestingly, these effects were observed only in women. In the man, there was no correlation between copeptin and blood ACTH level during hypoglycemia and only poor correlation was found between copeptin and blood cortisol level during hypoglycemia [240]. Studies conducted on AVP-deficient Brattleboro rats that were also suffering from diabetes mellitus showed that AVP does not play a significant role in the regulation of release of the HPA axis hormones during acute stress [241].

Balapattabi et al. (2021) examined associations of the liver failure with AVP secretion and hyponatremia in relevance to sex differences. They showed that male rats with a bile duct ligation (BDL) were hyponatremic, manifested significantly higher concentrations of plasma copeptin, and higher FosB expression in the supraoptic AVP neurons than the sham males, whereas similar associations were not observed in female BDL rats [242]. The study conducted in women with polycystic ovary syndrome, revealed that AVP peak responses to hypoglycemia were negatively correlated with testosterone, androstenedione, and endogenous insulin levels, however, there was no correlation between AVP and basal and hypoglycemia-induced peak cortisol concentrations [243].

4.3. Neurogenic Stress with Relevance to Sex Differences

It is well known that there are sex differences in tolerance of stress, and in predisposition to anxiety, and depression, and that they may at least partly result from different regulation of the HPA axis [244-245]. Experimental studies demonstrated that the female rats respond with larger increases of ACTH to neurogenic stress than the male rats and suggested that during the neurogenic stress the gonadal steroids involved in the regulation of sexual behavior and reproduction may have a potential impact on the pituitary secretion of ACTH [246]. Subsequently it has been shown that secretion of ACTH is regulated by testosterone-dependent effect on the synthesis of AVP and by corticosterone-dependent effect on the synthesis of CRH in the PVN [247]. It is likely that one of the reasons of differences in sex-related susceptibility to stress results from functional heterogeneity of GR and MR in the brains of females and males, because higher expression of MR was found in the brain of the male mice than in the brain of female mice manifesting depressive behavior [248]. Research performed by Woodward et al. (2023) on female and male mice, subjected to the UCMS procedure showed that female mice show anxiety and depressive behavior associated with FosB activation in neurons of the medial prefrontal cortex (mPFC) expressing parvalbumin after 4 weeks of exposure, while in male mice the behavioral and biochemical alterations is observed not earlier than after 8 weeks of UCMS. Furthermore, the use of patch-clamp electrophysiology allowed to demonstrate that there were time-corresponding sex-specific differences in altered neuronal excitability of the mPFC cells after 4 and 8 weeks of the exposure [245]. Rosinger et al. (2019) using a corticotropin-releasing factor 1 receptor (CRFR1) reporter mouse line, demonstrated that male mice showed a significantly higher distribution of cells expressing CRFR1 in the PVN compared to females, however it should be noted that this relationship was age-related, because it was observed only in older (20-24-month) mice, and not in mice during the early post-natal life. Gonadectomy in adult six-week-old mice resulted in a significant decrease in the number of CRFR1-immunoreactive cells in the PVN in males

but not in females. In addition CRFR1 cells showed moderate co-expression with estrogen receptor alpha and high co-expression with androgen receptor. The use of restraint stress resulted in greater activation of CRFR1 cells in the PVN of male than in the PVN of female mice [249]. Cox et al. (2015) examined the association of X chromosome genes with neurobehavioral disorders in an experimental model (fragile X syndrome, autism) using a mouse model with an atypical sex chromosome configuration resembling Turner (45, XO) and Klinefelter (47, XXY) syndromes. The researchers showed higher AVP expression in the amygdala of female mice with one copy of X-chromosome gene. Reduced level of plasma AVP was found in girls with Turner syndrome [250].

Recent clinical studies of Cohen et al., (2023) have revealed that gender differences in reaction to stress occur already in young people aged 18-25, and they may be related to different activation of the prefrontal cortex. Using GABA in magnetic resonance spectroscopy the authors were able to demonstrate significant differences in neuronal activity in responses to stress among the sexes. It should be noted that the differences were especially evident in the ventromedial prefrontal cortex, which plays an essential role in the regulation of the hypothalamic-pituitary, hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes [251].

5. Impact of Therapeutic Interventions on Interactions of Vasopressin with the Hypothalamo-Pituitary-Adrenal System in Health and Cardiovascular and Metabolic Diseases

As discussed in former parts of this review there are several interconnections between steroids and vasopressin that are significantly affected in cardiovascular, metabolic and psychogenic disorders [157, 168, 237]. Thus it is justified to assume that various therapeutic interventions, having impact on vasopressinergic system and the hypothalamo-pituitary-adrenal axis, may potentially influence effectiveness of the AVP-HPA interactions.

Systemically applied corticosteroids are widely used in therapy of inflammatory and autoimmune disorders [163, 236, 252]. Their influence on the HPA axis and vasopressin secretion resembles the role of endogenous corticosteroids in negative feedback loop. A post-mortem study of Erkut et al.(1998) on 9 patients treated with corticosteroid and on 8 control subjects demonstrated significant decrease of CRH and AVP releasing neurons in the hypothalamus. The study showed that the corticosteroid-treated patients retained only 3.3% of CRH releasing cells and 33% of AVP-releasing cells in comparison to the control group [253]. Thus far, clinical implications of these changes have not been fully recognized. A study on premature infants with bronchopulmonary dysplasia revealed that treatment with dexamethasone improves pulmonary functions, but does not modify AVP levels [254]. On the other hand, administration of corticosteroid in supraphysiological doses in the clinical trial on children with acute lymphoblastic leukaemia (ALL) resulted in suppression of the HPA axis for a few weeks in majority of patients. [255]. The decrease in AVP mRNA was also found in the SChN of patients treated with corticosteroid (2-fold lower level in the SChN of patients exposed to corticosteroid in comparison to the control subjects). Accordingly, it has been proposed that corticosteroid-induced changes in AVP synthesis may account for circadian rhythms abnormalities and sleep disturbances in steroid-treated patients [256].

It has been postulated that vasopressin synthesized in magnocellular cells of the hypothalamus participates in a phenomenon known as „corticosteroid escape“. According to this hypothesis inflammatory mediators (for instance IL-6) increase AVP release from the hypothalamic magnocellular PVN cells above the physiological concentrations, which results in strong activation of adenylyl cyclases (AC2 and AC7) and elevation of cAMP to a level, at which it can inhibit the negative feedback mediated by endogenous corticosteroids in the HPA axis. Most likely, rearrangement of mutual relations between CRH, AVP, interleukins and corticosteroids accounts for the “corticosteroid escape” that is observed during activation of the host immune system and that maintains corticosteroid release in spite of high dose of exogenous corticosteroid imposed by the therapy (Figure 3) [257]. However, the role of the „corticosteroid escape” in achievement of optimum results of systemic corticosteroid therapy is not yet fully determined.

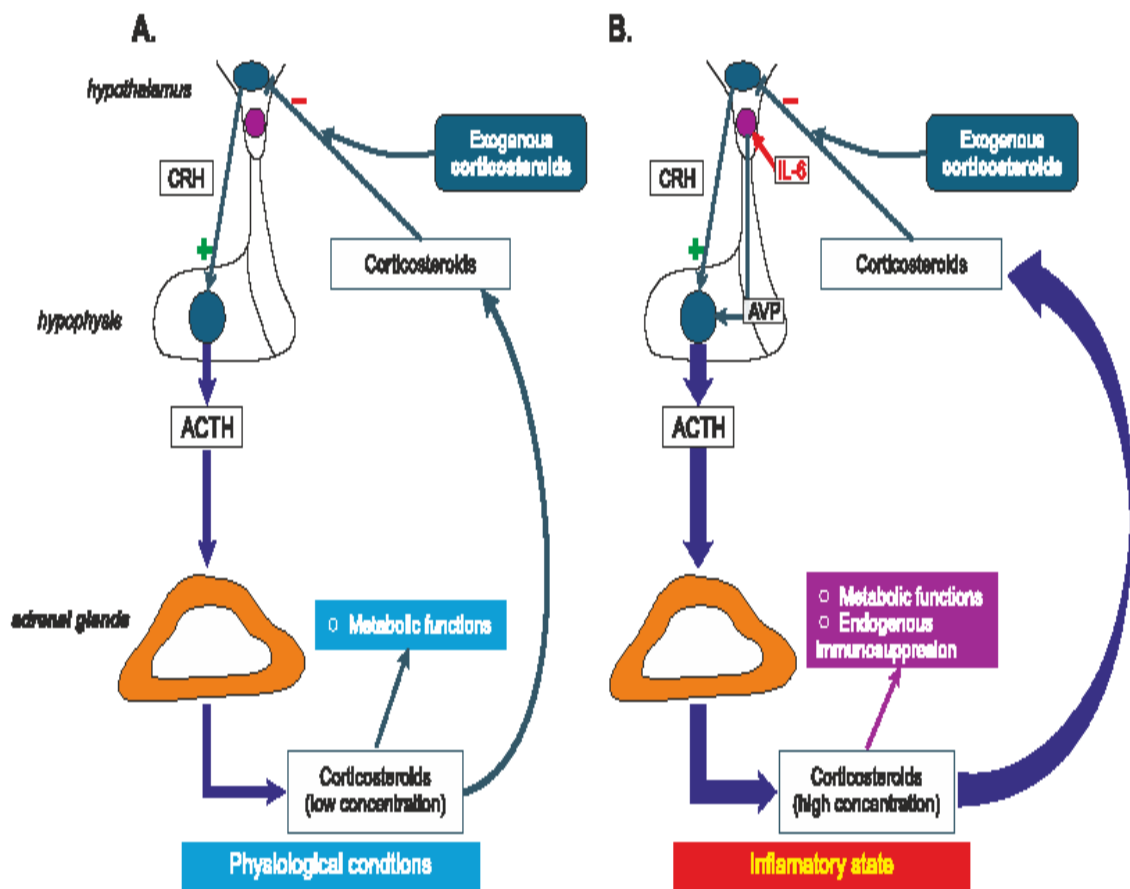


Figure 3. A phenomenon of „corticosteroid escape“. A - under normal conditions corticosteroids inhibit release of corticotropine-releasing hormone (CRH), B - during inflammatory state and activation of autoimmune processes inhibition of CRH secretion by negative feedback is impaired and activation of the HPA axis is maintained in spite of high concentration of corticosteroids. ACTH – adrenocorticotrophic hormone, IL-6 – interleukin 6.

5.1. Steroids and Vasopressin Treatment in Cardiovascular Diseases

It is likely that resetting of vasopressin-HPA system by corticosteroids plays beneficial role in treatment of severe cardiovascular disorders such as myocardial infarction, shock and cardiac arrest. A study on the rat model of myocardial infarction revealed that hydrocortisone administration during early reperfusion period results in decreased infarct size and in reduced oxidative stress [258]. The potentially beneficial role of corticosteroids may result from their anti-inflammatory activity, though there are some concerns regarding the use of corticosteroids in acute myocardial infarction because of their negative effects on wound healing and scar formation. The meta-analysis performed by Giugliano et al [259] indicated slight reduction in cardiovascular mortality in patients with acute myocardial infarction treated with corticosteroids. However, it should be noted that this survey was based mainly on studies including small number of patients (less than 100) and did not unequivocally indicated benefit of treatment with corticosteroids [259]. In another study the best survival rate (91%)

was found in patients with low baseline cortisol level and with appropriate adrenal response to ACTH analogue (difference between minimum and maximum cortisol levels higher than 9 µg/dl) [260]. A study on a cohort of 159 patients with septic shock revealed that survival rate was significantly greater when vasopressin was used together with hydrocortisone [261]. This finding suggested a potential benefit of joint application of corticosteroids and vasopressin in critically ill patients. More recently, randomized clinical trial on 512 patients of 10 hospitals in Denmark showed significant increase in probability of return of spontaneous circulation (ROSC) in patients receiving combined treatment of methylprednisolone and vasopressin in comparison to patients receiving placebo. However, there was no difference in 30-days mortality and neurological outcome of the patients [262].

5.2. Impact of Anti-Depressive and Neuroleptic Treatments on Vasopressin-HPA Interactions

As it was mentioned above, the vasopressin-HPA system is controlled by monoamine neurotransmitters, and administration of anti-depressive or other neuroleptic compounds, which are interfering with monoaminergic transmission, significantly influences AVP-HPA interactions (see 3.3). Moreover, it has been reported that activation of the HPA system during stress seems to be altered in patients with depression, and that vasopressin plays more important role than CRH in regulation of ACTH release in this group of patients [263,264]. Altered action of vasopressin in patients with depressive and stress-related disorders opens a discussion on the usefulness of selective AVP antagonists as anti-depressive or anxiolytic drugs [264-266]. Undoubtedly, further studies are needed to explain whether down-regulation of the vasopressinergic pathways would play a beneficial role in these disorders.

The study upon animal model of depression (olfactory bulbectomy in mice, OB mice) revealed that OB mice demonstrated higher vasopressin and ACTH plasma levels. Moreover, it was possible to reverse these elevations by chronic treatment with anti-depressive drugs, namely fluoxetine (SSRI) and venlafaxine (SNRI) [267]. Another study on healthy rats showed that antidepressant compounds, such as SSRI and desipramine (tricyclic antidepressant) influence function of HPA axis by means of vasopressin V1bRs [268]. Studies on Wistar rats have shown that AVP release from magnocellular and parvocellular cells may be affected by neuroleptic drugs and that clozapine and olanzapine are more effective than haloperidol [269].

A study upon six patients with atrial fibrillation qualified for electrical cardioversion and 6 patients with depression qualified for electroconvulsive therapy revealed significantly enhanced activation of HPA after these interventions. In particular, AVP concentration increased 7 times after electrical cardioversion and 2 times after electroconvulsive therapy, whereas plasma ACTH levels were elevated 3 times and 4 times, respectively [270].

6. Summary and Conclusions

The present review analyses complex mechanisms underlying cooperation of vasopressin with hormones of the hypothalamo-pituitary-adrenal axis. As shown in Figure 4 AVP cooperates with specific components of the HPA axis through interactions occurring both in the central nervous system and in the peripheral organs.

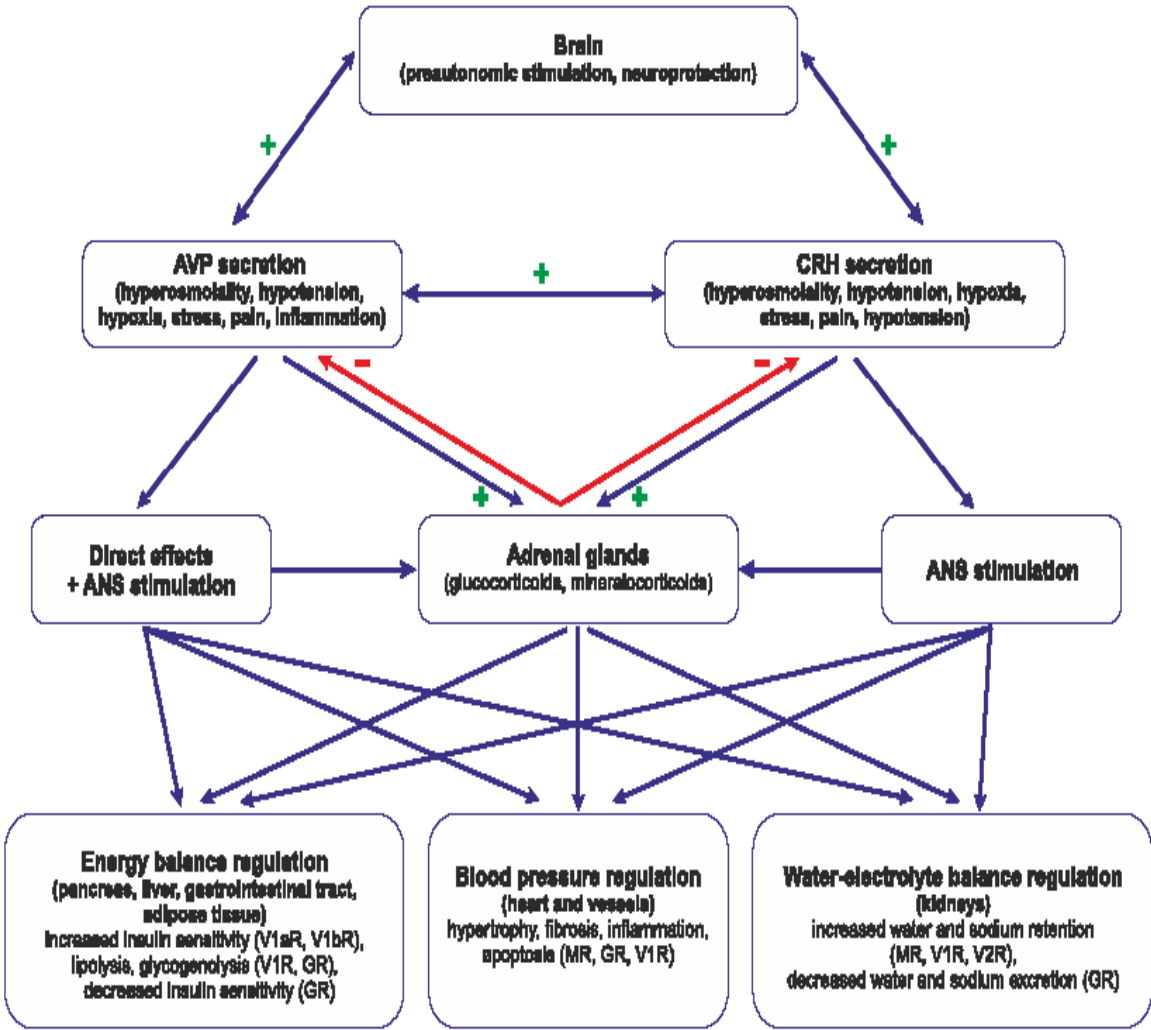


Figure 4. Stimulatory and inhibitory interactions between vasopressin and hormones secreted by the hypothalamo-pituitary-adrenal system that play essential role in the regulation of energy balance, water-electrolyte balance and blood pressure. ANS – autonomic nervous system, AVP – arginine vasopressin, GR – glucocorticoid receptor, MR – mineralocorticoids receptor, V1R, V1aR, V1bR – vasopressin receptors.

The cooperation plays significant role in the regulation of blood circulation, metabolism, water-electrolyte balance and behavioral adaptation to stress challenges. Vasopressin and components of the HPA axis closely interact and can be considered as the functionally united AVP-HPA system. Growing evidence shows that cardiovascular and metabolic diseases as well as inflammation and stress are associated with an inappropriate function of the AVP-HPA system and this question should be taken into consideration when the pharmacological treatment is planned.

7. Conclusions

1. Vasopressin (AVP) and steroid hormones are frequently released together and closely cooperate in the regulation of blood pressure, metabolism, water-electrolyte balance and behavior.

2. Vasopressin interacts with specific components of the hypothalamo-pituitary-adrenal axis in the brain and in several peripheral organs and tissues, including the heart, vessels, kidney and adipose tissue.
3. Appropriate interactions of AVP with the HPA axis is essential for efficient regulation of the water-electrolyte balance, blood pressure, and energy balance, and it is justified to consider vasopressin and the hypothalamo-pituitary axis as the highly coordinated functional AVP-HPA system.
4. Interactions between AVP and HPA are significantly altered in the cardiovascular, respiratory and metabolic diseases and during inflammation and the neurogenic stress.
5. Inappropriate interactions of AVP with steroid hormones may initiate or potentiate cardiovascular complications and metabolic diseases.
6. The interplay of vasopressin and steroid hormones is not yet fully recognized and further studies are needed to determine potentially beneficial or harmful consequences of interference with these factors in treatment of specific pathological states.

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Abbreviations

ACE1: ACE2 – angiotensin converting enzymes, Ach – acetylcholine, ACTH – adrenocorticotrophic hormone, AGT – angiotensinogen, AP – area postrema, AT1R, AT2R – angiotensin receptors, AVP – arginine vasopressin, BDL – bile duct ligation, cAMP – cyclic adenosine monophosphate, CBF – coronary blood flow, CBI – Coactivator Binding Inhibitor, CES – coronary endothelial cell, COVID - 19 – coronavirus disease 2019, CRF – corticotropin releasing factor, CRH – corticotropin-releasing hormone, dDAVP – desmopressin, an analog of AVP, dVNC – dorsal nucleus of vagus nerve, ERK – extracellular signal-regulated kinase, EAT – epicardial adipose tissue, EDR – endothelium dependent relaxation, ET – endothelin, GABA – gamma aminobutyric acid, GLUT – glucose transporter, GRK2 – G protein-coupled receptor kinase 2, HDL – high density lipoprotein, HOMA – homeostatic model assessment, HIF – hypoxia inducible factor, ICV – intracerebroventricular, IL – interleukin, IRAP – insulin regulated aminopeptidase, IRS – insulin receptor substrate, ISI – insulin sensitivity index, JNK – Jun N-terminal kinase, LDL – low density lipoprotein, L-NAME – N(ω)-nitro-L-arginine methyl ester, LV – left ventricle, MAPK – mitogen-activated protein kinase, MasR – MAS receptor for angiotensin-(1-7), MCP-1 – monocyte chemoattractant protein-1, MPTP – 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, mTOR – mammalian target of rapamycin, NADPH – dinicotinamide adenine dinucleotide phosphate, NAT – noradrenergic transporter activity, NcAmb – nucleus ambiguus, NCOAS – nuclear receptor co-activator, NFκB – nuclear factor kappa B, NO – nitric oxide, NTS – nucleus of the solitary tract, OVLT – organum vasculosum of the lamina terminalis, PET – positron emission tomography, PLA2 – phospholipase A2, PLC – phospholipase C, PVN – paraventricular nucleus, RAS – renin angiotensin system, RAAS – renin-angiotensin-aldosterone system, ROS – reactive oxygen species, ROSC – return of spontaneous circulation, RVLM – rostral ventrolateral medulla, SFO – subfornical organ, SHR – spontaneously hypertensive rat, SON – supraoptic nucleus, SNP – single nucleotide polymorphism, SRC – steroid receptor co-activator, TNF-α – tumor necrosis factor alpha, T1DM1 – diabetes mellitus of type 1, T1DM2 – diabetes mellitus of type 2, UCMS – unpredictable chronic mild stress UCP –

uncoupling protein, UT – urea transporter, VSMC – vascular smooth muscle cell, V1aR – vasopressin receptor of type V1a, V1bR – vasopressin receptor of type V1b, V2R – V2 vasopressin receptor of type 2, VS – vasopressin system, WKY – Wistar Kyoto rat, ZDF – Zucker diabetic fat.

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