We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,300
Open access books available

130,000
International authors and editors

155M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Non-Reproductive Effects of Estradiol: Hydromineral Homeostasis Control

Gislaine Almeida-Pereira, Lucila L.K. Elias and José Antunes-Rodrigues

Abstract

The hydromineral homeostasis is fundamental to survival due to maintenance constant the osmotic properties of the plasma and proper tissue perfusion pressure, being maintained primarily through the regulation of the ingestion and urinary excretion of water and electrolytes, mainly sodium. The Renin-Angiotensin System (RAS) plays an essential role in the maintenance of hydromineral homeostasis by eliciting sodium and water intake and by inducing sodium urinary retention through aldosterone release and hemodynamic effect via angiotensin II a key component of the RAS. The hypothalamus-pituitary system also plays a fundamental role in the maintenance of body fluid homeostasis by secreting vasopressin (AVP) and oxytocin (OT) in response to osmotic and non-osmotic, and volemic stimuli. Furthermore, some studies report that besides reproductive function and sexual behavior, ovarian gonadal hormones, mainly 17β-estradiol (E2), modulate other non-reproductive functions such as cardiovascular system, body fluid balance, mood, mental state, memory, and cognition. Estradiol is known to mediate hydromineral homeostasis and blood pressure mainly by attenuating RAS actions. On the other hand, estradiol modulates neurohypophysial hormones secretion in many different ways. In this chapter, we will discuss the main non-reproductive effects of E2 on the control of hydromineral homeostasis, focusing on ingestive behavior and neurohypophyseal hormonal release.

Keywords: angiotensin II, cell signaling, thirst, sodium appetite, vasopressin, oxytocin

1. Introduction

Because sodium is the most abundant cation in the extracellular fluid (ECF) and is an osmotically effective ion, sodium body content is the pivotal determinant of ECF volume. Then, when sodium moves between extracellular and intracellular compartments, water moves together in favor of the osmotic gradient. The osmolality and volume of body fluids are maintained, respectively, through the regulation of the ingestion (gain) and urinary excretion (loss) of water and electrolytes, mainly sodium (for review see [1]). The constancy of the sodium concentration and the osmolality of extracellular body fluid are essential to hydromineral homeostasis

and are therefore fundamental to survival since is very important for proper tissue perfusion pressure and osmotic gradient across the cellular membrane [1].

1.1 Renin-Angiotensin System role on the hydromineral homeostasis

The Renin-Angiotensin System (RAS) plays an essential role in the maintenance of the hydromineral homeostasis by eliciting sodium and water intake and by inducing sodium urinary retention through aldosterone release and hemodynamic effect via angiotensin II a key component of the RAS [2, 3]. The octapeptide hormone angiotensin II (ANGII) induces its effects on body fluids control mainly by acting on its angiotensinergic receptor type 1 (AT1) [4, 5]. The AT1 receptor is a member of the G-protein (heterotrimeric guanine nucleotide-binding protein)-coupled receptor (GPCR) superfamily of integral membrane proteins and is coupled to the Gq. Then, its stimulation leads to the activation of phospholipase C, protein kinase C (PKC), and members of the mitogen-activated protein kinase family (MAPK) as extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38 MAPK and c-Jun N-terminal Kinase (JNK) (for review see [6]). Hines et al. [7] showed that the activation of MAPKs, mediated by AT1, can be PKC dependent or independent according to the activated conformations that the receptor may adopt. Recently, some studies have postulated that these intracellular signaling pathways from the AT1 receptor are involved in different ingestive behavioral responses. In this context, ANGII-induced sodium intake requires the PKC-independent ERK1/2 signaling pathway while water intake requires PKC, JNK, and the mechanistic target of the rapamycin complex 1 (mTORC1) signaling pathways [8–10].

ANGII induces rapid and prominent water and sodium intake when injected centrally even in normohydration animals, as well in response to hypovolemic and hyponatremic stimuli [3]. In the brain, peripheral and central ANGII induces sodium and water intake by binding to AT1 in important forebrain structures involved in the generation of fluid intakes, such as the organum vasculosum of the lamina terminalis (OVLT), the median preoptic nucleus (MnPO), and the subfornical organ (SFO) [11, 12]. The SFO is a key sensory circumventricular organ (CVO) involved in the control of body fluids homeostasis, that receives, integrates, and responds to both blood-borne and central nervous system (CNS) signals [5]. The CVOs are specialized structures of CNS, comprising the SFO, area postrema, OVLT, median eminence, and neurohypophysis, which lack the normal blood–brain barrier and thus provide essential communication between the circulation and the CNS [13]. The increase in the circulating and central ANGII levels enhances the neural activity of the SFO, which sends axonal projections to the anteroventral third ventricle region (AV3V), particularly the OVLT and MnPO ventral, and to the hypothalamus as the supraoptic nucleus (SON), and the paraventricular nucleus (PVN) (for review see [5]).

1.2 Hypothamalo-neurohypophysial system role on the hydromineral homeostasis

Magnocellular neurosecretory neurons of the PVN and the SON synthesize vasopressin (AVP) and oxytocin (OT) which are released into the circulation from the neurohypophysis [14]. OT, beyond its classic effects on uterine contraction and myoepithelial cells of the breast alveoli, participates in body fluid control by eliciting natriuresis and sodium appetite inhibition [15–17]. The antidiuretic action of AVP is the main physiological effect of this hormone on body fluid control, exerting an important role in osmolality urinary regulation. The hypothalamo-neurohypophysial system plays a fundamental role in the maintenance of hydromineral

homeostasis by secreting AVP and OT in response to osmotic and non-osmotic, and volemic stimuli (for review see [11]). Furthermore, in response to AT1 receptor activation, SFO efferent angiotensinergic projections increase the excitability of vasopressinergic and oxytocinergic neurons in the PVN and SON, leading to AVP and OT secretion [18]. ANGII also can directly increase AVP and OT secretion by acting on its AT1 receptor expressed in the PVN [19]. Concerning the ANGII signaling pathway in neurohypophysial secretion, Felgendreger et al. [20] showed that the ERK1/2 activation induced by endogenous ANGII is not involved in AVP and OT secretion in male rats. However, PKC involvement was not analyzed in this study.

1.3 Interaction of body fluid balance with blood pressure control

The balance of body fluid involves a close correlation with blood pressure control, and thus, disturbances in one of these imply adjustments in the other. The proper maintenance of cardiovascular functions, such as peripheral vascular tone, cardiac activity, and, consequently, blood pressure involves orchestrated activities of the sympathetic and parasympathetic nervous system. The sympathetic activity also exerts an important control renal function in the regulation of plasma volume and osmolality, which influence cardiovascular function [11]. Moreover, some of the key brain regions that are involved in the control of hydromineral homeostasis also promote adjustments in the neuroendocrine and autonomic mechanisms of blood pressure control. For example, the peripheral portion of the SFO sends projections to areas important for fluid balance (magnocellular neurosecretory neurons in the PVN and SON) while the core projects to areas involved in blood pressure control (parvocellular presympathetic neurons in the PVN) [5]. Thus, during disturbances of hydromineral homeostasis that lead to increased peripheral and central ANGII results in activation of neurosecretory and presympathetic neurons in the PVN, via afferent projections from the SFO, inducing an increased systemic AVP release and renal sympathetic outflow which act together to restore hydromineral balance [11]. AVP from neurosecretory neuronal populations also modulates sympathetic outflow and consequently blood pressure by increasing the activity of the presympathetic neurons within the PVN that project to the rostral ventrolateral medulla, a region responsible for the sympathetic system control on the cardiovascular function [21]. In addition, both circulating ANGII and AVP modulate blood pressure through its effects on peripheral vascular tone, inducing potent vasoconstriction and consequently increased total peripheral resistance [6, 11].

Taken together, SFO and hypothalamus, particularly PVN, play an important role in the generation of integrative homeostatic responses through orchestrated activities of neuroendocrine and autonomic networks [5, 11, 22]. An imbalanced interaction among these circuits results in maladaptive responses that can lead to an increased risk of developing cardiovascular disease, such as hypertension [23].

1.4 Estradiol regulation of the hydromineral homeostasis

It is well known that besides reproductive function and sexual behavior, ovarian gonadal hormones, mainly 17β-estradiol (E2), modulate other non-reproductive functions such as cardiovascular function, body fluid balance, feeding, sleep cycles, temperature regulation, mood, mental state, memory, and cognition [3, 24–30]. Nevertheless, in this chapter, we will discuss the main non-reproductive effects of estradiol on the control of hydromineral homeostasis, focusing on ingestive behavior and neurohypophyseal hormonal release.

Mounting evidence reports changes in the hydromineral balance associated with the different phases of the reproductive cycle, gestation period, and reproductive

senescence [3, 31, 32]. Receptor for estrogens (ER) is expressed in several tissues that play pivotal roles in hydromineral homeostasis, comprising the kidney, adrenal gland, blood vessels, and brain structures such as lamina terminalis (i.e., OVLT, MnPO, and SFO), and hypothalamus (PVN and SON) (for review see [33]). ER expression in the tissues that are involved in body fluid control supports the hypothesis that estrogens modulate hydromineral homeostasis control. Thus, the study of the influence of E2 on hydromineral homeostasis has been widely appreciated in recent decades, although the precise mechanism of its control is not always in agreement.

1.5 Estrogen receptor signaling

Upon entering the cell, due to their lipophilic character, estrogens bind to their classical intranuclear receptors, which are classified as ER type alpha (ERα) and beta (ERβ), and mediate the regulation of genes and transcription factors, comprising their classic genomic signaling pathway. However, several studies have shown that estrogens can also trigger non-genomic events by binding plasmatic membrane-associated ER (mER), inducing rapid effects [34, 35]. In addition to other proteins, ER stimulation activates members of the MAPK family, such as ERK1/2, JNK, and p38 MAPK [30, 36, 37] as well increases PKC and PKA activities [38].

Importantly, most evidence supports that ERα and ERβ are trafficked to the membrane and also activated membrane estradiol cell signaling. Moreover, there are estrogen membrane-binding proteins that mediate estradiol non-genomic signaling, such as G protein-coupled estrogen receptor (GPER/GPR30), a putative receptor (ER-X), and splice variants of ERα and/or ERβ receptors (for review see [35]). However, the role of these mERs in estradiol signaling and effects remain to be better characterized.

2. Estradiol effects on the fluid intake

Thirst and sodium appetite and the water and sodium intake resulting comprise motivated behaviors involved in the regulation of the hydromineral and cardiovascular homeostasis [3]. A number of epidemiological, clinical, and genetic studies in humans and animals have been showing a link between chronically high salt consumption and the development of hypertension (for review see [24]). Although the involved mechanisms are not fully understood, it is known that occurs increased in the sympathetic and RAS activities, besides be associated with a reduced ability of the kidney to excrete large amounts of salt [23, 24]. Nevertheless, women during their reproductive period have a lower incidence of hypertension than age-matched men [39, 40]. On the other hand, women and females tend to have salt sensitivity and increased blood pressure at postmenopausal or reproductive senescence, suggesting sex differences in body fluid balance and blood pressure regulation [3, 24]. In fact, E2 is known to mediate hydromineral homeostasis and blood pressure mainly by attenuating RAS activity (**Figure 1**). E2 replacement therapy decreases ANGII-induced water and sodium intake [3, 9, 41]; blood pressure increased induced by ANGII and development of hypertension in spontaneously hypertensive rats (for review see [40, 42]); angiotensin-converting enzyme (ACE) and renin activities [43–45]; AT1 mRNA expression, ANGII-AT1 binding, and ANGII-induced Fos immunoreactivity in the OVLT and SFO [28, 46–48]. Moreover, women during reproductive period have lower (pro)renin and renin plasma levels than men [49]. In rats, females at proestrus and estrus respond less to RAS activation and ANGII administration than at other stages of the cycle [3, 50].

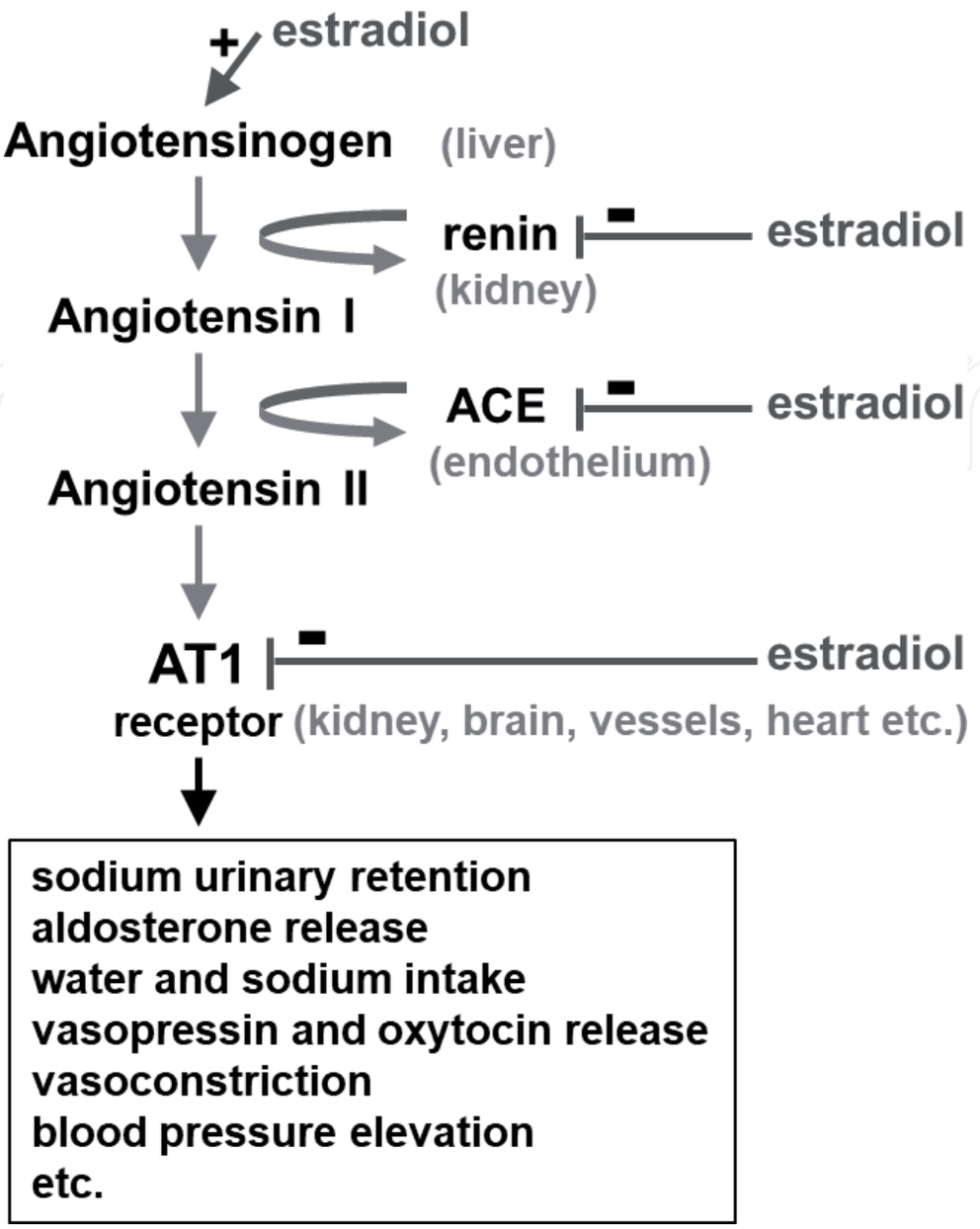

Figure 1.
Schematic summary displays the cascade leading to peripheral ANGII formation and subsequent AT1 receptor activation and the E2 influence on RAS components. Importantly, all these RAS components are also expressed within the brain, leading to central ANGII formation [19].

Although E2 and progesterone have complementary actions in reproductive function, regarding RAS, studies have shown that progesterone has an opposite effect of E2 [43, 51] and is not involved in water regulation in response to ANGII [52].

2.1 Interaction between E2 and ANGII signaling on the fluid intake

Interestingly, in ovariectomized (OVX) rats and during their period of most active, i.e., at night, both water and sodium intakes induced by ANGII require p38 MAPK, JNK, and PKC signaling pathways. ANGII-induced sodium intake also requires ERK1/2 signaling pathway PKC-independent in female [9, 41]. These observations corroborate with Coble et al. [53], which also showed that PKC is involved in both ANGII-induced water and sodium intake in the SFO in male mice. However, Daniels et al. [8] showed that PKC signaling is exclusively involved in ANGII-induced water intake in male rats. Thus, these divergent results suggest a

sexually dimorphic aspect to the AT1 signaling pathway involved in fluid intake induced by ANGII. Indeed, several studies report that the RAS is differentially regulated in males and females [3, 39, 40, 42].

In the brain, ERα is extensively distributed in the neurons of the nuclei of the basal forebrain, such as lamina terminalis. SFO neurons have been shown to express both AT1 and ERα [5, 33]. Evidence from our group showed that E2 impairs ANGII signaling [9, 41, 54] besides decreased AT1 mRNA expression in the SFO [28]. For example, E2 attenuates JNK phosphorylation as well as prevents p38 MAPK phosphorylation induced by ANGII in the lamina terminalis. Moreover, E2 attenuates ANGII-induced ERK1/2 phosphorylation within the SFO. These mechanisms can explain, at least in part, the E2 inhibitory effect on the fluid intake induced by ANGII.

An important feature of GPCRs is that they are rapidly phosphorylated by specific GPCR kinases (GRKs) in their serine and threonine residues within the intracellular loop and carboxyl-terminal tail domains. GRK family members selectively phosphorylate agonist activated GPCRs, promoting the binding with cytosolic cofactor proteins termed arrestins, which uncouple GPCRs from G proteins, interrupting the signaling pathway. This process is referred to as desensitization, which occurs within seconds to minutes (for review see [55, 56]). Nevertheless, it is currently known that arrestins can also act as scaffolds to recruit signaling molecules, such as ERK1/2 and JNK, to increase the repertoire of receptor responses. When β-arrestin binds to the AT1 receptor that is phosphorylated by GRK5 or GRK6, it functions as an intracellular signaling adapter leading to robust ERK1/2 activation [57, 58]. In this context, evidence from our group showed that E2 reduced the expression of GRK5 in the lamina terminalis [54]. This observation suggests that E2 may also impair the ANGII signaling pathway by decreasing the activation of ERK1/2 via negative regulation of the GRK5, which can be relevant to the inhibitory effect of E2 on sodium intake induced by ANGII.

Furthermore, Almeida-Pereira et al. [9] showed that the inhibitory effect of E2 on ANGII-induced water and sodium intake requires the ERK1/2 and JNK signaling pathways. Because these inhibitory effects of E2 were quickly reversed by the central inhibition of ERK1/2 and JNK activities, suggesting that there is the involvement of a non-genomic effect of ER agonism. E2 replacement therapy also induces ERK1/2 and JNK phosphorylation in the lamina terminalis [9], and these proteins are involved in the AT1 receptor desensitization process [59, 60]. These observations point to the idea that ERK1/2 and JNK activation from E2 signaling may contribute to the AT1 receptor desensitization process in the lamina terminalis.

Regarding PKC signaling, central PKC inhibition maintains the inhibitory effect of E2 on ANGII-induced fluid intake, and when analyzing PKC activation, E2 induced an increase in PKC (specifically alpha isoform) translocation to the plasmatic membrane in the lamina terminalis structures. Thus, perhaps PKC is not involved in the inhibitory effect of E2 on fluid intake induced by ANGII or E2 may change other protein activation from the sequence of PKC signaling cascade. Indeed, E2 prevents p38 MAPK phosphorylation induced by ANGII and does not activate p38 MAPK in the lamina terminalis [41]. In addition, as already described, E2 attenuates ERK1/2 and JNK phosphorylation in response to ANGII. Lastly, besides GRK, it is known that PKC also phosphorylates the AT1 receptor, exposed or not to agonists, inducing its desensitization [56]. Taken together, these findings lead to the hypothesis that E2 can modulate AT1 desensitization by PKC activation in the lamina terminals. A summary of all these signaling interactions is provided in **Figure 2**.

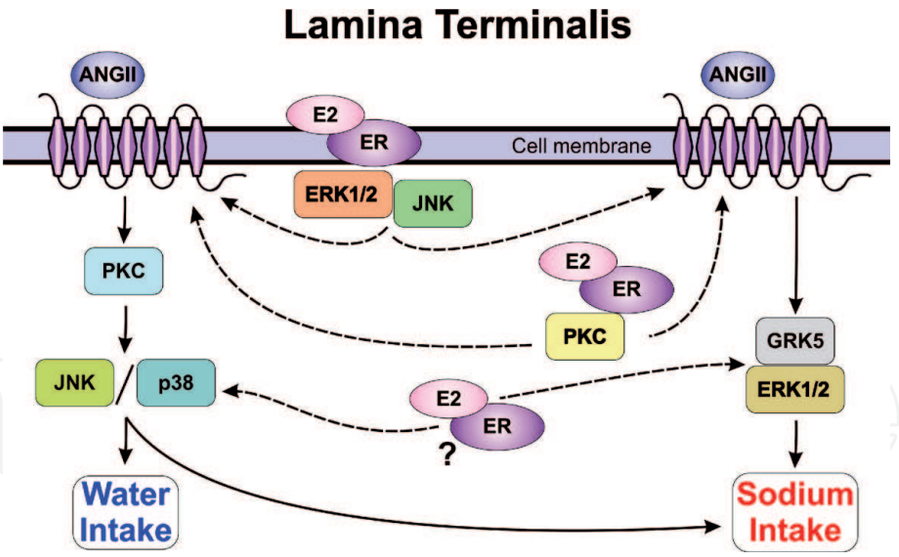

Figure 2.
Schematic summary of the proposed interaction between E2 and ANGII signaling within lamina terminalis structures involved in water and sodium intake. E2 impairs MAPKs phosphorylation in response to ANGII by inducing AT1 desensitization, reduced GRK5 expression, and (or) phosphatase activation (not identified), which leads to ANGII-induced fluid intake reduction. A possible explanation for the E2-induced AT1 desensitization is through ER-mediated ERK1/2 and (or) JNK signaling. Another is through PKC activation mediated by ER inducing AT1 phosphorylation and, consequently, its desensitization. Legend: continuous arrow indicates stimulation and dashed arrow indicates inhibition.

3. Estradiol effects on the neurohypophysial hormone release

It is widely known that OT plays a pivotal role in parturition and lactation by inducing contractions of the uterus and myoepithelial cells of the breast alveoli. In addition, OT participates in the hydromineral balance as a regulator of blood volume by eliciting natriuresis and sodium appetite inhibition [15–17]; and participates in the blood pressure control through its vascular and cardiac relaxation effects [61, 62]. In the central nervous system, OT acts as a neurotransmitter involved in sex and maternal behavior (for review see [63]).

The plasma hyperosmolality is the major stimulus for AVP secretion following by hypotension or decreased blood volume [64]. Thus, through its main antidiuretic effect, AVP plays a fundamental role in hydromineral homeostasis as a regulator of plasma osmolality [11]. Regarding blood pressure control, as described previously, AVP increases sympathetic outflow and peripheral vascular tone by eliciting vasoconstriction and increase consequently the blood pressure [11, 21].

In situ hybridization studies reported a wide distribution of mRNA expression for ERβ in the brain of rats, including in the neurons of SON and the parvo and magnocellular divisions of PVN [65, 66]. Hrabovszky et al. [67] showed that OT and AVP neurons from PVN and SON co-express mRNA for ERβ. These findings provide a neuroendocrine basis for E2 influence on the hypothalamo-neurohypophysial system by acting directly on the PVN and SON neurons. Importantly, E2 can also regulate neurohypophysial hormone release through ERα activation present in the lamina terminal structures and via connections with PVN and SON [33]. In this context, E2 is known to modulate OT release positively, besides increases mRNA expression for OT in the PVN and SON [68–70]. Conversely, the influence of E2 on AVP secretion is complex with controversial data in the literature. Nevertheless, in general, studies point out that there is a positive correlation between AVP secretion and E2 plasma levels associated with body water retention. Moreover, E2 decreases the osmotic threshold for AVP stimulation during dehydration without affect renal

free water clearance, suggesting that E2 may alter renal sensitivity to AVP or even interfere with AVP action in the kidney [71–73].

3.1 Interaction between E2 and ANGII signaling on the OT and AVP secretion

A decrease in blood volume and increased renal sympathetic outflow stimulate renin release from the kidney, which results in increased circulating levels of ANGII [3, 11]. Furthermore, during hypovolemia and hypotension, AVP secretion is stimulated mainly by neural (from cardiac baroreceptors and afferent inputs from the brainstem that project to the SON and PVN) and humoral (i.e., ANGII) signals. In dehydration and hyperosmolality conditions, both AVP and OT secretion are stimulated by an osmoregulatory circuit comprising osmoreceptors activation and axonal projections from the basal forebrain to the PVN and SON besides the intrinsic osmosensitivity of magnocellular neurons of the PVN and SON [11, 64]. Thus, hypovolemia (from hemorrhage or dehydration) and hyperosmolality (from dehydration) stimulate RAS activation as well as AVP and OT secretion.

Evidence from our group provides interesting insights that neurohypophysial secretion in response to ANGII involves distinct signal transduction pathways in OVX rats. We reported for the first time that PKC/p38 MAPK signaling is involved in ANGII-induced OT release while AVP release requires ERK1/2 and p38 MAPK signaling PKC-independent [9, 41]. However, Felgendreger et al. [20] showed that the ERK1/2 activation induced by endogenous ANGII is not involved in AVP secretion in male rats. These divergent results suggest a sexually dimorphic aspect to the AT1 signaling pathway involved in ANGII-induced AVP secretion. As already described, several studies reported that the RAS is differentially regulated in males and females, which can be attributed to differences in gonadal and steroid profiles [3, 39, 40, 42].

Concerning E2 modulation on ANGII-induced AVP and OT release, it was observed that E2 inhibits AVP and OT secretion in response to ANGII by impairing ERK1/2 and p38 MAPK phosphorylation, respectively, in the PVN and SON [9, 41]. MAPK proteins are inactivated by phosphatases, such as mitogen-activated protein kinase phosphatases (MKPs). MPKs are dual-specificity protein phosphatases (also known as DUSPs) that dephosphorylate both tyrosine and threonine residues on MAPK members [74]. MAPK phosphatase 1 (MKP-1) was the first of the MKPs to be characterized and is known for dephosphorylating all three major classes of MAPK (ERK, p38 MAPK, and JNK) being expressed in the brain besides many others tissues [75]. MKP-1 is under the positive regulation of E2 in the PVN and SON and thereby can participate in the inhibitory effect of E2 by eliciting ERK1/2 and p38 MAPK dephosphorylation [9]. In addition, it was hypothesized that E2 inhibits ANGII-induced AVP release via PKC-mediated MKP-1 induction and consequent ERK1/2 dephosphorylation, involving E2 non-genomic signaling [54]. A summary is provided in **Figure 3**.

Importantly, ANGII can also stimulate AVP and OT release by acting in the lamina terminalis structures which send angiotensinergic projections to magnocellular neurons of the PVN and SON [5, 13]. Thus, E2 can indirectly modulate AVP and OT release induced by ANGII via afferent inputs from the basal forebrain that project to the SON and PVN. Nevertheless, as E2 increases MKP-1 specifically in the PVN and SON and not in lamina terminalis structures, it is suggested that E2 plays an important direct modulation on AVP and OT release induced by ANGII in hypothalamic nuclei [9, 41]. In the same sense, Vilhena-Franco et al. [76] showed that E2 modulates AVP secretion in response to water deprivation via a direct mechanism mediated by ERβ expressed in the SON and PVN. Additionally, others studies have

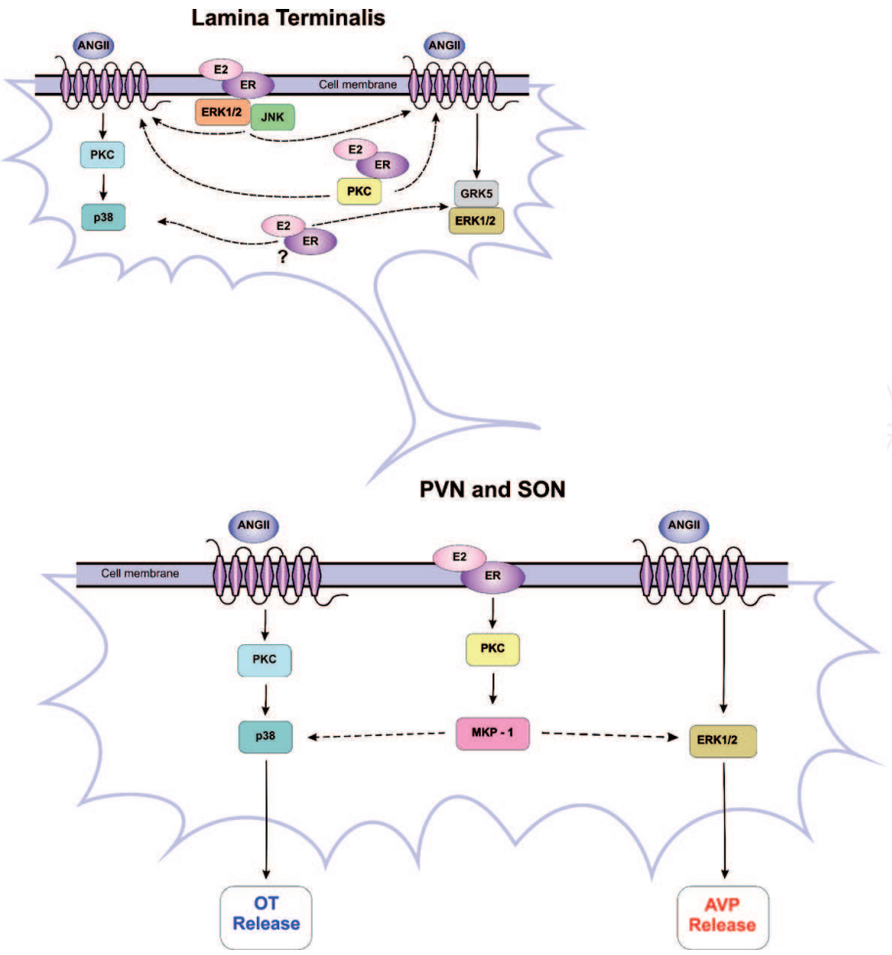

Figure 3.
Schematic summary of the regulatory mechanisms of E2 proposed on ANGII-induced OT and AVP release. Top: E2 can indirectly modulate AVP and OT release induced by ANGII via angiotensinergic afferent inputs from the lamina terminalis structures that project to the SON and PVN. E2 impairs ANGII signaling in neurons of the lamina terminalis leading thereby to the OT and AVP neurons decreased activity in the SON and PVN. Bottom: E2 directly acts in OT and AVP neurons in the PVN and SON, preventing MAPKs phosphorylation through PKC/MKP-1 signaling pathway. Legend: continuous arrow indicates stimulation and dashed arrow indicates inhibition.

demonstrated that E2 modulates OT and AVP release directly via its ERβ or mER (mainly AVP release) in magnocellular neurons of the PVN and SON [77–79].

3.2 Interaction between ovarian hormones, phoenixin and AVP release

A novel peptide, conserved across species, was recently described and named phoenixin (PNX). PNX is produced in the brain and heart binding selectively in the pituitary gland, ovary, and brain. The hypothalamus was identified to produce the most PNX of all tissues examined as well as presented the highest binding of labeled PNX [80]. PNX has been implicated to play an important role in the hypothalamic–pituitary-gonadal axis control by increasing the gonadal release hormone (GnRH) expression and its receptor in the hypothalamus besides increasing luteinizing hormone (LH) release [80, 81]. Using a deductive ligand-receptor matching strategy (U.S. Patent #9, 146, 240, B2), the orphaned G protein-coupled receptor (GPR)173 was identified to be a candidate PNX receptor [82].

The novel reproductive neuropeptide PNX and its receptor, GPR173, were also identified in magnocellular neurons of the PVN and SON, suggesting the participation of PNX on the hypothalamo-neurohypophysial system control and hence of the hydromineral homeostasis. [80, 82]. In fact, Gasparini et al. [83] demonstrated

that PNX induces AVP release through its candidate receptor, GPR173, besides depolarizes magnocellular neurons of the PVN. Interestingly, PNX does not modulate OT release. Despite there are no differences between males and females on PNX-induced AVP release, a potential estrogen response element (ERE) upstream of PNX was identified, suggesting that ovarian hormones, especially E2, can modulate PNX [80, 83]. Consistent with this idea, ovarian failure induced by OVX induces downregulation of PNX compared with intact females in the hypothalamus [84].

Circulating levels of ovarian steroids progesterone, and, mainly 17β-estradiol, increase throughout the pregnancy, reaching maximum values at the end of pregnancy in women [85, 86]. On the other hand, in rats, peripheral plasma levels of estradiol increase across pregnancy with a concomitant decrease in progesterone [87]. However, in both humans and animals, it is observed changes in hydromineral homeostasis over the pregnancy, such as blood volume expansion and low osmolality associated with a reduced threshold for hyperosmotic stimulation of AVP secretion. Thus, AVP secretion is paradoxically elevated during this hypervolemic and hyponatremic state of the pregnancy [32, 88] although is important to maintain water homeostasis offsetting AVP that is metabolized by vasopressinase in humans [89]. A dysfunction in the metabolism of vasopressinase and AVP can predispose women to develop cardiovascular diseases associated with hydromineral imbalance, as pregnancy-induced hypertension, that occurs after the second trimester of pregnancy [89, 90].

In this context, our group demonstrated upregulation of GPR173 during late post-puberty in the PVN, and importantly, upregulation during the last third of pregnancy in the hypothalamus. Moreover, it was observed an increase in the hypothalamic levels of PNX and AVP across pregnancy compared with levels present during diestrus with a positive correlation between both peptides [84]. Thus, these results suggest an important role of PNX on AVP release during late pregnancy, which can help to provide potential pharmacological targets for preventing the development of cardiovascular diseases across pregnancy.

4. Conclusions

Estradiol replacement therapy initiated at the time of or prior to menopause is usually employed for decreasing the risk of cardiovascular and neurodegenerative diseases [91–93]. Nowadays, the high composition of salt in the contemporary diet constitutes an important public health concern, since uncontrolled sodium consumption increases the risk of hypertension [24], particularly in women in later menopause, who have a greater risk of developing cardiovascular disease [3, 24]. The increased central and peripheral RAS activity is involved in the pathophysiology of hypertension. Given the wide complexity of the crosstalk signaling pathways, cellular and molecular studies are important to better elucidate the mechanisms of the interaction between E2 and ANGII signaling as well as mapping out the potential benefits of E2 replacement and its action on the central nervous system. In this context, advanced evidence has been contributed to the further understanding of E2 and ANGII interaction in the hydromineral homeostasis, which can reveal potential pharmacological targets to prevent cardiovascular diseases, with uncontrolled salt consumption as a predisposing factor, during female reproductive senescence. Taken together, E2 impairs ANGII signaling besides induces the downregulation of AT1 receptor. E2 attenuates MAPKs phosphorylation involved in ANGII physiological actions in the lamina terminalis structures and hypothalamic nuclei, namely, PVN and SON.

Acknowledgements

This study was supported by the Sao Paulo Research Foundation, Brazil (FAPESP, grant #2012/04620-0, #2014/25005-8, #2017/22140-0 from Gislaine Almeida-Pereira, and #2013/09799-1 from José Antunes-Rodrigues), Brazilian Council for Scientific and Technological Development (CNPq) and the Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES). The authors thank Santo Oliani Junior for his help in drawing the figures.

Author details

Gislaine Almeida-Pereira*, Lucila L.K. Elias and José Antunes-Rodrigues
Department of Physiology, Medical School of Ribeirao Preto of Sao Paulo University, Ribeirao Preto, Brazil

*Address all correspondence to: g.almeidapereira@gmail.com

References

[1] Cannon WB. 1929. Organization for physiological homeostasis. Physiology Review, 4(3):399-431.

[2] Hollenberg NK. 1984. The renin-angiotensin system and sodium homeostasis. Journal of Cardiovascular Pharmacology, 6: S176–S183.

[3] Fitzsimons JT. 1998. Angiotensin, thirst, and sodium appetite. Physiological Reviews, 78: 583-686.

[4] Beresford MJ and Fitzsimons JT. 1992. Intracerebroventricular angiotensin II-induced thirst and sodium appetite in rat are blocked by the AT1 receptor antagonist, losartan (DuP 753), but not by the AT2 antagonist, CGP 42112B. Experimental Physiology, 77: 761-764.

[5] Coble JP, Grobe JL, Johnson AK, Sigmund CD. 2015. Mechanisms of brain renin angiotensin system-induced drinking and blood pressure: importance of the subfornical organ. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology, 308: R238–R249.

[6] Mehta PK and Griendling KK. 2007. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. American Journal of Physiology: Cell Physiology, 292: C82–C97.

[7] Hines J, Fluharty SJ, Yee DK. 2003. Structural determinants for the activation mechanism of the angiotensin II type 1 receptor differ for phosphoinositide hydrolysis and mitogen-activated protein kinase pathways. Biochemical Pharmacology, 66: 251-262.

[8] Daniels D, Yee DK, Fluharty SJ. 2007. Angiotensin II receptor signalling. Experimental Physiology, 92: 523-527.

[9] Almeida-Pereira G, Coletti R, Mecawi AS, Reis LC, Elias LLK, Antunes-Rodrigues J. 2016. Estradiol and angiotensin II crosstalk in hydromineral balance: role of the ERK1/2 and JNK signaling pathways. Neuroscience, 322: 525-538.

[10] Muta K, Morgan DA, Grobe JL, Sigmund CD, Rahmouni K. 2016. mTORC1 signaling contributes to drinking but not blood pressure responses to brain angiotensin II. Endocrinology, 157: 3140-3148.

[11] Antunes-Rodrigues J, de Castro M, Elias LLK, Valença MM, McCann SM. 2004. Neuroendocrine control of body fluid metabolism. Physiological Reviews, 84: 169-208.

[12] Morris MJ, Wilson WL, Starbuck EM, Fitts DA. 2002. Forebrain circumventricular organs mediate salt appetite induced by intravenous angiotensin II in rats. Brain Research, 949(1-2):42-50.

[13] Ferguson AV and Bains JS. 1996. Electrophysiology of the circumventricular organs. Frontiers in Neuroendocrinology, 17: 440-475.

[14] Leng G, Brown CH, Russell JA. 1999. Physiological pathways regulating the activity of magnocellular neurosecretory cells. Progress in Neurobiology, 57:625-655.

[15] Stoeckel ME, Freund-Mercier MS, Falacios JM, Richard P, Porte A. 1987. Autoradiographic localization of binding sites for oxytocin and vasopressin in the rat kidney. Journal of Endocrinology, 113: 179-182.

[16] Tribollet E, Barberis C, Jard S, Dubois-Dauphin M, Dreifuss JJ. 1988. Localization and pharmacological characterization of high affinity binding sites for vasopressin and oxytocin

in the rat brain by light microscopic autoradiography. Brain Research, 442: 105-118.

[17] Amico JA, Morris M, Vollmer RR. 2001. Mice deficient in oxytocin manifest increased saline consumption following overnight fluid deprivation. American Journal Physiology, 281:1368-73.

[18] Ferguson AV and Renaud LP. 1986. Systemic angiotensin acts at subfornical organ to facilitate activity of neurohypophysial neurons. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology, 251: R712–R717.

[19] Lenkei Z, Palkovits M, Corvol P, Llorens-Cortes C. 1997. Expression of angiotensin type-1 (AT1) and type-2 (AT2) receptor mRNAs in the adult rat brain: a functional neuroanatomical review. Frontiers in Neuroendocrinology, 18: 383-439.

[20] Felgendreger LA, Fluharty SJ, Yee DK, Flanagan-Cato LM. 2013. Endogenous angiotensin II-induced p44/42 mitogen-activated protein kinase activation mediates sodium appetite but not thirst or neurohypophysial secretion in male rats. Journal of Neuroendocrinology, 25 (2):97-106.

[21] Son SJ, Filosa JA, Potapenko ES, Biancardi VC, Zheng H, Patel KP, Tobin VA, Ludwig M, Stern JE. 2013. Dendritic peptide release mediates interpopulation crosstalk between neurosecretory and preautonomic networks. Neuron, 78(6):1036-1049.

[22] Swanson LW and Sawchenko PE. 1980. Paraventricular Nucleus: A site for the Integration of Neuroendocrine and Autonomic Mechanisms. Progress in Neuroendocrinology, 31: 410-417.

[23] Toney GM and Stocker SD. 2010. Hyperosmotic activation of CNS sympathetic drive: implications for cardiovascular disease. Journal Physiology, 588.18: 3375-3384.

[24] Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA. 2005. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiological Reviews, 85: 679-715.

[25] Fink G, Sumner B, Rosie R, Wilson H, McQueen J. 1999. Androgen actions on central serotonin neurotransmission: relevance for mood, mental state and memory. Behavioural Brain Research, 105(1): 53-68.

[26] Panay N and Studd JW. 1998. The psychotherapeutic effects of estrogens. Gynecology Endocrinology, 12.5: 353-365.

[27] Hay M. 2016. Sex, the brain and hypertension: brain oestrogen receptors and high blood pressure risk factors. Clinical Science (Lond), 130(1): 9-18.

[28] Almeida-Pereira G, Rorato R, Reis LC, Elias LLK, Antunes-Rodrigues J. 2013. The role of estradiol in adrenal insufficiency and its interaction with corticosterone on hydromineral balance. Hormones and Behavior, 64: 847-855.

[29] Almeida-Pereira, G. 2018. Non-Reproductive Effects of Estradiol: Brain Behavior. EC Psychology and Psychiatry, 7.5: 261-262.

[30] Micevych PE and Kelly MJ. 2012. Membrane estrogen receptor regulation of hypothalamic function. Neuroendocrinology, 96: 103-110.

[31] Antunes-Rodrigues J and Covian MR. 1963. Hypothalamic control of sodium chloride and water intake. Acta Physiology Latin American, 13: 94-100.

[32] Brunton PJ, Arunachalam S, Russell JA. 2008. Control of

neurohypophysial hormone secretion, blood osmolality and volume in pregnancy. Journal Physiology Pharmacology, 59(8):27-45.

[33] Somponpun, SJ. 2007. Neuroendocrine Regulation of Fluid and Electrolyte Balance by Ovarian Steroids: Contributions from Central Oestrogen Receptors. Journal of Neuroendocrinology, 19:809-818.

[34] Toran-Allerand CD. 2004. Estrogen and the brain: beyond ER-a and ER-b. Experimental Gerontology, 39:1579-1586.

[35] Micevych P and Dominguez R. 2009. Membrane estradiol signaling in the brain. Front Neuroendocrinol, 30(3):315-327.

[36] Feng W, Webb P, Nguyen P, Liu X, Li J, Karin M, Kushner PJ. 2001. Potentiation of estrogen receptor activation function 1 (AF-1) by Src/JNK through a serine 118-independent pathway. Molecular Endocrinology, 15(1):32-45.

[37] Sétáló Jr. G, Singh, M, Guan, X, Toran-Allerand, CD. 2002. Cellular localization of estradiol-induced phospho-ERK1/2 in mouse cerebral cortical explants: the roles of heat shock protein 90 (Hsp90) and MEK2. Journal of Neurobiology, 50:1-12.

[38] Qiu, J, Bosch, MA, Tobias, SC, Grandy, DK, Scanlan, TS, Rønnekleiv, OK, Kelly, MJ. 2003. Rapid signaling of estrogen in hypothalamic neurons involves a novel G protein-coupled estrogen receptor that activates protein kinase C. Journal of Neuroscience, 23:9529-9540.

[39] Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. 2008. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. Hypertension, 52:818-827.

[40] Sandberg K and Ji H. 2012. Sex differences in primary hypertension. Biology of Sex Differences, 3: 7.

[41] Almeida-Pereira G, Vilhena-Franco T, Coletti R, Cognuck SQ, Silva HVP, Elias LLK, Antunes-Rodrigues J. 2019. 17β-Estradiol attenuates p38MAPK activity but not PKCα induced by angiotensin II in the brain. Journal of Endocrinology, 240(2):345-360.

[42] Fischer M, Baessler A, Schunkert H. 2002. Renin angiotensin system and gender differences in the cardiovascular system. Cardiovascular Research, 53: 672-677.

[43] Oelkers WKH. 1996. Effects of estrogens and progestogens on the renin-aldosterone system and blood pressure. Steroids, 61:166-171.

[44] Schunkert H, Danser AH, Hense HW, Derkx FH, Kürzinger S, Riegger GA. 1997. Effects of estrogen replacement therapy on the renin-angiotensin system in postmenopausal women. Circulation, 95(1):39-45.

[45] Gallagher PE, Li P, Lenhart JR, Chappell MC, Brosnihan KB. 1999. Estrogen regulation of angiotensin-converting enzyme mRNA. Hypertension, 33:323-328.

[46] Kisley LR, Sakai RR, Fluharty SJ. 1999. Estrogen decreases hypothalamic angiotensin II AT1 receptor binding and mRNA in the female rat. Brain Research, 844: 34-42.

[47] Tanaka J, Miyakubo H, Okumura T, Sakamaki K, Hayashi Y. 2001. Estrogen decreases the responsiveness of subfornical organ neurons projecting to the hypothalamic paraventricular nucleus to angiotensin II in female rats. Neuroscience Letters, 307(3):155-158.

[48] Krause EG, Curtis KS, Stincic TL, Markle JP, Contreras RJ. 2006. Oestrogen and weight loss decrease isoproterenol-induced Fos immunoreactivity and angiotensin type 1 mRNA in the subfornical organ of female rats. Journal of Physiology, 573: 251-262.

[49] Danser AH, Derkx FH, Schalekamp MA, Hense HW, Riegger GA, Schunkert H. 1998. Determinants of interindividual variation of renin and prorenin concentrations: evidence for a sexual dimorphism of (pro)renin levels in humans. Journal of Hypertension, 16(6):853-862.

[50] Findlay AL, Fitzsimons JT, Kucharczyk J. 1979. Dependence of spontaneous and angiotensin-induced drinking in the rat upon the oestrous cycle and ovarian hormones. Journal of Endocrinology, 82(2):215-225.

[51] Nickenig G, Strehlow K, Wassmann S, Bäumer AT, Albory K, Sauer H, Böhm M. 2000. Differential effects of estrogen and progesterone on AT(1) receptor gene expression in vascular smooth muscle cells. Circulation, 102(15):1828-1833.

[52] Kisley LR, Sakai RR, Ma LY, Fluharty SJ. 1999. Ovarian steroid regulation of angiotensin II-induced water intake in the rat. American Journal Physiology, 276(1):R90-R96.

[53] Coble JP, Johnson RF, Cassell MD, Johnson AK, Grobe JL, Sigmund CD. 2014. Activity of protein kinase C-α within the subfornical organ is necessary for fluid intake in response to brain angiotensin. Hypertension, 64: 141-148.

[54] Almeida-Pereira G, Elias LLK, Antunes-Rodrigues J. 2020. SUN-248 Estradiol Changes Angiotensin II-Induced ERK1/2 Phosphorylation by Different Pathways in the Hypothalamus and Lamina Terminalis. Journal of the Endocrine Society, 4. Issue Supplement 1.

[55] Lefkowitz RJ. 1998. G protein-coupled receptors. III. New roles for receptor kinases and beta-arrestins in receptor signaling and desensitization. Journal of Biological Chemistry, 273(30):18677-18680.

[56] Ferguson SS. 2001. Evolving concepts in G protein-coupled receptor endocytosis: the role in receptor desensitization and signaling. Pharmacology Review, 53: 1-24.

[57] Kim J, Ahn S, Ren XR, Whalen EJ, Reiter E, Wei H, Lefkowitz RJ. 2005. Functional antagonism of different G protein-coupled receptor kinases for beta-arrestin-mediated angiotensin II receptor signaling. Proceedings of the National Academy of Sciences U S A, 102(5):1442-1447.

[58] Shenoy SK, Lefkowitz RJ. 2011. β-Arrestin-mediated receptor trafficking and signal transduction. Trends in Pharmacological Sciences, 32(9):521-533.

[59] Wei H, Ahn S, Barnes WG, Lefkowitz RJ. 2004. Stable interaction between beta-arrestin 2 and angiotensin type 1A receptor is required for beta-arrestin 2-mediated activation of extracellular signal-regulated kinases 1 and 2. Journal of Biological Chemistry, 279(46):48255-48261.

[60] Vento PJ and Daniels D. 2012. Mitogen-activated protein kinase is required for the behavioural desensitization that occurs after repeated injections of angiotensin II. Experimental Physiology, 97(12):1305-14.

[61] Jankowski M, Hajjar F, AL Kawas S, Mukaddam-DaherS,HoffmanG,McCann S M, Gutkowska J. 1998. Proceedings of

the National Academy of Sciences USA, 95:14558-14563.

[62] Jankowski M, Wang D, Hajjar F, Mukaddam-Daher S, McCann SM, Gutkowska J. 2000. Oxytocin and its receptors are synthesized in the rat vasculature. Proceedings of the National Academy of Sciences USA, 97(11):6207-6211.

[63] Argiolas A and Gessa GL. 1991. Neuroscience & Biobehavioral Reviews, 15:217-231.

[64] Stricker EM and Sved AF. 2002. Controls of vasopressin secretion and thirst: similarities and dissimilarities in signals. Physiology Behavior, 77(4-5):731-6.

[65] Simerly RB, Chang C, Muramatsu M, Swanson LW. 1990. Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an in situ hybridization study. Journal of Comparative Neurology, 294:76-95.

[66] Shughrue PJ, Lane MV, Merchenthaler I. 1997. Comparative distribution of estrogen receptor-alpha and -beta mRNA in the rat central nervous system. Journal of Comparative Neurology, 388:507-525.

[67] Hrabovszky E, Kallo I, Hajszan T, Shughrue PJ, Merchenthaler I, Liposits Z. 1998. Expression of estrogen receptor-beta messenger ribonucleic acid in oxytocin and vasopressin neurons of the rat supraoptic and paraventricular nuclei. Endocrinology, 139: 2600-2604.

[68] Yamaguchi K, Akaishi T, Negoro H. 1979. Effect of estrogen treatment on plasma oxytocin and vasopressin in ovariectomized rats. Endocrinol Jpn, 26:197-205.

[69] Van Tol HH, Bolwerk EL, Liu B, Burbach JP. 1988. Oxytocin and vasopressin gene expression in the hypothalamo-neurohypophyseal system of the rat during the estrous cycle, pregnancy, and lactation. Endocrinology, 122:945-951.

[70] Nomura M, McKenna E, Korach KS, Pfa. DW, Ogawa S. 2002. Estrogen receptor-beta regulates transcript levels for oxytocin and arginine vasopressin in the hypothalamic paraventricular nucleus of male mice. Molecular Brain Research, 109:84-94.

[71] Forsling ML, Strömberg P, Akerlund M. 1982. Effect of ovarian steroids on vasopressin secretion. Journal of Endocrinology, 95(1):147-151.

[72] Peysner K and Forsling ML. 1990. Effect of ovariectomy and treatment with ovarian steroids on vasopressin release and fluid balance in the rat. Journal of Endocrinology, 124(2):277-284.

[73] Stachenfeld NS. 2008. Sex hormone effects on body fluid regulation. Exercise and Sport Sciences Reviews, 36(3):152-9.

[74] Salojin K and Oravecz T. 2007. Regulation of innate immunity by MAPK dual-specificity phosphatases: knockout models reveal new tricks of old genes. Journal of Leukocyte Biology, 81: 860-869.

[75] Caunt CJ and Keyse SM. 2012. Dual-specificity MAP kinase phosphatases (MKPs): shaping the outcome of MAP kinase signaling. FEBS Journal, 280: 489-504.

[76] Vilhena-Franco T, Mecawi AS, Almeida-Pereira G, Lucio-Oliveira F, Elias LLK, Antunes-Rodrigues J. 2019. Oestradiol acts through its beta receptor to increase vasopressin neuronal activation and secretion induced by dehydration. Journal of Neuroendocrinology, 2019: e12712.

[77] Swenson KL and Sladek CD. 1997. Gonadal steroid modulation of vasopressin secretion in response to osmotic stimulation. Endocrinology, 138: 2089-2097.

[78] Somponpun S and Sladek CD. 2002. Role of estrogen receptor-beta in regulation of vasopressin and oxytocin release in vitro. Endocrinology, 143: 2899-2904.

[79] Somponpun SJ, Holmes MC, Seck JR, Russell JA. 2004. Modulation of oestrogen receptor-b mRNA expression in rat paraventricular and supraoptic nucleus neurones following adrenal steroid manipulation and hyperosmotic stimulation. Journal of Neuroendocrinology, 16: 472-482.

[80] Yosten GL, Lyu RM, Hsueh AJ, Avsian-Kretchmer O, Chang JK, Tullock CW, Dun SL, Dun N, Samson WK. 2013. A novel reproductive peptide, phoenixin. Journal of Neuroendocrinolody, 25(2):206-215.

[81] Treen AK, Luo V, Belsham DD. 2016. Phoenixin Activates Immortalized GnRH and Kisspeptin Neurons Through the Novel Receptor GPR173. Molecular Endocrinology, 30(8):872-888.

[82] Stein LM, Tullock CW, Mathews SK, Garcia-Galiano D, Elias CF, Samson WK, Yosten GL. 2016. Hypothalamic action of phoenixin to control reproductive hormone secretion in females: importance of the orphan G protein-coupled receptor Gpr173. American Journal Physiology Regulatory Integrative Comparative Physiology, 311(3):R489-496.

[83] Gasparini S, Stein LM, Loewen SP, Haddock CJ, Soo J, Ferguson AV, Kolar GR, Yosten GLC and Samson WK. 2018. Novel regulator of vasopressin secretion: phoenixin. American Journal Physiology Regulatory Integrative Comparative Physiology, 314:R623-R628.

[84] Haddock CJ, Almeida-Pereira G, Stein LM, Yosten GLC, Samson WK. 2020. A novel regulator of thirst behavior: phoenixin. American Journal Physiology Regulatory Integrative Comparative Physiology, 318: R1027–R1035.

[85] Dörr HG, Heller A, Versmold HT, Sippell WG, Herrmann M, Bidlingmaier F, Knorr D. 1989. Longitudinal study of progestins, mineralocorticoids, and glucocorticoids throughout human pregnancy. The Journal of Clinical Endocrinology and Metabolism, 68(5):863-868.

[86] Kuijper EA, Ket JC, Caanen MR, Lambalk CB. 2013. Reproductive hormone concentrations in pregnancy and neonates: a systematic review. Reproductive BioMedicine Online, 27(1):33-63. Erratum in: Reprod Biomed Online. 2013 Oct;27(4):448-449.

[87] Wilson L Jr, Stanisc D, Khan-Dawood F, Dawood MY. 1982. Alterations in reproductive tissue prostaglandins E and F, 6-keto-prostaglandin F1 alpha and thromboxane B2 with gestational age in the rat. Biology of Reproduction, 27(5):1207-1215.

[88] Tkachenko O, Shchekochikhin D, Schrier RW. 2014. Hormones and hemodynamics in pregnancy. International Journal of Endocrinology and Metabolism, 12(2):e14098.

[89] Krege JH and Katz VL. 1990. A proposed relationship between vasopressinase altered vasopressin and preeclampsia. Medical Hypotheses, 31(4):283-287.

[90] Cornelius DC. 2014. Copeptin: a new biomarker that is specific for preeclampsia? Hypertension, 64(6):1189-1191.

[91] Bold MLK. 1999. Estrogen, natriuretic peptides and

renin-angiontesin system. Cardiovascular Research, 41(3):524-531.

[92] Bowling M, Oparil S, Hage F, Hilgers R, Xing D. 2012. Sex Hormones and Vascular Function. Chapter 1, Sex Hormones, Raghvendra K. Dubey, IntechOpen. Available from: https://www.intechopen.com/books/sex-hormones/sex-hormones-and-vascular-function.

[93] Arevalo MA, Azcoitia I, Garcia-Segura LM. 2015. The neuroprotective actions of oestradiol and oestrogen receptors. Nature Reviews Neuroscience, 16(1):17-29.