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News and Reviews

Are neuropeptides relevant for the mechanism of action of SSRIs?

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are drugs of first choice in the therapy of moderate to severe depression and anxiety disorders. Their primary mechanism of action is via influence of the serotonergic (5-HT) system, but a growing amount of data provides evidence for other non-monoaminergic players in SSRI effects. It is assumed that neuropeptides, which play a role as neuromodulators in the CNS, are involved in their mechanism of action. In this review we focus on six neuropeptides: corticotropin-releasing factor – CRF, galanin – GAL, oxytocin – OT, vasopressin – AVP, neuropeptide Y – NPY, and orexins – OXs. First, information about their roles in depression and anxiety disorders are presented. Then, findings describing their interactions with the 5-HT system are summarized. These data provide background for analysis of the results of published preclinical and clinical studies related to SSRI effects on the neuropeptide systems. We also report findings showing how modulation of neuropeptide transmission influences behavioral and neurochemical effects of SSRIs. Finally, future research necessary for enriching our knowledge of SSRI mechanisms of action is proposed. Recognition of new molecular targets for antidepressants will have a significant effect on the development of novel therapeutic strategies for mood-related disorders.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are broadly applied drugs. They are the drugs of first choice in treating moderate to severe depression, not only because of therapeutic efficacy but also because of their superior tolerability and safety compared to other antidepressants, such as tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). When used chronically for six to twelve months they reduce risk of relapse. However, they are imperfect drugs as, among patients with depression, given standard doses of SSRIs, a relatively high rate of non-responders have been reported. They also induce side effects, especially in the initial period of therapy. These undesirable effects are more frequent with some drugs, including apathetic recoveries, gastrointestinal disturbances (nausea, vomiting, diarrhea), weight gain, sexual dysfunction, anxiety, restlessness that resembles akathisia, psychomotor retardation, sleep disturbances and metabolic impairments (dysglycemia, dyslipidemia) (Baldessarini, 2006; Reid and Barbui, 2010; Hieronymus et al., 2016; Chávez-Castillo et al., 2018). SSRIs are frequently prescribed for the long-term treatment of anxiety disorders: generalized anxiety disorders, phobias, obsessive-anxiety compulsive disorders, posttraumatic stress disorders and panic disorders (Baldessarini, 2006; Reid and Barbui, 2010; Hieronymus et al., 2016). These comprise the primary anxiety disorders according to the American Psychiatric Association DSM-V (American Psychiatric Association, 2013). Today, depressive and anxiety disorders are considered a critical health problem. The World Health Organization (WHO) has reported a significant increase in the number of people living with depression-related illnesses. It is estimated that 15–25% of people in Western communities may experience at least one episode of major depression (WHO, 2012). As WHO describes, between 1990 and 2013 the number of people suffering from depression/anxiety increased by nearly 50% (from 416 million to 615 million) (WHO, 2016). Epidemiological data indicate that one third of the world's population suffers from anxiety disorders (Bandelow and Michaelis, 2015).

There are six commercially available SSRIs: fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine and sertraline (Baldessarini, 2006). Although they clearly share the same primary mechanism of action, they have no identical secondary pharmacologic characteristics (Sanchez et al., 2014). Their primary mechanism of action is thought to occur via their modulation of monoaminergic, mainly serotoninergic (5-HT), transmission in which somatodendritic 5-HT_{1A} autoreceptors play an essential role in 5-HT self-regulation.

After short-term administration, these drugs act as inhibitors of serotonin transporter (5-HTT, also known as SERT) and induce a modest extracellular increase in 5-HT associated with attenuation of neuronal 5-HT synthesis and release in response to activation of

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somatodendritic 5-HT_{1A} autoreceptors. Eventually, following multiple SSRI administrations, which are required to achieve a therapeutic effect, progressive neuroadaptative changes develop. 5-HT-induced desensitization of raphe 5-HT_{1A} autoreceptors resulted in increased 5-HT release, followed by desensitization of postsynaptic 5-HT receptors (Artigas, 2013). However, several critical arguments were raised against the monoamine theory of depression, revealing its weaknesses (Krishnan and Nestler, 2008), and, consequently, suggesting that the mechanism of action of antidepressants is more complex. In fact, several non-monoaminergic explanations for antidepressive drug effects relating to SSRIs have been proposed. Preclinical and clinical studies have demonstrated anti-inflammatory and anti-neuroinflammatory effects of SSRIs (Kubera et al., 2011; Tynan et al., 2012), pro-neurogenic and neurotrophic properties of SSRIs (Mahar et al., 2014) and an ability of SSRIs to modulate glutamatergic neurotransmission (Freudenberg et al., 2015). Moreover, interconnected roles of 5-HT, neutrophins and the immune system in depression and antidepressant therapy have been shown (Haase and Brown, 2015).

Additionally, this review of the leading hypotheses on the action of SSRIs has been extended to include findings related to the influence of SSRIs on neuropeptides. In the central nervous system (CNS), neuropeptides are the most highly expressed neuromodulators. The relevance of neuropeptide systems to the neurobiology of stress-related mood disorders has been previously summarized in several systematic reviews (Binder and Nemeroff, 2010; Morales-Medina et al., 2010; Catena-Dell'Osso et al., 2013; Kormos and Gaszner, 2013). As substances involved in the mechanisms of resilience and vulnerability to stress (Charney, 2004), neuropeptides are important for the successful development of stress adaptations, which are critical players in anxiety and in depressive illnesses (Leonard and Myint, 2009; Schatzberg and Nemeroff, 2010). Moreover, some neuropeptides have been shown to impact an animal's metabolic status, which in turn greatly influences mood and motivation (Kishi and Elmquist, 2005).

In this review we focus on six neuropeptides: corticotropin-releasing factor (CRF), galanin (GAL), oxytocin (OT), vasopressin (AVP), neuropeptide Y (NPY) and orexins (OXs). First, we summarize the most salient findings from preclinical studies concerning neuropeptide changes in animal models of depressive/anxiety disorders and we present data on neuropeptide changes in patients suffering from these mood disturbances. Then, information regarding interactions between neuropeptides and the 5-HT system is described, followed by the presentation of current data regarding the role of neuropeptides in SSRI effects. Finally, we discuss how particular neuropeptides effect the mechanism of action of SSRIs, as demonstrated by preclinical and clinical studies.

2. The role of neuropeptides in anxiety and depressive disorders

Neuropeptides are short amino-acid chains that differ from classic neuromediators with regard to their biosynthesis, storage and release mechanisms (Reiner, 1991). They are primarily synthesized by neurons, exhibiting a wide spectrum of secretory functions and acting via specific G protein-coupled metabotropic receptors (GPCRs) (Ögren et al., 2010). Here, we present a short characterization of six neuropeptides in order to highlight important findings relating to their contribution to the mechanisms of anxiety and depressive disorders. The most significant data from preclinical studies have been summarized in Table 1.

2.1. Corticotropin-releasing factor (CRF)

Four peptides, CRF, Urocortin-1 (Ucn-1), Urocortin-2 (Ucn-2, also known as stresscopin-related peptide) and Urocortin-3 (Ucn-3, also known as stresscopin), belong to a single neuropeptide family involved in anxiety and stress responses (Spina et al., 1996; Lewis et al., 2001; Reyes et al., 2001). These peptides have differing affinities for two receptor subtypes: CRF_1 and CRF_2 (Eckart et al., 2002). CRF, described by Vale et al. (1981), is a well-known essential mediator in the physiological response to stressors and in the pathophysiology of anxiety and depression (Binder and Nemeroff, 2010). CRF stimulates the hypothalamic-pituitary-adrenal (HPA) axis. This neuropeptide, released from the hypothalamic PVN, stimulates expression of adrenocorticotropic hormone (ACTH) preprohormone mRNA, namely proopiomelanocortin (POMC) mRNA in the pituitary (Arborelius et al., 1999). Other hypothalamic peptides, such as vasopressin (AVP), which are synchronically secreted with CRF, increase ACTH action (Itoi et al., 2004). ACTH then causes stimulation of glucocorticosteroid synthesis and release from adrenal gland. During stress, negative feedback develops, leading to the inhibition of further glucocorticosteroid secretion from the adrenal cortex (Jacobson and Sapolsky, 1991) as a result of glucocorticosteroid receptor (GR) stimulation in the PVN, anterior pituitary and hippocampus (Joëls and de Kloet, 1991). Numerous studies have reported that approximately 50% of depressed patients show HPA axis hyperactivity (Plotsky et al., 1998; Bhagwagar et al., 2005; Keller et al., 2017), evidenced by pathological results of the dexamethasone or dexamethasone/CRF tests. These tests are utilized for estimating adrenal negative feedback loop activity, essential for homeostasis in the HPA axis. Dexamethasone did not suppress cortisol secretion in a majority of the patients that exhibited an acute episode of depression. After CRF administration, depressed patients exhibited lower ACTH levels, but a normal cortisol response, compared to healthy controls (Holsboer et al., 1986). Recently, Kumsta et al. (2018) found evidence that conceptual endophenotype termed CRF-hypoactivity that shares symptoms with atypical depression is associated with MR haplotype 1. They proposed that the mentioned MR haplotype might be served as a biomarker for a syndrome characterized by the reduced HPA axis activity. Physiologically MR are important regulator of the HPA axis because they bind cortisol/corticosterone with higher affinity than GR even under basal conditions.

A study by Dunn and Berridge (1990) provided evidence that CRF_1 receptor mediates the anxiogenic effect of CRF. They showed that various CRF_1 antagonists normalize stress-induced anxiety and have minor effects on spontaneous anxiety behavior. In addition, CRF_1 antagonists were able to abolish the anxiety induced by exogenous CRF. It appears that CRF_1 receptors primarily mediate the activity of CRF neuropeptides under conditions of pronounced stress. The CRF_2 receptor is highly expressed in the posterior BNST (pBNST) and CRF_2 receptor expressing neurons send inhibitory projections to the PVN, medial amygdala and locus coeruleus and therefore inhibits HPA axis activity, autonomic and behavioral response to stress (Henckens et al., 2017). CRF_2 knock-out mice display an anxiogenic phenotype and elevation of CORT level in stress reaction (Coste et al., 2001). It is known, that CRF_2 plays a critical role in stress recovery. In mice optogenetic activation of CRF_2 neurons in the pBNST reduced anxiety expression levels, attenuated neuroendocrine stress response and ameliorated the fear memory of the stress event. (Henckens et al., 2017).

It has been shown that CRF_2 receptor stimulation by Ucn-2 or Ucn-3, but not stimulation of CRF_1 and CRF_2 receptor by Ucn-1, induced antidepressant-like effects in mice in a modified FST (Tanaka and Telegdy, 2008).

2.2. Vasopressin (AVP)

Vasopressin (arginine-vasopressin peptide–AVP, also known as antidiuretic hormone) is synthesized in the hypothalamus. In the CNS, it acts via two subtypes of receptors: $V1_A$ (AVP-R1a) and $V1_B$ (AVP-R1b) (Jard et al., 1987).

AVP is involved in the pathophysiology of mood disorders because of its contribution to the regulation of HPA axis activity (Frank and Landgraf, 2008). This peptide, released from the hypothalamus, controls, together with CRF, ACTH release in the pituitary through V_{1B} (Antoni, 1993; de Keyzer et al., 1994). Stress increases V_{1B} expression in the pituitary in rats (Aguilera and Rabadan-Diehl, 2000).

Table 1
Effects of neuropeptides and neuropeptide alterations in animal models of stress-related disorders.

Neuropeptide	Effect	Alterations in animal models	Reference
CRF	↑ activity of the HPA axis in lab animals		Arborelius et al., 1999
	Anxiogenic effect through activation of CRF receptors in the amygdala of lab animals		Koob and Heinrichs., 1999
		↑ CRF mRNA in brain, CRF levels in forebrainand CRF_1, CRF_2 rec. Concentrations in fish species subjected to various stress paradigms	Backstrom et al., 2011; Piato et al., 2011
	Anxiety-like behavior in several animal models after CRF ICV administration		Britton et al., 1986; Dunn and File, 1987
		↑ CRF mRNA and CRF release in the amygdala in rats subjected to stress	Herringa et al., 2004
	↓ anxiety behavior in CRF_1 but not CRF_2 knock-out mice		Coste et al., 2001
		↑ CRF mRNA in the paraventricular nucleus and forebrain in rats exposed to stress	Banerjee et al., 2010; Rouwette et al., 2011
	Male but not female CRF_2 knock-out mice exhibit anxiety behavior		Bale et al., 2000
	↓ anxiety and depressive-like behaviors in mice with lentiviral CRF over-expression in the dorsal BNST and central amygdala		Regev et al., 2011; Flandreau et al., 2012
AVP	V_{1B} antagonist produces antidepressant effects in FST in rats		Griebel et al., 2002
	V_{1B} antagonist causes ↓ ACTH and CORT responses to AVP in rats		Spiga et al., 2009
		↑ hypothalamic AVP concentration in stressed rats	Schmidt et al., 1996
	Injected IP or into the septum produces an anxiolytic effect in EPM in rats		Appenrodt et al., 1998
		↑ pituitary V_{1B} mRNA expression in stressed rats	Aguilera and Rabadan-Diehl, 2000
	V_{1A} antagonist attenuates the anxiety- and depressive-like behavior in rats		Zelena and Jain, 2010
		↑ AVP plasma level in OB mice	Poretti et al., 2016
	V_{1B} knock-out mice display ↓ ACTH and CORT concentration		Lolait et al., 2007
	Knock-out V_{1A}, but not V_{1B} mice display less anxiety-like behavior in various paradigms		Zelena and Jain, 2010
GAL	Depression-like behavior in the FST		Weiss et al., 1998
		↑ GAL mRNA in the hypothalamus, amygdala and locus coeruleus induced by chronic stress	Cryan and Holmes, 2005; Moller et al., 1999; Bing et al., 1993
	GAL_1 and GAL_2 knock-out mice display depressive behavior		Gottsch et al., 2005; Holmes et al., 2003
		↑ density of GAL binding sites in dorsal raphe nucleus of FSL rats	Bellido et al., 2002
	agonist of GAL_3 injected systematically induces antidepressive-like effects in rats		Saar et al., 2013
	blockade of GAL_3 produces antidepressive-like effects		Swanson et al., 2005
OT	↑ glucocorticosteroides secretion		Windle et al., 1997
	Injected ICV ↓ reaction on the fear factors and stressors in rats		Cohen et al., 2010; Onaka, 2004
	Intranasal administration ↓ ACTH stress response in monkeys		Parker et al., 2005
	Injected IP at high doses induces anxiolytic effect in male rats		Uvnas-Moberg et al., 1994
		↑ OT mRNA in the paraventricular nucleus and supraoptic nucleus induced by chronic stress in rats	Babygirija et al., 2010; Babygirija et al., 2012
	↓ CORT plasma level and CRF release in stressed animals		Windle et al., 2004
		↓ OT neurons in the parvocellular region of paraventricular nucleus in adult rats from MS paradigm	Todeschin et al., 2009
	Administrated ICV ↓depressive-like behaviors in ELS mice		Amini-Khoei et al., 2017
	injected into central amygdala causes anti-depressive and anti-anxiety-like effects in mice		Han et al., 2018
NPY	Administrated into the paraventricular nucleus evokes ↑ CRF and serum ACTH, CORT levels in rats		Suda et al., 1993
		↑ NPY concentration in brain associated with stress tolerance in DPP-4 deficient rats	Canneva et al., 2015
	After intranasal administration reverses anxiety/depressive-like behaviors in PTSD model in rats		Serova et al., 2014
	Central administration induces anxiolytic or anxiogenic effect in lab animals		Sørensen et al., 2004
		↓ NPY level in the striatum by chronic stress in rats	Husum et al., 2002
	Anxiolytic effect is mediated by Y_1 receptor and anxiogenic effect by Y_2 receptor in rats		Morales-Medina et al., 2012a; Bacchi et al., 2006
	Y_2 antagonist administered centrally or into central amygdala induces anxiolytic effect in control rats		Cippitelli et al., 2011
	Y_2 antagonist given chronically induces antidepressant-like effect in rats		Ishida et al., 2007
	Y_5 agonist induces anxiolytic effect in rats		Morales-Medina et al., 2012b

(*continued on next page*)

Table 1 (*continued*)

Neuropeptide	Effect	Alterations in animal models	Reference
OXs	↑ plasma ACTH level after ICV injections in rats CRF mediates OX-induced stress reaction in lab animals		Samson et al., 2002 Ida et al., 2000
		↑ OX-A and ↓ OX-B levels in the hypothalamus of ELS rats	Feng et al., 2007
	Induces anxiogenic or antidepressant-like effect dependent on stress susceptibility in mice exposed to chronic stress		Chung et al., 2014
		↑ activation of hypothalamic OX neurons in mice subjected to UCMS	Nollet et al., 2011
	Antagonist of OX receptors induces antidepressant-like effect and blockade of HPA dysregulation in mice subjected to UCMS		Nollet et al., 2012
		The higher number of OX-positive neurons in the hypothalamus of FSL than FRL female rats	Mikrouli et al., 2011
	OX_1 or OX_2 null mice display antidepressant or pro-depressant activity, respectively		Scott et al., 2011
	Almorexant, OX receptors antagonist, induces antidepressive-like effects and normalization of the HPA axis activity		Gaillard et al., 2012

ACTH – adrenocorticotropin hormone; AVP – arginin-vasopressin peptide; CORT- corticosterone; CRF – corticotropin-releasing factor; ELS – early-life stress; EPM – elevated plus-maze test; FST – forced swimming test; GAL – galanin; FSL – Flinders Senstitive Line rats; FRL – Flinders Resistant Line rats; $GAL_1/GAL_2/GAL_3$ – galanin receptors; HPA axis – hypothalamo-pituitary-adrenal axis; MS – maternal separation; NPY – neuropeptide Y; OT – oxytocin; OXs – orexins; OX_1/OX_2 – orexins receptors; UCMS – unpredictable chronic mild stress; Y_1/Y_2 – neuropeptide Y receptors; V_{1A}/V_{1B} – arginin-vasopressin receptors; ↑ – an increase; ↓ – a decrease.

Interestingly, V_{1B} KO mice are characterized by lower ACTH and CORT levels in comparison to naïve mice (Lolait et al., 2007). Blockade of extra-hypothalamic V_{1B} induces antidepressive and anxiolytic effects in behavioral tests, even in lab animals not exposed to stressors (Appenrodt et al., 1998; Stemmelin et al., 2005; Salomé et al., 2006). In rats, a lack of AVP resulted in a less intense anxious and depressive state in several behavioral tests compared to the effect of $V1_B$ blockade (Zelena and Jain, 2010). Administration of an V_{1A} antagonist also diminished anxiety- and depressive-like behavior in rats (Zelena and Jain, 2010). In response to repeated stress, AVP transcription increased at the same time that the CRF response attenuated, suggesting AVP is more responsive to chronic stress than CRF (Ma and Lightman, 1998).

Patients with major depressive disorder exhibited significantly elevated plasma AVP levels compared to healthy controls (Van Londen et al., 1997). Recently, Griebel et al. (2012) administered V_{1B} antagonist (SSR149415) to patients with generalized anxiety disorder (GAD) or major depressive disorder (MDD). They noticed that the treatment was not effective in individuals with GAD. However, in patients with MDD, the authors observed antidepressant effects after 8 weeks of administration. Further, genetic association studies showed connections between single nucleotide polymorphisms (SNPs) in the V_{1B} with mood disorders (Dempster et al., 2007). Van West et al. (2004; 2010) also studied these connections. They found that the SNP V_{1B}-s3 showed a positive correlation with depression and SNP V_{1B}-s5 at a higher frequency was detected in control. These data suggest that genetic variations in the AVP receptor may contribute to the occurrence of depression in humans.

2.3. Galanin (GAL)

GAL is widely distributed throughout the CNS, but has been primarily localized to the hypothalamus (Qualls-Creekmore et al., 2017), where it co-localizes with γ-aminobutyric acid (GABA). This neuropeptide is synthesized by norepinephrinergic (NE) neurons of the locus coeruleus, 5-HT neurons of the dorsal raphe nucleus (DRN) and dopaminergic (DA) neurons in the ventral tegmental area (Melander et al., 1986; Holets et al., 1988; Hökfelt et al., 1998). GAL inhibits NE, 5-HT and DA, as well as glutamate (Glu) and acetylcholine (Ach) release (Melander et al., 1986; Seutin et al., 1989; Zini et al., 1993; Pieribone et al., 1995; Kehr et al., 2002). It acts through three cloned receptors, GAL_1, GAL_2, GAL_3 (Branchek et al., 2000) and only a single paper has indicated a putative receptor GAL-RL (galanin-receptor-like) (Ignatov et al., 2004). In the CNS, GAL regulates numerous processes including feeding, nociception, nerve regeneration, memory and neuroendocrine release (Picciotto et al., 2010) and modulates pituitary activity (Kaplan et al., 1988).

Several experimental studies have demonstrated that GAL induces depressive-like behavior in rats [after intracerebroventricular (ICV) infusion or administration to VTA], reversible by GAL-R antagonism (Weiss et al., 1998; Weiss et al., 2005; Kuteeva et al., 2008), An opposing role for GAL_2 and GAL_3 receptors was reported with regards to their involvement in depression-like behavior. Agonists of GAL_2 administrated systemically [IV injection] induced an antidepressant-like effect that was abolished in GAL_2 KO mice (Saar et al., 2013), whereas, this same effect was elicited in response to blockade of GAL_3 receptors by acute or chronic administration of the selective antagonist. An anxiolytic effect of this compound was also observed (Swanson et al., 2005). In rats, GAL produced anxiety (after intra-amygdala administration) (Moller et al., 1999). Under stress conditions, GAL expression is upregulated in several rat brain structures (Holmes et al., 2002). Interestingly, the acute ICV administration of alarin, a recently identified member of the GAL peptide family, in mice exposed to unpredictable chronic mild stress (UCMS), induced antidepressant-like effects, decreased HPA axis activity and upregulated brain-derived neurotrophic factor mRNA expression in several limbic structures (Wang et al., 2014).

Clinical studies have shown a strong association between single nucleotide polymorphisms (SNPs) within the gene coding for GAL and major depression (Davidson et al., 2011; Wray et al., 2012; da Conceição Machado et al., 2018) and anxiety disorders, as well as an association with major depression and HPA axis activity in females (Unschuld et al., 2010). Moreover in people characterized by vulnerability to early or recent life stressful events, an association between variants in genes for galanin and its receptors (GAL_1, GAL_2, GAL_3) and increased risk of depression and anxiety has been reported (Juhasz et al., 2014).

2.4. Oxytocin (OT)

OT (also known as OXT) as a hypothalamic hormone is involved in the regulation of pituitary activity. It also plays the role of neurotransmitter and neuromodulator in the mammalian CNS. OT acts through the OT receptor (OT-R), a member of the class I GPCR family (Soloff et al., 1979).

In rats exposed to a stressor, e.g., social stimuli, OT contributes to the attenuation of anxiogenic, depressive and stress effects induced by CRF because it inhibits CRF release and, in consequence, downregulates the HPA response (Windle, 2004). OT causes anxiolytic effects only in

stressed animals, most likely through stimulation of OT-Rs expressed on CRF neurons (Dabrowska et al., 2011). Anti-stress and anti-anxiety effects of OT are also a result of its action in the amygdala. OT-containing neurons arising from the PVN target several limbic structures (i.e., amygdala, hippocampus and lateral septum) (Buijs, 1978; Burbach et al., 2006). In mice subjected to long-term isolation intracentral amygdala (CeA) injection of OT attenuated depression and anxiety-related behaviors. These behavioral disturbances were associated with down-regulation of OT-R transcription in the CeA but not in the hypothalamus and diminished OT-induced inhibitory synaptic transmission in the CeA (Han et al., 2018). In mice, antidepressive effects of OT were reported, but they were not reversed by administration of an OT antagonist (Ring et al., 2010).

Reports of plasma OT concentration in depressed patients differ (Zetzsche et al., 1996; Ozsoy et al., 2009; Parker et al., 2010). It has been suggested that blunted OT secretion may be related to loss of appetite and reduction of libido in depressive illness. A positive correlation was found between OT plasma levels and positive emotion, described as happiness (Zetzsche et al., 1996). No significant differences were found for cerebrospinal fluid (CSF) OT concentrations in depressed patients compared to controls (Purba et al., 1996). Interesting data reported by McQuaid et al. (2013) found an association between an OT-R polymorphism and increased vulnerability to stress in people who experienced trauma in childhood.

Antidepressant efficacy of OT analogs was studied in clinical trials (for review see Catena-Dell'Osso et al., 2013), but OT analogs have not been approved for marketing in any country. Recently, intranasal OT used as an adjunct to escitalopram in therapy of patients with treatment-resistant depression significantly improved mood (Scantamburlo et al., 2015).

2.5. Neuropeptide Y (NPY)

NPY is widely distributed throughout the CNS—it is localized in the cortex, limbic system and brainstem (Adrian et al., 1983). Its effects are mediated by five receptors Y_1, Y_2, Y_4, Y_5 and Y_6 in mammals (Michel et al., 1998). NPY acts as a neuromodulator and neurohormone. NPY influences several processes including feeding behavior, energy balance, anxiety, circadian rhythms, memory and alcohol-seeking (Cippitelli et al., 2010; Morales-Medina et al., 2010; Kageyama et al., 2010). The role of NPY in the pathomechanism of stress and its implications for depression and anxiety disorders are relatively well-documented. NPY is involved in the regulation of the HPA axis and in turn, is regulated by corticosterone (CORT) and insulin (INS). In response to subchronic stress, changes in NPY mRNA in several brain structures were noted in relation to high CORT or low INS plasma levels (e.g., increased NPY mRNA expression in the arcuate nucleus and unchanged expression in the locus coeruleus) (Makino et al., 2000). In a rat model of depression, suppressed central NPY levels have been reported (Caberlotto et al., 1999) and differing roles for its receptors, in terms of antidepressive effects in response to NPY, have been shown (Ishida et al., 2007). Two-week ICV administration of the Y_1 receptor agonist or Y_2 receptor antagonist in olfactory bulbectomized (OB) rats, an animal model of depression and anxiety, reduced depressive- and anxiogenic-like behaviors estimated by a number of tests (FST, SIT, OF, EPM). Moreover, increased levels of Y_2 receptor binding in the hippocampus and basolateral amygdala in OB rats confirmed the results of the behavioral studies suggesting that Y_2 receptors mediate the depressive-like effect of NPY (Morales-Medina et al., 2012a). Antidepressant-like effects were also observed in the challenged rats (OB, CMS) after administration of a Y_5 receptor antagonist (Morales-Medina et al., 2012b; Packiarajan et al., 2011). In various behavioral tests NPY induced an anxiolytic effect (Heilig et al., 1989; Broqua et al., 1995; Kokare et al., 2005) or anxiogenic effect in a dose-dependent manner (Nakajima et al., 1998). After intraperitoneal (IP) injections of NPY, a long-lasting anxiolytic effect was observed as far out as eight weeks (Sajdyk et al., 2008). Several reports evidenced that the anxiolytic activity of NPY is mediated by Y_1 receptor (Heilig et al., 1993; Sørensen et al., 2004; see for review Enman et al., 2015), which is indirectly supported by findings of Primeaux et al. (2005) who reported an anxiogenic effect induced by Y_1 receptor antagonism, e.g. BIBP 3226. In contrast, stimulation of Y_2 receptors elicited an anxiogenic effect (Sajdyk et al., 2002) that was blocked by BIIE0246, a specific antagonist of Y_2 (Kallupi et al., 2014; Tasan et al., 2010). Data on the role of Y_5 is limited and controversial. Kask et al. (2002) noticed that its antagonist failed to modify anxiety-like behavior in the social interaction task (SIT) and EPM, whereas, results from Morales-Medina et al. (2012a) indicate that stimulation of Y_5 receptors induces an anxiolytic effect evaluated by the EPM, OF and SIT tests. Moreover, recently it has been shown that conditional inactivation of Y_1 receptors in Y_5 receptor containing neurons augments stress-related anxiety without affecting stress-activated HPA axis activity in mice (Longo et al., 2015).

The clinical studies of NPY in patients with MDD are not consistent. In patients with depression, NPY levels in CSF and serum were lower than in controls (Nilsson et al., 1996; Westrin et al., 1999; Ozsoy et al., 2016) and a decreased concentration of NPY was measured in the brain of suicide victims (Widdowson et al., 1992). Nikisch and Mathé (2008) found significantly increased NPY concentrations in the CSF levels of patients with drug resistant depression following electroconvulsive therapy (ECT) that induced clinical improvement. However, Soleimani et al. (2015) detected higher CSF NPY-LI levels in medication-free depressed patients compared to healthy volunteers. Similar results were published by Martinez et al. (2012). Soleimani et al. (2015) hypothesized that two groups of MDD may exist with different NPY responses to stress. They reported a positive correlation between CSF NPY-LI levels and childhood trauma. Moreover, an association between a diagnosis of depression and two polymorphisms of the preproNPY gene has been reported (Heilig, 2004).

2.6. Orexins (OXs)

Orexin A (OX-1, OXA, also known as hypocretin 1) and Orexin B (OX-2, OXB, or hypocretin 2) act via orexin-1 receptor (OX_1, also nominated OX-1R) and orexin-2 receptor (OX_2, also known as OX-2R). In the CNS, both neuropeptides are primarily synthesized by neurons in the lateral hypothalamus. OXB perycarions were noticed in amygdala, striatum and around the third ventricle (Sakurai and Mieda, 2011). OX neurons have widespread projections, modulating the function of 5-HT neurons, NE neurons and DA neurons. Receptors for leptin, NPY and CRF_1 receptors are expressed on the cell body of OX neurons (Winsky-Sommerer, 2004; Mazza et al., 2005). In turn, OX-Rs are localized on cells expressing the other orexigenic neuropeptides, ghrelin, NPY, agouti related protein and POMC. OXs function as neuromodulators and neurohormones. They control sleep-wakefulness, arousal states, feeding, cognition, autonomic function and various neuroendocrine activities (Sakurai, 2014). Activity of OX neurons is regulated via the energetic status of the organism, particularly glucose levels in peripheral blood (Moriguchi et al., 1999).

Recently published findings suggest an important role for OX signaling in adaptive mechanisms to stressful stimuli (Kuwaki, 2011; Giardino and de Lecea, 2014) and for OXs in sex differences in endocrine and behavioral responses to repeated stress (Grafe et al., 2017). Results from studies utilizing several experimental paradigms (genetic animal models of depression, stress-induced depression) have suggested that OXs are involved in the pathophysiology of depression (Mikrouli et al., 2011; Nollet et al., 2011; Jalewa et al., 2014; Chung et al., 2014). In mice subjected to the UCMS paradigm, the OX antagonist almorexant induced antidepressive-like effects and normalized HPA axis activity (Gaillard et al., 2012).

Clinical studies have reported varying results. Compared to controls, a tendency towards higher OX levels in the CSF of patients suffering from major depressive disorder was detected (Salomon et al., 2003), but

in another study, which analyzed the CSF of suicidal patients, OX-A levels were lower in patients with major depressive disorder than in patients with dysthymia or adjustment disorders (Brundin et al., 2007). Then, in patients with major depressive disorder treated for one year after suicide attempt, a positive correlation between CSF OX levels and clinical improvement was shown (Brundin et al., 2009).

3. Interaction between neuropeptides and the serotonergic system

Anatomical and functional interaction between serotonergic and neuropeptide systems support the idea that neuropeptides partially mediate the pharmacological effects of SSRIs.

3.1. CRF

The DRN is innervated by CRF-immunoreactive fibers and CRF receptors are localized on 5-HT neurons (Valentino et al., 2010). Interaction between CRF and the DRN 5-HT system is complex. In naïve rats CRF administrated ICV had a dose-dependent effect on 5-HT concentration in the lateral striatum but after intraraphe administration it inhibited activity of 5-HT neurons in the DRN (Price et al., 1998). Interestingly, social stress has been shown to up-regulate CRF_2 receptors in the lateral DRN of rats (Bledsoe et al., 2011). It is known, that up-regulation of the CRF_2 receptors in this structure following peri-adolescent stress results in prolonged up-regulation of 5-HT release in the nucleus accumbens in adulthood (Lukkes et al., 2009). Further, a single administration of CRF into the DRN induced freezing behavior associated with regionally and temporally different serotonergic responses in the limbic structures (amygdala and prefrontal cortex) (Forster et al., 2006), the lateral septum and the striatum (Price and Lucki, 2001). Interestingly, activation of two different CRF receptors (CRF_1 and CRF_2) within the DRN resulted in opposite effects on 5-HT transmission in other brain structures implicated in stress-related psychiatric diseases (Amat et al., 2004). Several reports suggest that a relationship between CRF and 5-HT plays a role in the pathogenesis of affective and anxiety disorders. An anxiety-like effect induced by CRF was associated with increased 5-HT transmission in the ventral hippocampus (Kagamiishi et al., 2003). Mutant mice with CRF_1 deficiency are characterized by reduced HPA axis activity and augmented synthesis of 5-HT in the raphe-hippocampal system under stress conditions (Penalva et al., 2002). Moreover, both types of CRF receptors were reportedly involved in increasing raphe-hippocampal 5-HT system activity under stress (Linthorst et al., 2002). These findings seem to be contradictory to the results of (Price et al., 1998). However, a comparison of experimental design indicates that CRF has different effects under basal and stress conditions.

3.2. AVP

Anatomical and functional data have indicated that AVP and 5-HT systems interact with each other. A moderate-to-dense AVP innervation of the dorsal and median raphe, originating primarily from the extended amygdala, has been detected. This AVP circuit is gonadal steroid-dependent and sexually dimorphic (Rood et al., 2013). AVP, via stimulation of V_{1A}, induced activation of a subset of the dorsal raphe 5-HT neurons (Rood and Beck, 2014). In turn, ICV injection of selective 5-HT agonists increased peripheral AVP release (Jørgensen et al., 2003) and AVP enhanced synthesis and release of 5-HT from dentate gyrus slice cultures (Auerbach and Lipton, 1982). Some behaviors were modulated, at least in part, by interaction between 5-HT and AVP at the level of the anterior hypothalamus where both AVP- and 5-HT-containing projections are present (Delville et al., 2000). Stimulation of $5HT_{1A}$ receptors had a sex-dependent effect on the AVP-induced expression of offensive aggression (an inhibitory effect in males and an increased effect in females) (Terranova et al., 2016) and induced a sexually independent reduction of AVP-stimulated communicative behavior called flank marking (Albers et al., 2002).

3.3. Gal

GAL modulates activity of the raphe nucleus 5-HT system. Several studies have indicated that GAL is synthesized in the brainstem neurons of the DRN. Results from an immunohistochemical study raised questions because strong galanin-immunoreactivity (GAL-IR) had been shown throughout the DRN only after intra-raphe infusion of GAL there were no signs of GAL-IR in this region in artificial cerebrospinal fluid (aCSF)-infused control animals (Kehr et al., 2002). However, time-dependent reduction of GAL mRNA was found in the DRN after ICV administration of GAL. An interaction between GAL and $5\text{-}HT_{1A}$ receptors was postulated for several years until it was confirmed in a study that showed GAL, given ICV, caused a time-dependent decrease in GAL and $5\text{-}HT_{1A}$ mRNA levels in the DRN (Razani et al., 2000). In this way, GAL transmission has an influence on $5\text{-}HT_{1A}$ receptor expression that plays a critical role in the function of the raphe nucleus serotonergic system and in the mechanism of action of antidepressants, e.g., SSRIs as described in the introduction (Section 1). It has been proposed that involvement of GAL in modulation of the activity of 5-the HT system is mediated by GALR-$5\text{-}HT_{1A}$ heteromers (heterodimers or heterotrimers). Their existence is supported by the findings that GAL reduces firing in the ascending 5-HT neurons by inhibition of postjunctional $5HT_{1A}$ receptors via intramembrane receptor-receptor interactions. It is postulated that GALR-$5\text{-}HT_{1A}$ heteromers represent a novel target for antidepressant drugs (Fuxe et al., 2012). GAL administered centrally caused a long-lasting decrease of basal 5-HT, and, after elevation by acute SSRI administration, in the hippocampus via inhibition of 5-HT neurons in the raphe nucleus (Yoshitake et al., 2003). These data suggest that upregulation of GAL in the DRN is associated with hypofunction of the ascending 5-HT neurons. Mazarati et al. (2005) showed that GAL microinfusion into the DRN reduced the concentration of 5-HT in the hippocampus.

Results of a recent study by de Souza et al. (2018) support the possible role of GAL_2 in mood-related behavior. They showed that infusion of GAL or a GAL_2 agonist into the DRN decreased immobility time in the FST in rats. Intra-DRN pretreatment with a GAL_2 antagonist blocked GAL antidepressant-like effect. These results suggest that the antidepressant-like effect of GAL is possibly mediated by GAL_2 in the DRN.

3.4. OT

Serotonergic terminals originating from the raphe nuclei in the brainstem project to PVN magnocellular neurons where OT is synthesized (Renaud and Bourquet, 1991). In both nuclei, the PVN and supraoptic nucleus, a high degree of overlap between OT-labeled neurons and serotonin-IR fibers has been demonstrated, suggesting that 5-HT's influence on OT neurons is possibly mediated by 5-HTT (Emiliano et al., 2007). Alterations in OT transmission in response to stimulation of $5\text{-}HT_{2A}$ and $5\text{-}HT_{1A}$ receptors have been shown. After being challenged with a $5\text{-}HT_{2A}$ receptor agonist, increased secretion of OT and c-fos expression in OT neurons in the PVN (Van de Kar, 1991) and increased plasma OT levels (Damjanoska and Van de Kar, 2003) were observed. A $5HT_{1A}$ receptor agonist, given peripherally, increased plasma OT levels (Li et al., 1997). The studies on OT receptor-reporter mice provided some data that confirmed an interaction between OT and the 5-HT system. About one-half of tryptophan hydroxylase-immunoreactive neurons in the raphe nucleus appeared to express OT receptor. OT infusion increased 5-HT release within the medial raphe nucleus and induced an anxiolytic effect that was blocked by infusion of a $5\text{-}HT_{2A/2C}$ receptor antagonist. It was suggested that the increased activity of 5-HT system induced by OT may cause its anxiolytic effect (Yoshida et al., 2009).

Peripherally in humans, a positive correlation between OT and

Table 2
Effects of SSRIs on neuropeptide systems in preclinical studies.

SSRI	Treatment procedure	Animals	Result	Reference
Fluoxetine	Once a day (10 mg/kg) IP for 21 days	rats subjected to LH	Reversed changes in CRF and CRF_1 expression in basolateral amygdala and hippocampus	Fernández Macedo et al., 2013
	Once a day (10 mg/kg) PO for 28 days	sham-operated mice	↑ AVP and ↓ CRF plasma concentration ↑ CRF_1 and V_{1B} mRNA expression in pituitary	
	Once a day (10 mg/kg) PO for 28 days	OB mice	↓ CRF and AVP plasma concentration (normalization) ↑ CRF_1, but not V_{1B} mRNA expression in pituitary	Poretti et al., 2016
	Once a day (0,3 mg/kg) for 30 days	naïve hamsters	↑ AVP concentration in lateroanterior hypothalamus	Ricci and Melloni, 2012
	10 mg/kg SC single	naïve mice female V_{1B} KO mice	↑ AVP mRNA expression in the paraventricular nucleus in female	Stewart et al., 2008
	Once a day (20 mg/kg) IP for 14 days	CRS mice	↑ NPY and GAL expression in various structures	Christiansen et al., 2011
	Once a day (10 mg/kg) IP for 14 days	fa/fa rats	↑ GAL expression in various structures	Churruca et al., 2004
	Once a day (10 mg/kg) IP for 14 days	naïve rats	↓ NPY mRNA expression in various areas of brain	Myung et al., 2005
	Once a day (3 mg/kg) IP for 14 days	FSL rats	↑ NPY level in arcuate and anterior cingulate cortex	Caberlotto et al., 1999
		FSL/FRL rats	↑ Y_1 binding sites in medial amygdala and occipital cortex, but not Y_2	
	Once a day (3 mg/kg) IP for 14 days	FSL rats	↑ NPY mRNA expression in arcuate nucleus and dentate gyrus	Caberlotto et al., 1998
		FRL rats	↑ NPY mRNA expression in arcuate nucleus and ↓ in dentate gyrus	
	Once a day (10 mg/kg) IP for 14 days	fa/fa rats	↓ NPY level in the paraventricular nucleus	Gutierrez et al., 2002
Fluvoxamine	Once a day (100 mg/kg) PO for 10 days	food-restricted rats	↓ NPY level in the paraventricular nucleus and dorsomedial hypothalamus	Shinozaki et al., 2008
Sertraline	15-20 mg/kg in drinking water for 21 days	naive rats	↑ plasma AVP and OT concentrations	Magalhaes-Nunes et al., 2007
	Once a day (10 mg/kg) IP for 28 days	naive mice	↑ GAL mRNA expression in the ventral dentate gyrus	Yamada et al., 2013
Citalopram/Escitalopram	Once a day (20 mg/kg) IP for 14 days	naive rats	↑ OT plasma level	Uvnas-Moberg et al., 1999
	Once a day (10 mg/kg) SC for 14 days	naive rats	↓ accumulation of CRF-stimulated cAMP in pituitary glands	Jensen et al., 1999
	10 mg/kg via minipump single10 mg/kg via miniump for 14 days	naive rats	↑ OT mRNA expression in paraventricular nucleus	Hesketh et al., 2005

AVP – arginin-vasopressin peptide; cAMP – 3′,5′-cyclic adenosine monophosphate; CRS – chronić restraint stress; CRF – corticotropin-releasing factor; CRF_1 – corticotropin-releasing factor receptor 1; fa/fa – obese Zucker rats; FSL/FRL – Flinders Sensitive Line/Flinders Resistant Line; GAL – galanin; LH – learned helplessnes paradigm; NPY – neuropeptide Y; OT – oxytocin; SSRI – selective serotonin-reuptake inhibitor; V_{1B} – arginin-vasopressin peptide receptor 1b; V_{1B} KO – arginin-vasopressin peptide receptor 1b knock-out; ↑ – an increase; ↓ – a decrease.

SERT, as measured by [H3]-Par binding, has also been shown (Marazziti et al., 2012).

3.5. NPY

The documented expression of 5-HT receptors in cortical and subcortical telencephalon NPY-producing neurons (Bonn et al., 2012) and synaptic contacts between 5-HT-containing neurons and NPY neurons in the amygdala (Bonn et al., 2013) provide morphological evidence for a functional link between NPY and the 5-HT system in the regulation of emotions, such as anxiety. Additionally, co-localization of NPY and 5-HT was detected in brainstem neurons (Blessing et al., 1986; Everitt and Hokfelt, 1989). It has been postulated that under physiological conditions 5-HT neurons have a positive influence on NPY striatal neurons (Compan et al., 1996). A partial decrease in striatal 5-HT concentration induced a decrease in the number of NPY-producing neurons, but an opposite effect was observed in response to the nearly-complete lesion of 5-HT neurons. This latter effect, an increase in number of NPY neurons, was also observed in the hypothalamus (Kakigi and Maeda, 1992; Dryden et al., 1996). Estimation of basal 5-HT levels by differential pulse voltammetry after administration of an NPY or Y_1 receptor antagonist into the amygdala showed that NPY has a positive effect on the 5-HT system (Crespi, 2011). A similar effect of NPY was reported by Song et al. (1996). NPY knock-out mice were characterized as showing a modest decrease in SERT binding in several hippocampal regions and the olfactory bulb and decreased 5-HT in the hypothalamus (Gehlert et al., 2008). A study by Inaba et al. (2016) concerning the effect of NPY on sexual behavior under low-energy conditions also provided data about a connection between NPY and the 5-HT system. Injection of NPY or 8OH-DPAT (5-HT_{1A} agonist) into the DRN inhibited male sexual behavior in fed males. In contrast, BIBP-3226, a Y_1 antagonist or (+)-DOI hydrochloride, a 5-$HT_{2A/2C}$ agonist that activates 5-HT neurons, injected into the same area partially recovered male sexual behavior which suggests that NPY may inhibit 5-HT activity via Y_1 in the DRN.

Behavioral studies have confirmed a functional interaction between the 5-HT and NPY systems. Redrobe et al. (2005) noticed that 5-HT depletion by a tryptophan hydroxylase (TPH) inhibitor, *p*-chlorophenylalanine (PCPA), attenuated NPY antidepressive-like effects in the forced swimming test (FST) and induced upregulation of Y_1 binding sites in their high-affinity state in various brain regions.

3.6. OXs

Several studies have discovered links between OX and the 5-HT system. The dorsal raphe is innervated by OX neurons (Nambu et al., 1999). OXs activate 5-HT neurons (Brown et al., 2002) via specific receptors (Marcus et al., 2001). In turn, 5-HT neurons projecting from the dorsal raphe to the hypothalamus (Petrov et al., 1992) have an inhibitory influence on OX neurons in the perifornical-lateral hypothalamic area (Kumar et al., 2007). It has been proposed that this effect, mediated by $5HT_{1A}$ receptors localized on OX neurons, is important for regulating sleep-wakefulness states (Muraki, 2004). A recent study by Hasegawa et al. (2017) showed that the OX neuron-dorsal raphe 5-HT neuron-amygdala pathway is a critical circuit for suppression of cataplexy. This study clearly demonstrated functional connections between OX and DRN neurons.

4. Influence of SSRI on the neuropeptide transmission

To date, preclinical and clinical data indicate that SSRIs affect neuropeptide systems (Schloss and Henn, 2004). These data suggest

Table 3
Effects of SSRIs on neuropeptide systems in clinical studies.

SSRI	Treatment procedure	Groups/Patients	Results	Reference
Fluoxetine	No data	MDD (n = 9)	↓ CRF and AVP in CSF (normalization)	De Bellis et al., 1993
	20 mg/day for 1 month	MDD, only (n = 12)Women	↓ OT plasma concentration	Abbasinazari et al., 2018
	20 mg/day for8 weeks – 6 months	Various psychiatric disorders (e.g. MDD, GAD) (n = 7)	no effects (NPY serum concentration)	Ozsoy et al., 2016
Sertraline	for 5 weeks (no data about dose)	MDD (n = 15)	↓ OXs level in CSF	Salomon et al., 2003
	50 mg/day for 8 weeks – 6 months	Various psychiatric disorders (e.g. MDD, GAD) (n = 9)	no effects (NPY serum concentration)	Ozsoy et al., 2016
Citalopram/Escitalopram	40 mg/day for16 weeks	MDD (n = 20)	normalization of the CRF transmission (DEX/CRH test)	Nikisch et al., 2005b
	20-40 mg/day for4 weeks	MDD (n = 21)	↑ NPY-LI in CSF	Nikisch et al., 2005b
	10-20 mg/day for8 weeks - 6 months	Various psychiatric disorders (e.g. MDD, GAD) (n = 9)	↑ NPY serum concentration	Ozsoy et al., 2016
	20 mg/day for 1 month	MDD, only (n = 11)Women	No effects (OT plasma concentration)	Abbasinazari et al., 2018

AVP – arginin-vasopressin peptide; CRF – corticotropin-releasing factor; CSF – cerebrospinal fluid; DEX/CRH test – dexamethasone test; GAD – generalized anxiety disorder; MDD – major depressive disorder; NPY-LI – NPY- like immunoreactivity; OT – oxytocin; OXs – orexins; ↑ – an increase; ↓ – a decrease.

that potential relationships exist between neuropeptide signaling and antidepressant effects, which may additionally have implications relating to drug influence on mood, anxiety, neurohormone axes and control of feeding. Several studies have been conducted to evaluate the influence of SSRIs on neuropeptide systems (Tables 2 and 3).

4.1. SSRIs and CRF transmission

Effects of chronically administered SSRIs are related to their influence on HPA axis activity. Results from several studies showed that SSRIs diminish HPA axis responsiveness to stress (Marcilhac et al., 1999; Jensen et al., 1999; Ishiwata et al., 2005). They may influence HPA axis activity through the CRF pathway. Chronic fluoxetine reduced CRF mRNA expression in the PVN during exposure to chronic stress, suggesting that the drug diminished sensitivity of CRF neurons to stress (Stout, 2002). In rats not exposed to stress, repeated citalopram administration desensitized the HPA axis at the pituitary level as it decreased the expression of POMC mRNA (the CRF-dependent precursor to ACTH production) and reduced the accumulation of CRF-stimulated cAMP in the pituitary (Jensen et al., 1999). Normalization of HPA axis activity following long-term treatment with SSRIs is secondary to increased GR protein levels and GR mRNA levels (Barden et al., 1995), which are regulated by CRF and AVP (Hügin-Flores et al., 2003).

An opposite effect was observed after a single injection of citalopram (Jensen et al., 1999) or fluoxetine (Gibbs and Vale, 1983). Both drugs induced an increase in plasma ACTH and CORT concentrations. Fluoxetine also increased AVP concentrations in peripheral plasma and CRF and AVP concentrations in hypophysial portal plasma. These data suggest that increased secretion of ACTH induced by acute fluoxetine administration is mediated, at least in part, by an increase in hypothalamic secretion of both CRF and AVP (Gibbs and Vale, 1983). An observed overexpression of *c-fos* in neurons of the hypothalamic PVN, where CRF and AVP are produced, after a single injection of citalopram confirmed the SSRI-induced effect (Jensen et al., 1999).

Alterations in the CRF system beyond HPA axis structures were also noted. Chronic fluoxetine reversed changes in CRF and CRF_1 expression in the basolateral amygdala and hippocampus in rats exposed to the learned helplessness paradigm (LH), a model of depression (Fernández Macedo et al., 2013).

An effect of SSRIs on behavioral response to stress due to interference with CRF has been shown. In rats, acute administration of fluoxetine, with a dose sufficient to decrease serotonin metabolism in specific limbic brain structures, inhibited increased spontaneous non-ambulatory motor activity induced by CRF (Lowry et al., 2009). These data are consistent with the hypothesis that the 5-HT system is involved in the behavioral changes induced by CRF.

Interaction between serotonin and CRF in the regulation of anxiety has been confirmed in a study showing that chronic fluoxetine treatment abolished the acute anxiogenic effects of CRF observed in the social interaction test in rats. However, both CRF and fluoxetine given as a single dose had anxiogenic effects (To et al., 1999). Meanwhile, escitalopram, administered chronically via mini-pump, significantly decreased HPA axis reactivity in rats overexpressing CRF in the central nucleus of the amygdala, but only partially reversed anxiety-like behavior. Because of this discrepancy, amygdala CRF overexpression has been suggested as a potential animal model for studying treatment-resistant psychopathologies (Flandreau et al., 2013).

SSRIs also have an influence on body weight. It was demonstrated that escitalopram increased the rate of weight gain in rats overexpressing CRF in the central nucleus of the amygdala but not in control rats (Flandreau et al., 2013). It has been shown that the competitive CRF antagonist α-helical CRF (9–41) reversed a decrease in feeding induced by either CRF or a restraint stressor (Krahn et al., 1986). Central administration of CRF at a dose that did not affect HPA axis activity prevented an excessive weight gain in obese (*fa/fa*) rats not by modulating food intake but by influencing autonomic nervous system

control over metabolic function (Rohner-Jeanrenaud et al., 1989). Compared to control rats, fluvoxamine induced weight loss despite unaltered food intake (Rohner-Jeanrenaud et al., 1989), suggesting the drug evoked an increased energy expenditure. This effect may be mediated by CRF stimulation of brown adipose tissue metabolism via increased sympathetic system activity resulting from its activity in the hypothalamic medial preoptic area (Egawa et al., 1990).

Some clinical data support the hypothesis that normalization of CRF neurotransmission essential for HPA axis activity plays a causal role in the mechanism of action of SSRIs and other antidepressant drugs (Nikisch et al., 2005a; Brothers et al., 2012) because its normalization is associated with improved clinical outcome in patients with depressive and anxiety disorders (Paslakis et al., 2010; Hinkelmann et al., 2012). In depressed patients treated with escitalopram (Nikisch et al., 2005a) or fluoxetine (De Bellis et al., 1993) normalization of CRF concentration in CSF has been observed concurrently with clinical improvement according to the Hamilton Depression Rating Scale (HAM-D). However, in patients with chronic posttraumatic stress disorder, CSF-CRF concentration, which was similar to the concentrations found in healthy controls, remained the same after treatment with paroxetine despite clinical improvement (Bonne et al., 2011).

Among all neuropeptides studied to date, CRF is the most relevant to the pathogenesis of stress-related affective disorders and the mechanism of action of SSRIs.

4.2. SSRIs and AVP transmission

SSRIs, via influence on AVP transmission, may alter HPA axis activity, neurochemistry in the brain and hydromineral balance. AVP plays a crucial role in water balance and sodium homeostasis (Mogi et al., 2012).

V_{1B} was shown to be essential for the HPA axis response to acute SSRI administration, as fluoxetine at a single dose diminished plasma ACTH and CORT levels in male as well as female V_{1B} KO mice but did not induce this effect in wild-type controls. AVP mRNA expression in the PVN was increased in fluoxetine-treated female but not male wild-type mice, indicating sex-related differences in the regulation of PVN and AVP gene expression following administration of this antidepressant (Stewart et al., 2008). A reduced ACTH response to acute restraint stress following chronic treatment with citalopram was associated with an elevated expression of AVP mRNA but not CRF mRNA in the PVN, suggesting that parvocellular AVP mediates the effects of SSRIs on HPA axis activity (Hesketh et al., 2005).

Behavioral study results suggest that the antidepressive action of SSRIs and their influence on anxiety is partly mediated by AVP. In olfactory bulbectomized (OB) mice, chronic fluoxetine reversed depressive-like behavior as evaluated in the tail suspension test (TST) and reduced AVP and ACTH plasma levels. Whereas in OB-saline mice displaying depressive-like behavior, a high level of plasma AVP and increased V_{1B} expression in the pituitary were detected. Antidepressive effects of chronic fluoxetine may be mediated by a reduction of AVP because AVP administrated ICV blocked this effect in OB mice, and treatment with a selective V_{1B} antagonist reduced the expression of the depressive-like behavior in OB mice. Chronic fluoxetine treatment upregulated V_{1B} gene expression in sham-operated mice (Poretti et al., 2016). Fluvoxamine given chronically induced anti-anxiety effects in wild-type male mice but not in V_{1B} knock-out mice and V_{1B} antagonist-treated mice (Ishizuka et al., 2010). In turn, a paradoxical anxiogenic-like effect produced by short-term fluoxetine treatment in adolescent male rats was associated with increased expression of AVP mRNA in the PVN (Gomez et al., 2014).

In male hamsters, peripheral administration of fluoxetine blocked aggression induced by AVP administration into lateroanterior hypothalamus or ventrolateral hypothalamus. Fluoxetine given chronically to adolescent male hamsters increased adulthood offensive aggression correlated with an increase in AVP fiber innervation in the lateroanterior hypothalamus and had no influence on social interest (Ricci and Melloni, 2012).

In rats, De Magalhães-Nunes et al. (2007) investigated the effects of long-term administration of sertraline on water and sodium intake and on AVP plasma levels in basal conditions and after water deprivation. In basal and stimulated conditions, sertraline reduced water intake. Sertraline reduced plasma sodium levels and increased plasma AVP concentration. Other studies have shown that fluoxetine also increased plasma AVP concentration in rats (Gibbs and Vale, 1983). Additionally, Satish et al. (2014) indicated that escitalopram has an antidiuretic action in rats.

In clinical studies, it has been observed that therapy with SSRIs results in a risk for developing syndrome of inappropriate secretion of antidiuretic hormone, SIADH, especially in elderly patients as manifested by hyponatremia, as well as low serum and high urine osmolalities (Jagsch et al., 2007; Rottmann, 2007). When fluvoxamine treatment was discontinued and hypertonic saline was infused serum sodium levels and osmolalities subsequently normalized (Inaguma et al., 2000).

Data from behavioral studies confirmed that antidepressive-like and anti-anxiety effects of SSRIs at least partially depend on their influence on AVP because SSRI action is blocked as a result of modulating AVP system activity. AVP mediates the effect of SSRIs (given chronically) on HPA axis activity and is involved in the development of side effects related to hydromineral balance.

4.3. SSRI and GAL transmission

In lab animals exposed to stress, various effects of repeated SSRI administration on GAL expression in different brain structures have been shown. In NMRI mice, repeated fluoxetine administration reverted depression-like behavior induced by chronic restraint stress (CRS) and increased GAL expression in the dorsal dentate gyrus, amygdala and piriform cortex (Christiansen et al., 2011). However, in C57BL/6J mice exposed to CRS, fluoxetine given chronically normalized behavioral disturbances but reversed the increased expression of GAL and GAL_2 in the nucleus accumbens (Zhao et al., 2013). After repeated fluoxetine administration in non-stressed rats, upregulation of GAL mRNA and enhanced density of GAL_2-binding sites in the DRN was observed. Moreover, it has been shown that modulating GAL system activation is relevant to its antidepressant-like effect. Namely, M40, a GAL receptor antagonist, diminished the effect of fluoxetine in the FST, and galnon, an agonist of the GAL receptor, produced an antidepressant-like effect in the same test. The published data suggested antidepressive role of the GAL_2 (Lu et al., 2005). Furthermore, the antidepressant-like effect induced by repeated fluoxetine administration in the FST was enhanced by the N-terminal fragment GAL (1–15). The behavioral effects of both substances, fluoxetine and GAL N-terminal fragment, were blocked by 5-HT_{1A} receptor antagonism (Flores-Burgess et al., 2017). Sertraline, another SSRI, given chronically in a dose sufficient to induce antidepressant-like effects, evoked GAL expression in ventral dentate gyrus but not in the dorsal dentate gyrus in mice (Yamada et al., 2013). The ventral dentate gyrus, versus the dorsal, is known for playing an important role in stress, emotion and affective disorders. These results suggest that the GAL system plays a role in the effects of antidepressant drugs given chronically. Divergent effects were noticed after acute fluoxetine administration. In C57BL/6J mice, anti-immobility behaviors in the TST, induced by fluoxetine given at a single dose, were unaltered in GAL overexpressing transgenic mice as well as in GAL_1 knock-out mice. GAL given ICV had no influence on behavior in the TST (Holmes et al., 2005). Thus, these results did not confirm a role for GAL in depression-related behavior in mice.

The potential involvement of the hypothalamic GAL system in an anorectic effect of repeated fluoxetine administration in genetically obese Zucker (*fa/fa*) rats has been studied (Churruca et al., 2004). Fluoxetine-treated rats displayed decreased food intake, reduced final

body weight and total body fat, decreased water intake and urine elimination and diminished body water content. It has been suggested that increased GAL immunostaining in the magnocellular region of the PVN is, at least partly, responsible for the fluoxetine-induced hydro-osmotic impairment because, in the hypothalamic nucleus, GAL, via coexistence with AVP, may be involved in the regulation of water balance (Landry et al., 2000). An increase in GAL immunostaining in the hypothalamus was interpreted as a compensatory mechanism against reduced food intake induced by fluoxetine (Churruca et al., 2004).

The presented data, suggesting that GAL plays a role in the mechanism of the antidepressive effects of SSRIs given chronically, are convincing because modulation of GAL system activity modifies SSRI effects. Taking into consideration the physiological relevance of GAL, its contribution to side effects of SSRIs, such as hydro-osmotic impairment, seems probable. It seems, that Gal_1 antagonist or Gal_2 agonist may represent new therapeutic principles for the development of antidepressants and may act in combination with SSRIs.

4.4. SSRI and OT transmission

An increase in oxytocin release is considered to be an indicator of SSRI efficacy in the treatment of disorders with a psychosocial origin. In male rats, increased plasma OT levels were demonstrated after acute and chronic treatment with citalopram (Uvnäs-Moberg et al., 1999). OT mRNA was also increased in the magnocellular PVN neurons after acute citalopram administration but not as a result of its chronic infusion (Hesketh et al., 2005). It was underlined, that OT receptors are localized on 5-HT cells (Crockett and Fehr, 2014). Further 5-HT receptors are located on OT neurons (Hunt et al., 2011). Nagano and co-workers (2018) showed that 5-HT_{1A} agonist 8OH-DPAT administrated in the early postnatal period gives very promising results in adult 15q dup mice (autism animal model). It is well-known also, that fluoxetine gave similar effects (Nagano et al., 2012). Bagdy and Kalogeras (1993) indicated that this selective drug increased OT plasma level in rats. Actually, 8-OH DPAT to elevate OT plasma levels in naïve and 15q dup mice (Nagano et al., 2018). Desensitization of 5-HT receptors induced by multiple administration of two SSRIs was associated with a reduced OT response. Namely, paroxetine diminished OT response to agonism of $5HT_{1A}$ receptors (Li et al., 1997) and fluoxetine reduced stimulation of OT levels by $5HT_{2A}$ receptor agonism in the rat PVN (Raap et al., 1999a; Raap et al., 1999b; Serres et al., 2000; Damjanoska and Van de Kar, 2003). These results indicate that adaptive changes in the serotonergic system induced by SSRIs are associated with alterations in OT signaling. In prepubescent male rats, fluoxetine given subchronically had no influence on basal plasma OT levels but suppressed the effect of 5-HT_{2A} receptor agonism, increasing plasma OT levels (Landry et al., 2005).

OT is thought to be involved in the development of the inhibitory effect of SSRIs on sexual behavior. A delayed ejaculation is at least partly related to altered OT transmission as a result of 5-HT_{1A} receptor desensitization induced by chronic treatment with SSRIs. Effects of fluoxetine and paroxetine were stronger than fluvoxamine and citalopram (for review see de Jong et al., 2007). These data confirmed the hypothesis that 5-HT suppresses ejaculation by attenuation of OT action. A role for OT in this SSRI effect was supported by results showing that systemic injection of OT reversed the fluoxetine-induced inhibition of ejaculation (Cantor et al., 1999).

Keating et al. (2013) evaluated OT plasma levels in 16 patients with major depressive disorder (newly diagnosed and recently untreated patients, after relapse) before and following 12 weeks of treatment with SSRI (citalopram, sertraline and fluoxetine). Therapy efficiently decreased anxiety and HPA axis activity but did not affect OT levels that were unrelated to psychological symptom scores. Similarly, Ozsoy et al. (2009) failed to detect differences in serum OT levels before and after treatment with antidepressant drugs in patients with depressive disorders. However, a positive relationship between plasma OT levels and sexual dysfunction scores after one month of therapy with citalopram or fluoxetine in women with major depressive disorder was reported in a study by Abbasinazari et al. (2018). In this clinical study, OT levels were lower in fluoxetine- than citalopram-treated patients.

The above mentioned preclinical data suggest that OT contributes to SSRI effects due to changes in the 5-HT system induced by SSRIs affecting OT signaling. Together, the above results provide evidence for a role of OT in the inhibitory effect of SSRIs on sexual behavior.

4.5. SSRIs and NPY transmission

Alterations in the NPY system after repeated SSRI administration were relatively rarely as studied in preclinical investigations. In NMRI mice, fluoxetine treatment reverted depression-like effects of chronic restraint stress and simultaneously increased NPY levels in the dentate gyrus and piriform cortex (Christiansen et al., 2011). In naive rats, citalopram given chronically increased 125I-PYY binding in the hippocampal regions but did not affect preproNPY mRNA and extracellular NPY in the hippocampus (Husum et al., 2000). In female Flinders Sensitive Line (FSL) rats, escitalopram induced antidepressant-like effects in the FST and had no effect on hippocampal NPY mRNA and Y_1 receptor mRNA (Bjørnebekk et al., 2010). FSL rats, which are purported to be a genetic animal model of depression, have shown disturbances, such as altered REM sleep, reduced body weight and increased immobility time in the FST, considered to be depressive-like behavior (Overstreet, 1993). In FSL rats, after chronic fluoxetine administration, increased NPY mRNA expression (Caberlotto et al., 1998), enhanced NPY levels (Caberlotto et al., 1999) in some brain regions (the arcuate nucleus and cingulate cortex) and an increase in Y_1 binding in some cerebral structures was found (Caberlotto et al., 1999). Fluoxetine produced an antidepressive-like effect in mice lacking Y_1 receptors, confirming that NPY transmission via Y_1 receptor is not necessary for fluoxetine's effect (Karlsson et al., 2008).

Fluoxetine and sertraline seem to be more related to anorexigenic effects than other SSRIs (Fava et al., 2000). Some preclinical studies demonstrated that fluoxetine induced two effects, an anorexigenic effect and reduction of NPY in the PVN in the obese (*fa/fa*) Zucker rats (Gutiérrez et al., 2002). Fluvoxamine given repeatedly in normophagic rats had no effect on weight gain and food intake, but, during the refeeding period, food-restriction-induced hyperphagic rats inhibited their weight gain and food intake. These effects were associated with low NPY levels in the PVN and dorsomedial hypothalamus (Shinozaki et al., 2008).

Clinical studies showed evidence of changes in NPY following SSRI administration. Nikisch et al. (2005b) reported a positive correlation between clinical improvement after long-term treatment with citalopram and increased NPY levels in CSF of depressive patients. An increase in serum NPY levels was found after treatment with escitalopram but not in patients with generalized anxiety disorder and adjustment disorder or after treatment with sertraline and fluoxetine in patients with major depression disorder. These results indicate that the effect on NPY is drug-dependent and suggests that it may be particular to depression (Ozsoy et al., 2016). They also clearly highlight how complex the mechanisms of affective disorders are and the differences between SSRIs in terms of their influence on neurochemical processes in the CNS.

The data concerning the influence of SSRIs on NPY are varied. Except for one study by Karlsson et al. (2008) carried out on mice lacking Y1 receptor, there are no studies clearly demonstrating whether changes in the NPY system induced by SSRIs are primary alterations important for their antidepressant/anti-anxiety effects or whether they are only secondary changes.

4.6. SSRIs and OX transmission

Until now, influence of SSRIs on OX transmission was the subject of

only a few investigations. In preclinical studies, effects of chronic treatment with fluoxetine or escitalopram were evaluated in different animal models. In mice subjected to UCMS, fluoxetine not only reversed behavioral alterations but also reversed activation of OX neurons in the dorsomedial and perifornical hypothalamic areas and blocked reduction of OX_2 expression in some brain structures (Nollet et al., 2011). In turn, escitalopram had no effect on the increased number of OX-positive neurons in the hypothalamus of FSL female rats (Mikrouli et al., 2011).

In the clinical study, it has been found that a five-week treatment with sertraline decreased OX levels in the CSF of patients with major depressive disorder compared to levels before treatment (Salomon et al., 2003).

While some data indicate that the OX system is involved in depression, anxiety and stress response, as described in Section 2.6, there are too few results concerning an interaction between SSRIs and OX to support a conclusion.

5. Concluding remarks

Findings from well-designed studies world-wide indicate that the mechanism of action of antidepressant drugs, including SSRIs, is complex. Based primarily on preclinical study results, it is thought that the pharmacological effects of SSRIs are partially mediated by neuropeptides.

In this paper we focused on well-known neuropeptides, CRF, OT, AVP, NPY, and the more recently discovered molecules, GAL and the OXs. The most important results related to neuropeptide effects and neuropeptide alterations in animal models of stress-related disorders are highlighted in Table 1. In general, the data indicates that the neuropeptides CRF, GAL, and AVP induce depressive-like behavior and cause anxiety in lab animals, whereas OT induces antidepressive and anti-anxiety effects in the stressed animals. These basic observations suggest that neuropeptides may contribute to the etiology of depression and anxiety. Preclinical studies have shown that neuropeptide effects are mediated by different subtypes of their receptors. For example, the anxiogenic effect of CRF is mediated by CRF_1 receptor, the blockade of both AVP receptors, V_{1A} and V_{1B}, induces antidepressant and anxiolytic effect in behavioral tests, and Y_1 but not Y_2 receptor mediates the antidepressant-like and anxiolytic effects of NPY.

The hypothesis that the neuropeptides reported in this work likely contribute to the mechanism of action of SSRIs is supported by the following findings: 1) in behavioral tests, modulation of neuropeptide transmission induced effects similar to SSRI effects, 2) neuropeptides are involved in regulation of HPA axis activity, which is an important mechanism of SSRI action, 3) neuropeptides are coupled to 5-HT transmission such that changes in the 5-HT system affect neuropeptide signaling and alterations in those systems may modify 5-HT transmission and 4) actions of SSRIs given chronically were blocked by modulation of neuropeptide system activity (AVP, GAL) and SSRIs administered chronically reversed neuropeptide (CRF) changes detected in an animal model of depression or abolished behavioral neuropeptide effects (CRF). Moreover, it seems that alterations in neuropeptide transmission induced by SSRIs may significantly influence side effects: OT – suppression of sexual behavior and loss of appetite, AVP – hydromineral imbalance and CRF – body weight changes. Alterations in GAL transmission are recognized as a compensatory response against the reduced food intake and hydro-osmotic impairment evoked by SSRIs. Future studies on more recently discovered neuropeptides like OXs, neuropeptide S (NPS), and relaxin-3 (RLN-3), which has a postulated role in stress response, may provide interesting new data.

The majority of the results cited here suggest that an interaction between SSRIs and neuropeptides seems credible but that future research in this field is necessary to clarify some uncertainties. Undoubtedly, more clinical studies are required because currently available clinical data is insufficient and equivocal. Neuropeptide concentrations in CSF or plasma from patients with various subtypes of depressive and anxiety disorders and differing therapeutic responses to SSRIs should be performed. Future preclinical research should focus on evaluating the exact involvement of neuropeptide signaling in the mechanism of action of different SSRIs utilized in various models of depressive and anxiety disorders. As shown in Tables 2 and 3, the majority of studies investigated fluoxetine. Since SSRIs are a non-homogeneous group of drugs (Baldessarini, 2006; Sanchez et al., 2014), more research with other SSRI representatives should be carried out to better recognize their potentially disparate effects. Furthermore, studies that use a specific agonist or antagonist of a particular subtype of neuropeptide receptor should provide more clear evidence of whether the neuropeptide alterations induced by SSRIs are significant for the drug mechanism of action or are only associated with their pharmacological effects. Clinical trials with small neuropeptide mimetics that have good blood-brain barrier penetration or trials with intranasal administration of neuropeptide analogs used alone or as an adjunctive treatment to SSRI may lead to achievement of better therapeutic effects in patients with depressive/anxiety disorders. Additional research is needed for the development of novel therapeutic strategies in mood-related disorders.

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