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Review

Behavioral effects of neuropeptides in rodent models of depression and anxiety

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ABSTRACT

In recent years, studies have advocated neuropeptide systems as modulators for the behavioral states found in mood disorders such as depression and anxiety disorders. Neuropeptides have been tested in traditional animal models and screening procedures that have been validated by known antidepressants and anxiolytics. However, it has become clear that although these tests are very useful, neuropeptides have distinct behavioral effects and dose-dependent characteristics, and therefore, use of these tests with neuropeptides must be done with an understanding of their unique characteristics. This review will focus on the behavioral actions of neuropeptides and their synthetic analogs, particularly in studies utilizing various preclinical tests of depression and anxiety. Specifically, the following neuropeptide systems will be reviewed: corticotropin-releasing factor (CRF), urocortin (Ucn), teneurin C-terminal associated peptide (TCAP), neuropeptide Y (NPY), arginine vasopressin (AVP), oxytocin, the Tyr-MIF-1 family, cholecystokinin (CCK), galanin, and substance P. These neuropeptide systems each have a unique role in the regulation of stress-like behavior, and therefore provide intriguing therapeutic targets for mood disorder treatment.

Contents

Abbreviations: ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; BLA, basolateral amygdala; CCK, cholecystokinin; CCK1, cholecystokinin-1 (receptor); CCK2, cholecystokinin-2 (receptor); CRF, corticotropin-releasing factor; CRF_1, corticotropin-releasing factor (receptor)-1; CRF_2, corticotropin-releasing factor (receptor)-2; EPM, elevated plus maze; FRL, Flinders resistant line; FSL, Flinders sensitive line; FST, forced swim test; GAL1, galanin-1 (receptor); GAL2, galanin-2 (receptor); GAL3, galanin-3 (receptor); HAB, high anxiety-like behavior (rat); HPA, hypothalamic-pituitary-adrenal; i.c.v., intracerebroventricular; i.p., intraperitoneal; LAB, low anxiety-like behavior (rat); MeA, medial nucleus of the amygdala; NK1, neurokinin-1 (receptor); NK2, neurokinin-2 (receptor); NK3, neurokinin-3 (receptor); NPY, neuropeptide Y; OTR, oxytocin receptor; PVN, paraventricular nucleus of the hypothalamus; SSRI, selective serotonin-reuptake inhibitor; TCAP, teneurin C-terminal associated peptide; MIF-1, melanocyte stimulating hormone-inhibiting factor-1; Ucn, urocortin; V1, vasopressin-1 (receptor); V1a, vasopressin-1a (receptor); V1b, vasopressin-1b (receptor); V2, vasopressin-2 (receptor); VTA, ventral tegmental area; Y1, neuropeptide Y-1 (receptor); Y2, neuropeptide Y-2 (receptor); Y5, neuropeptide Y-5 (receptor).

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1. Introduction

In recent years, there has been a rapid expansion of information regarding neuropeptides and their role in modulating behavior, as peptides are increasingly being recognized as potential targets for treating mood and anxiety disorders [35,72,86,88,132,133]. The monoamine hypothesis of depression has provided an important theoretical and experimental framework within which to test hypotheses about mood regulation, but it has become clear that neuropeptides play an essential role in mood regulation as well. Peptides are widely distributed in the brain in key areas of emotional regulation. Moreover, peptides play a modulatory role on monoamine systems, and in particular when the nervous system is stressed, challenged, or diseased [87]. However, given that peptides have unique mechanisms of action, behavioral effects may not always be apparent under standard testing conditions using animal tests that have been validated against benzodiazepines, tricyclics and selective serotonin reuptake inhibitors (SSRIs). In many cases, peptidergic effects are dose-dependent and are only seen in some tests but not others. Therefore, the behavioral effects of peptides must be evaluated differently as compared with monoamine systems and small-molecule receptor antagonists.

This review will focus on the effects of neuropeptides and their receptor agonists and antagonists in preclinical models of depression and anxiety. Major neuropeptides of interest in drug development will be discussed, namely: corticotropin-releasing factor (CRF), urocortin (Ucn), teneurin C-terminal associated peptide (TCAP), neuropeptide Y (NPY), arginine vasopressin (AVP), oxytocin, the Tyr-MIF-1 family, cholecystokinin (CCK), galanin, and substance P. This review will not examine the effects of knockout or knockdown animals in these models, as the focus is strictly on the effects of pharmacological manipulations of intact peptide systems.

2. The use of *in vivo* models

Many preclinical models for testing and screening potential new antidepressants and anxiolytics have been developed. It is generally agreed that converging evidence from more than one behavioral test is required, and similarly that no animal model will ever be able to adequately take into account all of the complex aspects of mood and anxiety disorders. The tests are not meant to be "models" of a disorder *per se*, but instead mimic characteristics of a disorder or behavioral dimension that are necessary to make psychiatric disorders amenable to study in a preclinical environment. As it can never be determined if an animal is truly depressed, the term "model" is used in the current paper to refer to validated tests that measure behavioral changes that are reasonably analogous to the human disorder, and that are reversed by treatments that are effective in humans [38]. Models have traditionally been validated using known antidepressants and anxiolytics. However, when it comes to assessing the antidepressant or anxiolytic potential of compounds with novel mechanisms of action, such as peptides or synthetic analogs of their receptor ligands, there may be unique behavioral profiles that emerge. These must be evaluated carefully and new compounds not be rejected simply because they do not perform in the same way as the tricyclics, SSRIs, or benzodiazepines.

Another difficulty in using animal models is the vast array of variables that can be, and are, manipulated differently from laboratory to laboratory. Behavioral testing is notoriously difficult to replicate, even when all efforts to duplicate testing situations are followed [224]. Thus, findings of different results in the various laboratories are not always due to the test compound, but may in large part be due to differences in testing conditions.

3. Preclinical models of depression

Several tests have been used extensively and have been validated using a wide range of compounds. These tests involve subjecting rodents to acute or chronic stress which induces depressive-like characteristics. The most widely used and accepted screening test for antidepressant potential is the forced swim test (FST). This test was first reported as a rodent model that was

sensitive to antidepressants and insensitive to other compounds, such as benzodiazepines [168,169]. The FST involves placing a rodent into an inescapable container of water for a specified amount of time (usually 15 min), and then treating the animal with a drug, typically at 3 time points over 24 h, but can involve longer treatment periods. Upon completion of the treatment, the rodent is reintroduced to the swim chamber and the time spent immobile is recorded. Immobility is a characteristic behavior that is reduced by antidepressant treatment (for a review, see [24,40]). Another related test, the tail suspension test, is similar to the FST, in that immobility is the dependent measure of interest. In this test a mouse is suspended by the tail and time spent immobile is recorded. This test is generally more sensitive to SSRIs than the FST [39].

In the learned helplessness model of depression, rodents are initially exposed to inescapable stress (for example, footshocks). After this acquisition period, animals are then presented with the same environment, but now escape is possible. Untreated animals often make no attempt to escape, an effect that is reversed by some antidepressant treatments [4,69,94].

Another animal model of depression is chronic mild stress, which models the anhedonic behavior associated with major depression (for a review, see [229]). This test involves introducing a rodent to a highly palatable sugar solution, which provides the baseline sugar intake. Animals are then exposed to a chronic regimen (often lasting many weeks) of mild stressors, for example, food or water deprivation, cage tilt, paired housing, continuous lighting, soiled cage, or reduced ambient temperature [230]. Potential antidepressant drugs are then administered during the chronic stress period. Upon completion of the chronic stress regimen and drug treatment, animals are again presented with sugar solution. Untreated animals will generally decrease their sugar intake, whereas antidepressant treatment, such as desipramine or imipramine, will return sugar preference to baseline [99,230]. This test is hypothesized to be a disease model for depression, as the chronic nature of the stressor is thought to produce enduring effects akin to those seen in depressed patients. Since stress is a precipitating factor in depression, it is thought that exposing the animals to chronic stress will reproduce the physiological effects that lead to depression. The decrease in sucrose consumption is thought to reflect the anhedonia that is a core feature of depression. However, it is very difficult to reliably elicit an anhedonic effect, as chronic mild stress paradigms are variable and difficult to reproduce. Furthermore, hyperphagia, especially of carbohydrates, is often seen in some subtypes of depression. These findings, combined with the labor-intensive nature of the studies, have resulted in this model being used less frequently than others.

Another option for attempting to model depression is to use a genetically selected line of rodents, which display behavioral characteristics of depression or anxiety in validated tests. Several such lines have been developed, but again must be interpreted with caution, as they are not known to model all of the physiological and behavioral characteristics of the illness, but rather to embody certain relevant phenotypes.

4. Preclinical models of anxiety

Many tests of anxiety have been developed and validated, and as mentioned previously, positive results on multiple tests are desirable in evaluating novel therapeutics. The tests below are not necessarily an exhaustive list but provide a wide sample of behavioral states that are commonly investigated when dealing with novel anxiolytic or anxiogenic compounds. The tests mentioned in this review can be roughly grouped into tests of exploratory behavior, social behavior, reflexive fear responding, conflict behavior, and defensive behavior.

4.1. Exploratory behavior tests

The most common screening test for anxiolytic compounds is the elevated plus maze (EPM), which is an unconditioned model of anxiety (for a review, see [124,184]). This maze consists of four narrow arms arranged in a cross, which are connected to a central platform. Two arms are not enclosed whereas two arms are enclosed by unscalable walls. The entire maze is elevated on a single stand below the center platform. Animals are introduced to the maze and are allowed to freely explore. Treatment with anxiolytic drugs, such as benzodiazepines, tends to increase the amount of time spent on and number of entries into the open arms, whereas anxiogenic treatments decrease the amount of time spent on and number of entries into the open arms [165]. It is thought that the open spaces produce a stressful environment [211].

Other tests that feature exploratory behavior and utilize similar anxiogenic stimuli of open spaces include the elevated zero maze [191], defensive withdrawal test [204], light-dark box, and the open field test [124]. It is important to note that exploratory tests are sensitive to changes in locomotion, and peptidergic effects on motor activity may be mistaken for changes in anxiety-like behavior. Therefore, converging evidence from other types of anxiety tests may be required to validate a novel compound.

4.2. Social behavior tests

The social interaction test is another model of anxiety, which examines social behavioral responses [61,124]. Pairs of rodents are placed in an arena and are allowed to interact. The amount of time spent interacting with the test mate is decreased in unfamiliar arenas or bright lighting conditions, or following the administration of anxiogenic drugs. The decrease in social interaction is prevented by treatment with anxiolytics, such as chlordiazepoxide [62] but not antidepressants like imipramine [165]. Other tests that utilize social behavior are alarm tests, such as the rat ultrasonic vocalization test or gerbil foot tapping test. Rodents will produce alarm calls in response to anxiety-inducing stimuli, such as maternal separation, isolation, or shock. Anxiolytic manipulations, such as diazepam, tend to reduce vocalizations [223] or foot tapping [13].

4.3. Reflexive fear tests

The acoustic startle test measures the reflexive response to a sudden loud noise [43,118]. Animals that have been previously exposed to stressors will have a higher response on the acoustic startle test (reviewed in [9]). In the fear-potentiated startle test, an animal is conditioned to an electric shock paired with a light. Subsequently, the presence of the light prior to the acoustic stimuli will potentiate the startle response. Treatment with anxiolytics such as diazepam or buspirone will block the potentiation effect [42,101], but antidepressants such as imipramine will not [33]. Another test that utilizes fear circuitry includes the conditioned freezing test, which measures the freezing behavior in response to a conditioned cue that paired with an aversive stimulus, like a shock. Treatment with midazolam [76] or diazepam [129] will reduce conditioned freezing in this paradigm.

4.4. Conflict tests

Another group of tests include the punished responding tasks, such as the Vogel conflict test [136], conditioned lick suppression

test [166], and four-plate test [182]. These tests measure the amount of "punished" responding (punishment occurs usually via a mild shock) to a desirable stimulus, such as food, water, or exploration. Anxiolytic manipulations will tend to increase the amount of punished responding.

4.5. Defensive behavior tests

Defensive behavior tests are tests of anxiety that measure defensive reactions to a novel stimulus. These tests include the shock-probe burying test, where a rodent will spread bedding towards a shock probe placed in the test cage after a shock has been delivered, and the marble burying test, where rodents, specifically mice, will bury novel objects in their bedding. Finally, the mouse defence test battery is a series of tests that measure defence behaviors in response to a predator [21]. Anxiolytics such as benzodiazepines reduce the incidence of defensive behavior [21,210].

5. Corticotropin-releasing factor (CRF)

The role of CRF in depression and anxiety has been extensively documented [6,47,138]. CRF is a key peptide in the co-ordinating the behavioral, neuroendocrine, and autonomic responses to stress [81,215]. The CRF family of peptides in humans consists of CRF, urocortin, urocortin 2 and urocortin 3. CRF acts in the brain through at least two different receptor subtypes, CRF_1 and CRF_2. The CRF_1 receptor, which binds only CRF and the urocortins, is implicated in the stress-producing effects of CRF, and is widely distributed throughout the brain, including key regions of cortex and limbic system. The CRF_2 receptor binds to all four peptide ligands but shows a more limited distribution [219].

5.1. Depression

There is a great deal of evidence implicating CRF in the etiology of depression [89] (Table 1). However, preclinical models of

Table 1
Effects of neuropeptide receptor ligands in rodent tests or models of depression.

Ligand	Receptor	Model	Species	Dose	Route	Duration	Effect	Reference
CRF receptor ligands in depression								
Antalarmin	CRF_1 antagonist	FST	Mouse	3–30 mg/kg	i.p.	Acute	0	[150]
		FST	Mouse	3–30 mg/kg	i.p.	Subchronic	0	[150]
		Tail suspension	Mouse	3–30 mg/kg	i.p.	Acute	0	[150]
		Tail suspension	Mouse	3–30 mg/kg	i.p.	Subchronic	0	[150]
CP-154,526	CRF_1 antagonist	Inescapable stress	Rat	10–32 mg/kg	i.p.	Subchronic	↓	[131]
		FST	Mouse	1–30 mg/kg	i.p.	Acute	0	[85]
		FST	Rat	30 mg/kg	i.p.	Acute	↓	[85]
		FST	Flinders rat	10 mg/kg	i.p.	Chronic	↓	[159]
		Tail suspension	Mouse	1–30 mg/kg	i.p.	Acute	0	[85]
		Tail suspension	Mouse	0.3–3 mg/kg	i.p.	Acute	0	[233]
DMP 696	CRF_1 antagonist	FST	Mouse	3–30 mg/kg	i.p.	Acute	0	[150]
		FST	Mouse	3–30 mg/kg	i.p.	Subchronic	0	[150]
		Tail suspension	Mouse	3–30 mg/kg	i.p.	Acute	0	[150]
		Tail suspension	Mouse	3, 10 mg/kg	i.p.	Subchronic	↓	[150]
DMP 904	CRF_1 antagonist	FST	Mouse	3–30 mg/kg	i.p.	Acute	0	[150]
		FST	Mouse	3–30 mg/kg	i.p.	Subchronic	0	[150]
		Tail suspension	Mouse	3–30 mg/kg	i.p.	Acute	0	[150]
		Tail suspension	Mouse	3–30 mg/kg	i.p.	Subchronic	0	[150]
R121919	CRF_1 antagonist	FST	Mouse	3–30 mg/kg	i.p.	Acute	0	[150]
		FST	Mouse	3–30 mg/kg	i.p.	Subchronic	0	[150]
		Tail suspension	Mouse	3–30 mg/kg	i.p.	Acute	0	[150]
		Tail suspension	Mouse	30 mg/kg	i.p.	Subchronic	↓	[150]
SSR125543	CRF_1 antagonist	FST	Flinders Rat	3–30 mg/kg	i.p.	Chronic	↓	[156]
Urocortin 1	CRF_1/CRF_2 agonist	FST	Mouse	0.13–0.5 μg	i.c.v.	Acute	0	[206]
Urocortin 2	CRF_2 agonist	FST	Mouse	0.13–0.5 μg	i.c.v.	Acute	↓	[206]
Urocortin 3	CRF_2 agonist	FST	Mouse	0.13–0.5 μg	i.c.v.	Acute	↓	[206]
NPY receptor ligands in depression								
Neuropeptide Y (NPY)	Y agonist	FST	Mouse	0.1 nmol	i.c.v.	Acute	↓	[176]
		FST	Rat	0.5, 10 ng	i.c.v.	Subchronic	↓	[201]
		FST	Rat	1–2.1 ng	i.c.v.	Acute	↓	[71]
		Learned helplessness	Rat	500 ng	i.c.v.	Acute	↓	[91]
		Learned helplessness	Rat	5 ng	CA3	Acute	↓	[91]
		Learned helplessness	Rat	0.5–500 ng	DG	Acute	0	[91]
BIBO3304	Y1 antagonist	FST	Mouse	0.003–0.3 nmol	i.c.v.	Acute	0	[176]
		Learned helplessness + NPY	Rat	1 ng	CA3	Acute	↑	[91]
BIBP3226	Y1 antagonist	FST	Mouse	0.03–3 nmol	i.c.v.	Acute	0	[176]
		Learned helplessness	Rat	1 ng	CA3	Acute	0	[91]
BIIE0246	Y2 antagonist	FST	Mouse	3 nmol	i.c.v.	Acute	↓	[176]
		Learned helplessness	Rat	10 ng	CA3	Acute	↓	[91]
[Leu(31) Pro(34)]PYY	Y1/Y5 agonist	FST	Mouse	3 nmol	i.c.v.	Acute	↓	[176]
		FST	Rat	0.4–0.6 ng	i.c.v.	Acute	↓	[71]
		Learned helplessness	Rat	1 ng	CA3	Acute	↓	[91]

Table 1 (*Continued*)

Ligand	Receptor	Model	Species	Dose	Route	Duration	Effect	Reference
AVP receptor ligands in depression								
SSR149415	V1b antagonist	FST	Mouse	1–30 mg/kg	i.p.	Acute	0	[85]
		FST	Rat	10–30 mg/kg	i.p.	Acute	↓	[73]
		FST	Rat	10–100 ng	Lat. Septum	Acute	↓	[200]
		FST	Rat	1–100 ng	Amygdala	Acute	↓	[188]
		FST	Rat	1–30 mg/kg	i.p.	Acute	0	[85]
		FST	Flinders Rat	3–30 mg/kg	i.p.	Chronic	↓	[157]
		FST + Stress	Mouse	10–30 mg/kg	i.p.	Chronic	↓	[73]
		Tail suspension	Mouse	1–30 mg/kg	i.p.	Acute	0	[85]
D-$(CH_2)_5$Tyr(Me)AVP	V1a antagonist	FST	HAB Rat	5 ng	PVN	Acute	↓	[228]
Oxytocin receptor ligands in depression								
Oxytocin	OTR agonist	FST	Mouse	0.25–1 mg/kg	i.p.	Acute	↓	[8]
		FST	HAB Rat	1 μg	i.c.v.	Acute	0	[196]
		FST	HAB Rat	1 μg	i.c.v.	Subchronic	0	[196]
		FST	LAB Rat	1 μg	i.c.v.	Subchronic	0	[196]
		Learned helplessness	Mouse	0.5 mg/kg	i.p.	Subchronic	↓	[8]
		Tail suspension	Mouse	0.3 μg	i.c.v.	Acute	↓	[181]
		Tail suspension	Mouse	30 mg/kg	i.p.	Acute	↓	[181]
WAY-267464	OTR agonist	Tail suspension	Mouse	1–10 μg	i.c.v.	Acute	0	[181]
		Tail suspension	Mouse	10–56 mg/kg	i.p.	Acute	0	[181]
WAY-162720	OTR antagonist	Tail suspension	Mouse	30 mg/kg	i.p.	Acute	0	[181]
		Tail suspension + Oxytocin	Mouse	30 mg/kg	i.p.	Acute	0	[181]
OXT-A	OTR antagonist	FST	LAB Rat	10 ng/h	i.c.v.	Acute	0	[196]
		FST	HAB Rat	10 ng/h	i.c.v.	Subchronic	0	[196]
		FST	LAB Rat	10 ng/h	i.c.v.	Subchronic	0	[196]
Tyr-MIF-1 family receptor ligands in depression								
Endomorphin-1	μ-opioid agonist	FST	Mouse	0.3–30 μg	i.c.v.	Acute	↓	[59]
		Tail suspension	Mouse	1–30 μg	i.c.v.	Acute	↓	[59]
Endomorphin-2	μ-opioid agonist	FST	Mouse	0.3–30 μg	i.c.v.	Acute	↓	[59]
		Tail suspension	Mouse	1–30 μg	i.c.v.	Acute	↓	[59]
MIF-1	Unknown	Chronic mild Stress	Rat	0.1–1 mg/kg	i.p.	Chronic	↓	[167]
		Chronic mild Stress	Rat	10 mg/kg	i.p.	Chronic	↑	[167]
		FST	Mouse	0.15–1.2 mg/kg	i.p.	Acute	0	[7]
		FST	Rat	0.1 mg/kg	i.p.	Subchronic	↓	[98]
		FST	Rat	1–30 mg/kg	i.p.	Subchronic	0	[98]
		FST	Rat	1 mg/kg	i.p.	Subchronic	↓	[108]
		FST	Rat	0.01 mg/kg	i.p.	Subchronic	↓	[171]
		FST + Amitriptyline	Rat	0.01 mg/kg	i.p.	Subchronic	↓	[108]
		FST + Desipramine	Rat	0.01 mg/kg	i.p.	Subchronic	↓	[108]
		FST + Haloperidol	Rat	0.01 mg/kg	i.p.	Subchronic	0	[171]
		FST + Sulpiride	Rat	0.01 mg/kg	i.p.	Subchronic	0	[171]
		Learned helplessness	Mouse	0.3 mg/kg	i.p.	Subchronic	↓	[7]
Nemifitide (INN 00835)	Unknown	FST	Flinders Rat	0.025–0.3 mg/kg	i.p.	Subchronic	↓	[158]
		FST	Flinders Rat	3–15 mg/kg	i.p.	Subchronic	↓	[158]
Tyr-MIF-1	Tyr-MIF-1 agonist	FST	Rat	0.01 mg/kg	i.p.	Subchronic	↓	[171]
		FST + Haloperidol	Rat	0.01 mg/kg	i.p.	Subchronic	0	[171]
		FST + Sulpiride	Rat	0.01 mg/kg	i.p.	Subchronic	0	[171]
CCK receptor ligands in depression								
Cholecystokinin-8 (CCK8)	CCK agonist	FST	Mouse	88 nmol/kg	i.p.	Acute	0	[84]
Devazepide	CCK_1 antagonist	FST	Mouse	0.5–4 mg/kg	i.p.	Acute	0	[84]
BC-264	CCK_2 agonist	FST	Mouse	10 pmol	i.c.v.	Acute	0	[84]
CI-988	CCK_2 antagonist	Chronic mild stress	Rat	1 mg/kg	i.p.	Chronic	↓	[15]
		FST	Rat	1 mg/kg	i.p.	Chronic	↓	[15]
L-365,260	CCK_2 antagonist	FST	Mouse	1–2 mg/kg	i.p.	Acute	↓	[84]
Galanin receptor ligands in depression								
Galanin	GAL agonist	FST	Rat	0.003–3 μg	VTA	Acute	↑	[227]
		FST	Rat	3 nmol	i.c.v.	Acute	↑	[116]
		FST	Rat	3 nmol	i.c.v.	Acute	↑	[115]
		Tail suspension	Mouse	0.3–3 μg	i.c.v.	Acute	0	[174]
Galnon	GAL agonist	FST	Rat	20–40 mg/kg	i.p.	Acute	↓	[126]
		FST	Rat	1–10 mg/kg	i.p.	Acute	0	[174]
		Tail suspension	Mouse	1–5.6 mg/kg	i.p.	Acute	0	[174]
Galantide	GAL antagonist	FST	Rat	0.3 μg	VTA	Acute	↓	[227]
		FST + Galanin	Rat	0.3 μg	VTA	Acute	↓	[227]
M35	GAL antagonist	FST	Mouse	0.3–30 μg	i.c.v.	Acute	0	[174]
		FST	Rat	1 nmol	i.c.v.	Acute	↓	[116]
		FST + Galanin	Rat	1 nmol	i.c.v.	Acute	↓	[116]

Table 1 (*Continued*)

Ligand	Receptor	Model	Species	Dose	Route	Duration	Effect	Reference
M40	GAL antagonist	FST	Mouse	1–10 μg	i.c.v.	Acute	0	[174]
M617	GAL1 antagonist	FST	Rat	3 nmol	i.c.v.	Acute	↑	[115]
M871	GAL2 antagonist	FST	Rat	3 nmol	i.c.v.	Acute	↑	[115]
AR-M1896	GAL2/3 antagonist	FST	Rat	1 nmol	i.c.v.	Acute	↓	[115]
SNAP37889	GAL3 antagonist	FST	Rat	3–10 mg/kg	i.p.	Acute	↓	[202]
		FST	Rat	30 mg/kg	i.p.	Chronic	↓	[202]
GalR3	GAL3 antagonist	FST	Rat	30 mg/kg	i.p.	Acute	↓	[14]
		Tail suspension	Mouse	30–50 mg/kg	i.p.	Acute	↓	[14]
Substance P receptor ligands in depression								
CP-96,345	NK1 antagonist	FST	Rat	2.5–10 mg/kg	i.p.	Subchronic	↓	[41]
GR205171	NK1 antagonist	FST	Mouse	10–30 mg/kg	i.p.	Acute	0	[36]
		FST	Mouse	0.08–0.63 mg/kg	i.p.	Acute	0	[26]
		FST + Citalopram	Mouse	30 mg/kg	i.p.	Acute	↓	[36]
		FST + Desipramine	Mouse	10–30 mg/kg	i.p.	Acute	0	[36]
		FST + Paroxetine	Mouse	10–30 mg/kg	i.p.	Acute	↓	[36]
NKP608	NK1 antagonist	Chronic mild stress	Rat	0.03–0.1 mg/kg	i.p.	Chronic	↓	[164]
SPA	NK1 antagonist	FST	Rat	3 mg/kg	i.p.	Acute	0	[130]
		FST	WKY Rat	3 mg/kg	i.p.	Acute	↓	[130]
SR 48968	NK2 antagonist	FST	Rat	2.5–10 mg/kg	i.p.	Subchronic	↓	[41]
SR 142801	NK3 antagonist	FST	Rat	2.5–10 mg/kg	i.p.	Subchronic	↓	[41]
Vestipitant	NK1 antagonist	FST	Mouse	0.04–0.63 mg/kg	s.c.	Acute	0	[26]

FST: forced swim test; HAB: high anxiety-like behavior; LAB: low anxiety-like behavior; WKY: Wistar-Kyoto (rat); i.p.: intraperitoneal; i.c.v.: intracerebroventricular; i.v.: intravenous; s.c.: subcutaneous; PVN: paraventricular nucleus of the hypothalamus; BLA: basolateral nucleus of the amygdala; DG: dentate gyrus; VTA: ventral tegmental area; Acute: single dose; Subchronic: multiple doses, <14 days; Chronic: 14 days +; ↑: pro-depressive effect; 0: no effect; ↓: antidepressant effect.

depression have shown mixed results regarding an antidepressant-like profile of CRF_1 antagonists. Acute dosing in mice with several CRF_1 antagonists such as CP-154,526, DMP 696, DMP 904 or antalarmin, did not produce antidepressant effects in the tail-suspension and FST [85,150,233]. However, in some cases, such as R121919 and DMP 696, antidepressant-like effects of CRF_1 antagonists can be seen only after subchronic or chronic dosing, but not acute dosing [131,150]. Furthermore, in the rat FST, and other rat models, some CRF_1 antagonists do show antidepressant-like activity [149,160].

A further issue is that many of the tests use "normal" rats, whereas antidepressants are generally only effective in individuals with depression. The Flinders Sensitive Line (FSL) rats have been genetically selected and bred for sensitivity to cholinergic agonists, and is an accepted model of depression. FSL rats exhibit increased immobility in the FST, which is attenuated by chronic treatment with antidepressants from a variety of classes [154,155], and which is not seen in the Flinders Resistant Line (FRL). Chronic treatment with CRF_1 antagonists SSR125543 or CP-154,526 showed antidepressant-like effects in FSL but not FRL [156,159]. Thus, the effects of CRF_1 antagonists may be more obvious using rat lines bred for differences in performance on these tests.

CRF_1 antagonists have shown promising effects in clinical trials [20,114,237] indicating that traditional animal models may not capture the potential antidepressant effects of novel receptor antagonists. Variations on the standard models may be necessary to see the effects of peptide-based compounds.

5.2. Anxiety

The effects of CRF_1 antagonists in animal models of anxiety are similarly dependent upon the test parameters and the baseline anxiety state of the animal (Table 2). For example, a non-peptide CRF_1 antagonist, R121919, displayed anxiolytic effects in the EPM,

Table 2
Effects of neuropeptide receptor ligands in rodent tests or models of anxiety.

Ligand	Receptor	Model	Species	Dose	Route	Duration	Effect	Reference
CRF receptor ligands in anxiety								
α-helical CRF_{9-41}	CRF_1/CRF_2 antagonist	EPM + stress	Rat	1 μg	i.c.v.	Acute	↓	[82]
Antalarmin	CRF_1 antagonist	Conditioned freezing	Rat	20 mg/kg	i.p.	Acute	↓	[45]
Anti-Svg-30	CRF_2 antagonist	Acoustic startle	Mouse	1–10 nmol	i.c.v.	Acute	0	[183]
		Acoustic startle + Stress	Mouse	1–10 nmol	i.c.v.	Acute	↓	[183]
		Conditioned Freezing	Rat	2–20 μg	i.c.v.	Acute	↓	[203]
		Defensive withdrawal	Rat	5–10 μg	i.c.v.	Acute	↓	[203]
		EPM	Mouse	100 pmol	Lat. Septum	Acute	0	[173]
		EPM	Rat	1–10 μg	i.c.v.	Acute	↓	[203]
		EPM + Stress	Mouse	100 pmol	Lat. Septum	Acute	↓	[173]
CP-154,526	CRF_1 antagonist	Acoustic startle + Stress	Rat	17.8 mg/kg	i.p.	Acute	↓	[190]
		EPM	Rat	0.63–80 mg/kg	i.p.	Acute	0	[137]
		EPM	Rat	1–30 mg/kg	i.p.	Acute	0	[85]
		EPM + Stress	Rat	3–10 mg/kg	i.p.	Acute	↓	[152]
		Induced vocalizations	Guinea pig	1–30 mg/kg	i.p.	Acute	↓	[85]
		Induced vocalizations	Rat	2.5–80 mg/kg	i.p.	Acute	0	[137]
		Induced vocalizations	Rat	1–30 mg/kg	i.p.	Acute	↓	[85]
		Light-dark box	Mouse	10–30 mg/kg	i.p.	Acute	0	[152]
		Light-dark box + Stress	Mouse	10 mg/kg	i.p.	Acute	↓	[152]
		Marble burying	Mouse	1–30 mg/kg	i.p.	Acute	0	[85]

Table 2 (*Continued*)

Ligand	Receptor	Model	Species	Dose	Route	Duration	Effect	Reference
		Social Interaction	Rat	2.5 mg/kg	i.p.	Acute	↓	[137]
		Vogel conflict test	Rat	80 mg/kg	i.p.	Acute	↓	[137]
		Vogel conflict test	Rat	1–30 mg/kg	i.p.	Acute	0	[85]
CRA1000	CRF_1 antagonist	EPM + Stress	Rat	1 mg/kg	i.p.	Acute	↓	[152]
		Light-dark box	Mouse	3–10 mg/kg	i.p.	Acute	0	[152]
		Light-dark box + Stress	Mouse	3–10 mg/kg	i.p.	Acute	↓	[152]
CRA1001	CRF_1 antagonist	EPM + Stress	Rat	3–10 mg/kg	i.p.	Acute	↓	[152]
		Light-dark box	Mouse	3–10 mg/kg	i.p.	Acute	0	[152]
		Light-dark box + stress	Mouse	10 mg/kg	i.p.	Acute	↓	[152]
DMP 695	CRF_1 antagonist	EPM	Rat	0.63–40 mg/kg	i.p.	Acute	0	[137]
		Induced vocalizations	Rat	2.5–40 mg/kg	i.p.	Acute	0	[137]
		Social Interaction	Rat	40 mg/kg	i.p.	Acute	↓	[137]
		Vogel conflict test	Rat	40 mg/kg	i.p.	Acute	↓	[137]
NBI3b1996	CRF_1 antagonist	Social interaction	Rat	3–10 mg/kg	i.p.	Acute	0	[68]
		Social interaction + Stress	Rat	10 mg/kg	i.p.	Acute	↓	[68]
R121919	CRF_1 antagonist	Defensive withdrawal + Stress	Rat	20 mg/kg	i.p.	Acute	↓	[80]
		EPM	HAB Rat	20 mg/kg	i.p.	Acute	↓	[100]
		EPM	LAB Rat	20 mg/kg	i.p.	Acute	0	[100]
		EPM - Stress	Rat	20 mg/kg	i.p.	Acute	↓	[80]
		Shock probe burying test + Stress	Rat	20 mg/kg	i.p.	Acute	↓	[80]
Urocortin 1	CRF_1/CRF_2 agonist	Acoustic startle	Rat	1–10 μg	i.c.v.	Acute	0	[92]
		EPM	Mouse	100 pmol	i.c.v.	Acute	↑	[142]
		EPM	Rat	1 μg	i.c.v.	Acute	↑	[92]
		Light-dark test	Mouse	60 pmol	i.c.v.	Acute	↑	[142]
		Social Interaction	Rat	50 fmol	BLA	Acute	↑	[199]
Urocortin 2	CRF_2 agonist	EPM	Rat	1 μg	i.c.v.	Acute	↓	[213]
		Light-dark box	Mouse	240 pmol	Lat. Septum	Acute	↑	[83]
		Light-dark box + Stress	Mouse	48 pmol	Lat. Septum	Acute	↑	[83]
		Open field test	Mouse	0.48–240 pmol	Lat. Septum	Acute	0	[83]
		Open field test + stress	Mouse	48 pmol	Lat. Septum	Acute	↑	[83]
Urocortin 3	CRF_2 agonist	Defensive withdrawal	Rat	2 nmol	i.c.v.	Acute	↓	[236]
		EPM	Rat	0.1–10 μg	i.c.v.	Acute	↓	[214]
		Shock probe burying test	Rat	0.04–1 nmol	i.c.v.	Acute	0	[236]
		Social interaction	Rat	0.04–1 nmol	i.c.v.	Acute	0	[236]
TCAP receptor ligands in anxiety								
TCAP-1	unknown	Acoustic startle test	Rat	3–300 pmol	BLA	Acute	↓↑	[226]
		Acoustic startle test	Rat	30 pmol	i.c.v.	Subchronic	↓	[226]
		Acoustic startle test	Rat	300 pmol	i.c.v.	Subchronic	0	[205]
		Acoustic startle test + Stress	Rat	300 pmol	i.c.v.	Subchronic	↓	[205]
		EPM	Rat	300 pmol	i.c.v.	Subchronic	0	[205]
		EPM	Rat	300 pmol	i.v.	Subchronic	0	[3]
		EPM + Stress	Rat	300 pmol	i.c.v.	Subchronic	↑	[205]
		EPM + Stress	Rat	300 pmol	i.v.	Subchronic	0	[3]
		Open field test	Rat	300 pmol	i.c.v.	Subchronic	0	[205]
		Open field test	Rat	300 pmol	i.v.	Subchronic	0	[3]
		Open field test + stress	Rat	300 pmol	i.c.v.	Subchronic	↑	[205]
		Open field test + stress	Rat	300 pmol	i.v.	Subchronic	↓	[3]
NPY receptor ligands in anxiety								
Neuropeptide Y (NPY)	Y agonist	Conditioned freezing	Mouse	0.5–1 nmol	i.c.v.	Acute	↓	[95]
		EPM	Mouse	7, 700 pmol	i.c.v.	Acute	↓↑	[144]
		EPM	Mouse	0.5–1 nmol	i.c.v.	Acute	↓	[95]
		EPM	Rat	1–5 nmol	i.c.v.	Acute	↓	[78]
		EPM	Rat	0.07–2.3 nmol	i.c.v.	Acute	↓	[27]
		EPM	Rat	4 μg	i.c.v.	Acute	↓	[25]
		EPM	Rat	0.2–6 nmol	i.c.v.	Acute	↓	[198]
		EPM	Rat	10–20 nmol	Amygdala	Acute	↓	[107]
		EPM	Rat	0.3 nmol	i.c.v.	Acute	↓	[11]
		EPM	Rat	10 pmol	Amygdala	Subchronic	0	[187]
		EPM + Stress	Rat	4 μg	i.c.v.	Acute	↓	[25]
		Fear-potentiated startle	Rat	0.23–2.3 nmol	i.c.v.	Acute	↓	[27]
		Light-dark box	Mouse	0.5–1 nmol	i.c.v.	Acute	↓	[95]
		Open field test	Mouse	0.5–1 nmol	i.c.v.	Acute	↓	[95]
		Open field test	Rat	0.1, 3 nmol	i.c.v.	Acute	↓	[198]
		Open field test	Rat	5 ng	CA3	Acute	0	[91]
		Open field test	Rat	5 ng	DG	Acute	0	[91]
		Operant conflict test	Rat	0.2–5 nmol	i.c.v.	Acute	↓	[77]
		Operant conflict test + Stress	Rat	1 μg	i.c.v.	Acute	↓	[25]
		Social interaction	Rat	10 pmol	Amygdala	Acute	↓	[187]
		Social interaction	Rat	10 pmol	Amygdala	Subchronic	↓	[187]
		Social Interaction + Stress	Rat	10 pmol	Amygdala	Subchronic	↓	[187]

Table 2 (*Continued*)

Ligand	Receptor	Model	Species	Dose	Route	Duration	Effect	Reference
		Vogel conflict test	Rat	0.2–1 nmol	i.c.v.	Acute	↓	[78]
BIBO3304	Y1 antagonist	Open field test	Mouse	0.003–0.3 nmol	i.c.v.	Acute	0	[176]
BIBP3226	Y1 antagonist	EPM	Rat	5 μg	i.c.v.	Acute	↑	[96]
		Open field test	Mouse	0.03 nmol	i.c.v.	Acute	↑	[176]
		Open field test	Rat	5 μg	i.c.v.	Acute	0	[96]
[cPP]hPP	Y5 agonist	Open field test	Mouse	0.03–3 nmol	i.c.v.	Acute	0	[176]
		EPM	Rat	0.2–3 nmol	i.c.v.	Acute	↓	[198]
[D-His(26)]NPY	Y1 agonist	EPM	Rat	0.8–3 nmol	i.c.v.	Acute	↓	[198]
BIIE0246	Y2 antagonist	EPM	Rat	1 nmol	i.c.v.	Acute	↓	[11]
		Open field test	Mouse	0.003–3 nmol	i.c.v.	Acute	0	[176]
C2-NPY	Y2 agonist	EPM	Rat	0.2–3 nmol	i.c.v.	Acute	0	[198]
[Leu(31) Pro(34)]NPY	Y1/Y5 agonist	EPM	Mouse	70 pmol	i.c.v.	Acute	↓	[144]
		EPM	Rat	2.3–7 nmol	i.c.v.	Acute	↓	[27]
		EPM	Rat	5–10 nmol	Amygdala	Acute	↓	[107]
		Fear-potentiated startle	Rat	13.2 nmol	i.c.v.	Acute	↓	[27]
Y-28	Y1 agonist	Conditioned freezing	Rat	0.01–0.4 μg	Amygdala	Acute	0	[58]
Y-36	Y1 agonist	Conditioned Freezing	Rat	0.62 μg	Amygdala	Acute	0	[58]
AVP receptor ligands in anxiety								
Arginine vasopressin (AVP)	V agonist	EPM	Rat	250 pg	Septum	Acute	0	[123]
		EPM	Rat	200 pg	Septum	Acute	↓	[5]
		EPM	Rat	500 ng	i.p.	Acute	↓	[5]
		Social Interaction + Phencyclidine	Rat	0.01–3 μg	CeA	Acute	0	[120]
		Social Interaction + Stress	Rat	0.001–3 μg	CeA	Acute	0	[119]
D-$(CH_2)_5$Thyr(Et)VAVP	V1/V2 antagonist	EPM	Rat	40 ng	Septum	Acute	0	[5]
		EPM	Rat	1 ng/h	Septum	Subchronic	↑	[54]
		Shock probe burying test	Rat	1 ng/h	Septum	Subchronic	0	[54]
D-$(CH_2)_5$Tyr(Me)AVP	V1a antagonist	EPM	Rat	5 ng	Septum	Acute	↓	[123]
		EPM	HAB Rat	5 ng	PVN	Acute	↓	[228]
JNJ-17308616	V1a antagonist	Conditioned lick suppression	Rat	30 mg/kg	i.p.	Acute	↓	[22]
		EPM	Rat	100 mg/kg	i.p.	Acute	↓	[22]
		Elevated zero maze	Rat	30 mg/kg	i.p.	Acute	↓	[22]
		Induced vocalizations	Rat	100 mg/kg	i.p.	Acute	↓	[22]
		Marble burying	Mouse	100 mg/kg	i.p.	Acute	↓	[22]
SSR149415	V1b antagonist	EPM	Rat	10 mg/kg	i.p.	Acute	↓	[73]
		EPM	Rat	1–100 ng	Lat. Septum	Acute	0	[200]
		EPM	Rat	1–10 ng	BLA	Acute	↓	[188]
		EPM	Rat	1–100 ng	CeA, MeA	Acute	0	[188]
		EPM	Rat	1–30 mg/kg	i.p.	Acute	↓	[85]
		EPM + Stress	Mouse	3 mg/kg	i.p.	Acute	↓	[73]
		EPM + Stress	Mouse	30 mg/kg	i.p.	Chronic	↓	[73]
		Induced vocalizations	Guinea pig	30 mg/kg	i.p.	Acute	↓	[85]
		Induced vocalizations	Rat	30 mg/kg	i.p.	Acute	↓	[85]
		Light-dark box	Rat	1–30 mg/kg	i.p.	Acute	↓	[73]
		Marble burying	Mouse	1–30 mg/kg	i.p.	Acute	0	[85]
		Mouse defense test battery	Mouse	1–30 mg/kg	i.p.	Acute	↓	[73]
		Mouse defense test battery + Stress	Mouse	30 mg/kg	i.p.	Chronic	↓	[73]
		Social interaction	Rat	0.1–0.3 mg/kg	i.p.	Acute	↓	[193]
		Social interaction	Flinders Rat	10–30 mg/kg	i.p.	Chronic	↓	[157]
		Vogel conflict test	Rat	3–10 mg/kg	i.p.	Acute	↓	[73]
		Vogel conflict test	Rat	1–100 ng	Lat. Septum	Acute	0	[200]
		Vogel conflict test	Rat	30 mg/kg	i.p.	Acute	↓	[85]
Oxytocin receptor ligands in anxiety								
Oxytocin	OTR agonist	EPM	Mouse (OVX)	3 mg/kg	i.p.	Acute	0	[135]
		EPM	Rat	100 ng/h	i.c.v.	Acute	0	[232]
		EPM + Estradiol	Mouse (OVX)	3 mg/kg	i.p.	Acute	↓	[135]
		EPM + Stress	Rat	100 ng/h	i.c.v.	Acute	↓	[232]
		Elevated zero maze	Mouse	1 μg	i.c.v.	Acute	↓	[180]
		Four-plate test	Mouse	10 μg	i.c.v.	Acute	↓	[180]
		Four-plate test	Mouse	10 mg/kg	i.p.	Acute	↓	[180]
		Holeboard test	Mouse	3 mg/kg	i.p.	Acute	0	[135]
		Light-dark box	Rat	1 μg	i.c.v.	Acute	0	[196]
		Light-dark box	HAB Rat	1 μg	i.c.v.	Acute	0	[196]
		Light-dark box	LAB Rat	1 μg	i.c.v.	Acute	0	[196]
		Light-dark box	HAB Rat (female)	10 ng/h	i.c.v.	Chronic	↓	[196]
		Light-dark box	HAB Rat (male)	10 ng/h	i.c.v.	Chronic	0	[196]
		Open field	Rat	1 μg	CeA	Acute	0	[120]

Table 2 (*Continued*)

Ligand	Receptor	Model	Species	Dose	Route	Duration	Effect	Reference
		Open field + phencyclidine	Rat	1 μg	CeA	Acute	0	[120]
		Open field + stress	Rat	0.3 mg/kg	i.p.	Subchronic	↓	[106]
		Social interaction + phencyclidine	Rat	1 μg	CeA	Acute	↓	[120]
		Social interaction + stress	Rat	1 μg	CeA	Acute	↓	[119]
des Gly-NH_2 $d(CH_2)_5$ $[Tyr(Me)^2,Thr^4]OVT$	OTR antagonist	EPM	Rat	0.75 μg	i.c.v.	Acute	0	[147]
		EPM	Rat (lactating)	0.75 μg	i.c.v.	Acute	↓	[146]
OXT-A	OTR antagonist	Light-dark box	LAB Rat	0.75 μg	i.c.v.	Acute	0	[196]
		Light-dark box	LAB Rat (female)	7.5 ng/h	i.c.v.	Chronic	↑	[196]
WAY-267464	OTR agonist	Elevated zero maze	Mouse	3 μg	i.c.v.	Acute	↓	[181]
		Four-plate test	Mouse	10 μg	i.c.v.	Acute	↓	[181]
		Four-plate test	Mouse	10–30 mg/kg	i.p.	Acute	↓	[181]
Tyr-MIF-1 family receptor ligands in anxiety								
Endomorphin-1	μ-opioid agonist	EPM	Mouse	30 nmol	i.c.v.	Acute	↓	[10]
MIF-1	unknown	Vogel conflict test	Rat	1 mg/kg	i.p.	Acute	↑	[170]
Tyr-MIF-1	Tyr-MIF-1 agonist	EPM	Mouse	3–30 mg/kg	i.p.	Acute	0	[67]
CCK receptor ligands in anxiety								
Cholecystokinin-4 (CCK4)	CCK agonist	Conditioned freezing	Mouse	10–100 ng	i.c.v.	Acute	0	[192]
		EPM	Mouse	25–100 ng	i.c.v.	Acute	↑	[192]
		Open field test	Mouse	10 ng	i.c.v.	Acute	0	[192]
		Open field test	Rat	75 μg/kg	i.p.	Acute	↑	[134]
Cholecystokinin-8S (CCK8S)	CCK agonist	EPM	Rat	0.01–0.1 μg	CA1	Acute	↑	[179]
Caerulein	CCK agonist	EPM	Rat	1–10 nmol	i.c.v.	Acute	↑	[195]
CAM1481	CCK_1 antagonist	EPM	Mouse	1 mg/kg	i.p.	Acute	0	[231]
		EPM + Stress	Mouse	0.1–1 mg/kg	i.p.	Acute	0	[231]
Devazepide	CCK_1 antagonist	Open field test	Rat	1 mg/kg	i.p.	Acute	0	[134]
		Open field test	Rat	1 mg/kg	i.p.	Subchronic	0	[134]
MK-329	CCK_1 antagonist	EPM	Rat	50 μmol/kg	i.p.	Acute	↓	[195]
Pentagastrin	CCK_2 agonist	Acoustic startle	Rat	100 nmol	Amygdala	Acute	↑	[66]
		EPM	Rat	0.3–10 nmol	i.c.v.	Acute	↑	[195]
CAM1028	CCK_2 antagonist	EPM	Mouse	1 mg/kg	i.p.	Acute	0	[231]
		EPM	Rat	1 mg/kg	i.p.	Acute	0	[231]
		EPM + Stress	Mouse	0.1–1 mg/kg	i.p.	Acute	↓	[231]
		EPM + Stress	Rat	1 mg/kg	i.p.	Acute	↓	[231]
CI-988	CCK_2 antagonist	EPM	Mouse	1 mg/kg	i.p.	Acute	0	[231]
		EPM	Rat	0.5–5 μmol/kg	i.p.	Acute	↓	[195]
		EPM + Stress	Mouse	0.1–1 mg/kg	i.p.	Acute	↓	[231]
L-365,260	CCK_2 antagonist	Acoustic Startle	Rat	0.1–10 mg/kg	i.p.	Acute	0	[93]
		EPM	Mouse	0.01–1 mg/kg	i.p.	Acute	↓	[175]
		EPM	Rat	0.5–50 μmol/kg	i.p.	Acute	↓	[195]
		Fear-potentiated startle	Rat	1–10 mg/kg	i.p.	Acute	↓	[93]
		Open field test	Rat	1 mg/kg	i.p.	Acute	0	[134]
		Open field test	Rat	1 mg/kg	i.p.	Subchronic	0	[134]
LY225910	CCK_2 antagonist	Conditioned freezing	Mouse	495 pmol	i.c.v.	Acute	0	[192]
		EPM	Mouse	495 pmol	i.c.v.	Acute	0	[192]
		EPM	Rat	0.1–0.5 μg	CA1	Acute	↓	[179]
		EPM + CCK4	Mouse	495 pmol	i.c.v.	Acute	↓	[192]
		Open field test	Mouse	495 pmol	i.c.v.	Acute	0	[192]
PD134308	CCK_2 antagonist	EPM	Rat	0.01–1 mg/kg	s.c.	Acute	↓	[90]
		Light-dark box	Mouse	0.0001–30 mg/kg	s.c.	Acute	↓	[90]
		Social interaction	Rat	0.001–1 mg/kg	s.c.	Acute	↓	[90]
PD135158	CCK_2 antagonist	Light-dark box	Mouse	0.0001–30 mg/kg	s.c.	Acute	↓	[90]
Galanin receptor ligands in anxiety								
Galanin	GAL agonist	Conditioned Freezing	Mouse	0.5–1 nmol	i.c.v.	Acute	0	[95]
		EPM	Mouse	0.5–1 nmol	i.c.v.	Acute	0	[95]
		EPM	Rat	0.6 nmol	Amygdala	Acute	0	[140]
		Elevated zero maze	Mouse	0.1 μg	i.c.v.	Acute	↓	[174]
		Four-plate test	Mouse	1 μg	i.c.v.	Acute	↓	[174]
		Light-dark box	Mouse	0.5–1 nmol	i.c.v.	Acute	0	[95]
		Open field test	Mouse	0.5–1 nmol	i.c.v.	Acute	0	[95]
		Vogel conflict test	Rat	3 nmol	i.c.v.	Acute	↓	[19]
		Vogel conflict test	Rat	0.2–0.6 nmol	Amygdala	Acute	↑	[140]
Galnon	GAL agonist	Elevated zero maze	Mouse	0.3–3 mg/kg	i.p.	Acute	↓	[174]
		Four-plate test	Mouse	0.1–1 mg/kg	i.p.	Acute	↓	[174]

Table 2 (*Continued*)

Ligand	Receptor	Model	Species	Dose	Route	Duration	Effect	Reference
GalR3	GAL3 angatonist	EPM	Mouse	10–50 mg/kg	i.p.	Acute	0	[14]
M35	GAL antagonist	Four-plate test	Mouse	10 μg	i.c.v.	Acute	0	[174]
		Four-plate test + Galanin	Mouse	10 μg	i.c.v.	Acute	↑	[174]
		Four-plate test + Galnon	Mouse	10 μg	i.c.v.	Acute	↑	[174]
		Open field test	Rat	6 nmol	Intranasal	Acute	↑	[128]
M40	GAL antagonist	EPM	Rat	1 nmol	BnST	Acute	0	[104]
		EPM + Stress	Rat	4 nmol	CeA	Acute	0	[103]
		EPM + Stress	Rat	0.2–1 nmol	BnST	Acute	↓	[104]
		Shock probe burying test	Rat	0.2–2 nmol	Lat. Septum	Acute	↓	[50]
		Shock probe burying test + Galanin	Rat	2 nmol	Lat. Septum	Acute	↓	[50]
		Social interaction	Rat	1 nmol	BnST	Acute	0	[104]
		Social Interaction + Stress	Rat	0.2–1 nmol	BnST	Acute	↓	[104]
SNAP37889	GAL3 antagonist	Social interaction	Rat	3–30 mg/kg	i.p.	Acute	↓	[202]
		Vogel conflict test	Rat	3–10 mg/kg	i.p.	Acute	↓	[202]
SNAP398299	GAL3 antagonist	Social interaction	Rat	1–10 mg/kg	i.p.	Acute	↓	[202]
Substance P Receptor Ligands in Anxiety								
Substance P	NK1 agonist	Acoustic startle	Rat	0.5–1 nmol	PnC	Acute	↑	[113]
		EPM	Mouse	1–10 pmol	i.c.v.	Acute	↑	[209]
		EPM	Mouse	10 pmol	i.c.v.	Acute	↑	[207]
		EPM	Mouse	10 pmol	i.c.v.	Acute	↑	[208]
		EPM	Rat	10 pmol	i.c.v.	Acute	↑	[46]
		EPM	Rat	0.1–1 pmol	MeA	Acute	↑	[48]
		EPM	Rat	100–1000 ng	Dorsal HC	Acute	↓	[32]
		EPM	Rat	10–1000 ng	Ventral HC	Acute	0	[32]
		Open field test	Rat	100 ng	Dorsal HC	Acute	↓	[32]
		Open field test	Rat	10–1000 ng	Ventral HC	Acute	0	[32]
Compound A (ComA)	NK1 antagonist	EPM	Rat	0.1–1 nmol	MeA	Acute	0	[48]
		EPM + Stress	Rat	1 nmol	MeA	Acute	↓	[48]
CP-96,345	NK1 antagonist	EPM + Stress	Rat	10 nmol	PnC	Acute	↓	[113]
CP-99,994	NK1 antagonist	EPM	Gerbil	3–30 mg/kg	i.p.	Acute	0	[220]
		EPM + Stress	Rat	4–100 nmol	PnC	Acute	↓	[113]
		Foot-tapping	Gerbil	3 mg/kg	i.p.	Acute	↓	[13]
		Foot-tapping	Gerbil	5–10 mg/kg	i.p.	Acute	↓	[26]
		Induced vocalizations	Rat	40 mg/kg	i.p.	Acute	↓	[26]
		Marble burying	Mouse	40 mg/kg	i.p.	Acute	↓	[26]
		Social interaction	Gerbil	0.16–5 mg/kg	i.p.	Acute	0	[26]
		Vogel conflict test	Rat	10–40 mg/kg	i.p.	Acute	0	[26]
CP-122,721	NK1 antagonist	EPM	Gerbil	30 mg/kg	Oral	Acute	↓	[220]
FK888	NK1 antagonist	EPM	Mouse	1, 100 pmol	i.c.v.	Acute	↓	[209]
		EPM	Mouse	100 pmol	i.c.v.	Acute	↓	[207]
		EPM	Rat	100 pmol	i.c.v.	Acute	0	[46]
		EPM + Stress	Mouse	100 pmol	i.c.v.	Acute	↓	[207]
		EPM + Substance P	Rat	100 pmol	i.c.v.	Acute	↓	[46]
		EPM + Substance P	Mouse	100 pmol	i.c.v.	Acute	↓	[207]
GR-205,171	NK1 antagonist	Foot-tapping	Gerbil	0.01–0.04 mg/kg	i.p.	Acute	↓	[26]
		Induced vocalizations	Guinea pig	0.04–0.63 mg/kg	i.p.	Acute	↓	[26]
		Induced vocalizations	Rat	40 mg/kg	i.p.	Acute	↓	[26]
		Marble burying	Mouse	10–40 mg/kg	i.p.	Acute	↓	[26]
		Social interaction	Gerbil	0.16 mg/kg	i.p.	Acute	↓	[26]
		Vogel conflict test	Rat	10–40 mg/kg	i.p.	Acute	↓	[26]
L-733,060	NK1 antagonist	EPM	Gerbil	10 mg/kg	Oral	Acute	↓	[220]
		Foot-tapping	Gerbil	10 mg/kg	i.p.	Acute	↓	[26]
		Induced vocalizations	Guinea pig	3 mg/kg	i.p.	Acute	↓	[110]
		Induced vocalizations	Rat	2.5–40 mg/kg	i.p.	Acute	0	[26]
		Marble burying	Mouse	10–40 mg/kg	s.c.	Acute	↓	[26]
		Social interaction	Gerbil	2.5 mg/kg	i.p.	Acute	↓	[26]
		Vogel conflict test	Rat	20 mg/kg	i.p.	Acute	↓	[26]
L-742,694	NK1 antagonist	EPM	Gerbil	3–10 mg/kg	Oral	Acute	↓	[220]
L-760,735	NK1 antagonist	Foot-tapping	Gerbil	3 mg/kg	i.p.	Acute	↓	[186]
		Four-plate test	Gerbil	3 mg/kg	i.p.	Acute	↓	[186]
MK-869 (Aprepitant)	NK1 antagonist	EPM	Gerbil	0.03–3 mg/kg	Oral	Acute	↓	[220]
		Foot-tapping	Gerbil	1–3 mg/kg	i.p.	Acute	↓	[13]
NKP608	NK1 antagonist	Social interaction	Rat	0.01–0.1 mg/kg	i.p.	Acute	↓	[60]
		Social interaction	Rat	0.03 mg/kg	i.p.	Chronic	↓	[60]

Table 2 (*Continued*)

Ligand	Receptor	Model	Species	Dose	Route	Duration	Effect	Reference
SPA	NK1 antagonist	Open field test	Rat	3 mg/kg	i.p.	Acute	0	[130]
		Open field test	WKY Rat	3 mg/kg	i.p.	Acute	0	[130]
SR 48968	NK2 antagonist	EPM	Mouse	1–100 pmol	i.c.v.	Acute	↓	[209]
		EPM	Rat	100 pmol	i.c.v.	Acute	0	[46]
		EPM + Substance P	Rat	100 pmol	i.c.v.	Acute	↓	[46]
Vestipitant	NK1 antagonist	Foot-tapping	Gerbil	0.63 mg/kg	i.p.	Acute	↓	[26]
		Induced vocalizations	Guinea pig	2.5–10 mg/kg	i.p.	Acute	↓	[26]
		Induced vocalizations	Rat	10 mg/kg	i.p.	Acute	↓	[26]
		Marble burying	Mouse	2.5–40 mg/kg	s.c.	Acute	↓	[26]
		Social interaction	Gerbil	0.04–0.63 mg/kg	s.c.	Acute	0	[26]
		Vogel conflict test	Rat	20–40 mg/kg	i.p.	Acute	↓	[26]

EPM: elevated plus maze; HAB: high anxiety-like behavior (rat); LAB: low anxiety-like behavior (rat); OVX: ovariectomized; WKY: Wistar-Kyoto (rat); i.c.v.: intracerebroventricular; i.p.: intraperitoneal; s.c.: subcutaneous; BLA: basolateral nucleus of the amygdala; BnST: bed nucleus of the stria terminalis. CeA: central nucleus of the amygdala; HP: hippocampus; MeA: medial nucleus of the amygdala; PnC: pontine reticular nucleus; PVN: paraventricular nucleus of the hypothalamus; VTA: ventral tegmental area; Acute: single dose; Subchronic: multiple doses, <14 days; Chronic: 14 days +; ↑: anxiogenic effect; 0: no effect; ↓: anxiolytic effect.

but only in rats selectively bred for high anxiety-like behavior (HAB rats), and had no anxiolytic effect in rats selectively bred for low anxiety-like behavior (LAB rats) [100]. R121919 significantly inhibited stress-induced ACTH release in both rat strains, and did not affect activity in the open field in either rat strain. This highlights a key point that the ability of drugs to alter anxiety-related behavior in the EPM is highly dependent on the innate or baseline emotionality of the rats.

Many studies with CRF receptor antagonists have demonstrated that a stressor is necessary in order to see clear anxiolytic effects of the antagonist [45,72,80,82,131,152,190,197]. The CRF peptide antagonist α-helical CRF_{9-41} had no effect in non-stressed controls on EPM behavior, but it had a clear anxiolytic effect in rats that had previously received either restraint, swim or a social stressor [82]. Interestingly, only the lowest dose (1 μg) of α-helical CRF_{9-41} tested was effective at blocking the stress-induced decrease in exploration on the EPM. Higher doses of 5 and 25 μg were ineffective, even with the prior stress, indicating a non-linear dose-response curve.

In some models, however, CRF_1 antagonists show anxiolytic effects without prior stressors. This is likely due to the more stressful nature of these tests. For example, the non-peptidergic CRF_1 antagonists, CP-154,526 and DMP695, were ineffective the in the EPM [85,137], conditioned lick suppression test [85], and have shown mixed effects in ultrasonic vocalization models [85,137], but showed dose-dependent anxiolytic effects in the Vogel conflict test and the social interaction test [137]. Furthermore, R121919 showed anxiolytic-like actions in the shock-probe burying test and the defensive withdrawal test [80]. This demonstrates that these compounds are not always active in all preclinical models of anxiety, and are highly dependent upon the test conditions and the antagonist used.

To summarize, CRF_1 antagonists generally do not show anxiolytic effects under basal conditions, but rather they block the heightened anxiety produced by such factors as stress or selective breeding for high anxiety [160]. Some models that are intrinsically more stressful may show effects of CRF_1 antagonists at baseline. Thus, it is important to evaluate CRF_1 antagonists using models that take these factors into consideration when evaluating the anxiolytic potential of a new compound.

6. Urocortins

The urocortins are a heterologous group of peptides. Urocortin 1 is a 40-residue peptide found in mammals and is related to frog sauvagine and fish urotensin-I [221]. Urocortins 2 and 3 are 38 residues in length and are paralogous to each other and although they are part of the CRF family, they are distinct from CRF and urocortin 1. In the brain, the highest levels of urocortin 1 are produced in the midbrain in the Edinger-Westphal nucleus [109]. It is also produced in the hypothalamus, pituitary and substantia nigra [162]. Urocortin 1 (Ucn 1) binds with high affinity to the CRF_1 and CRF_2 receptors, whereas urocortins 2 (Ucn 2) and 3 (Ucn 3) preferentially bind to the CRF_2 receptor [122,178,221]. Ucn 1 is involved in many behaviors, particularly the suppression of food intake [162], however, it also plays a role in anxiety and stress. This is likely due to its action on the CRF_1 receptor.

6.1. Depression

Ucn 1, 2, and 3 were tested in the mouse FST using doses of 0.13–0.5 μg (i.c.v.) [206] (Table 1). Ucn 1 had no effect on behavior, whereas Ucn 2 and 3 displayed an antidepressant-like profile by decreasing immobility time, and additionally increased climbing and swimming behavior. The authors proposed that the stimulation of CRF_2 receptors by Ucn 2 and 3 contributed to the antidepressant effect, whereas stimulation of CRF_1 and CRF_2 by Ucn 1 resulted in the negative effect in this test.

6.2. Anxiety

I.c.v. injection of Ucn 1 has anxiogenic properties in the EPM in both mice [142] and rats [92] (Table 2). Ucn 1 injected into the basolateral amygdala (BLA) at a dose of 50 fmol has anxiogenic effects in the social interaction test [199]. Ucn 1-induced or stress-induced decreases in social interaction can be blocked with a specific CRF_1 antagonist (NBI3b1996), suggesting that the anxiogenic effects of Ucn 1 arise through its interaction with this receptor [68]. Interestingly, the CRF_1 antagonist had no effects on social interaction on its own, but antagonized the decreases in social interaction induced by stress or Ucn 1. Ucn 1 also increased grooming and exploratory behavior [44].

I.c.v. administration of Ucn 2 and Ucn 3 into rats suppressed locomotion in the locomotor activity test and produced an anxiolytic effect in the EPM, although the anxiolytic effect of Ucn 2 was delayed [213,214]. I.c.v. administration of Ucn 3 did not alter anxiety-like behavior in the shock-probe burying test or social interaction tests, but decreased anxiety-like behavior in the defensive withdrawal test [236]. However, i.c.v. injection of Ucn 2 in mice suppressed locomotion and produced an anxiogenic response in the light-dark box, and lateral septal injection of Ucn 2 in mice produced an anxiogenic effect in the light-dark box [83]. This is interesting, as CRF_2 receptors are highly expressed in the lateral septum [219]. These results indicate that the effects of Ucn 2 in rodent models may depend on both the species and the site of administration.

Studies that utilize the specific CRF_2 receptor antagonist, anti-Svg-30, indicate that the CRF_2 receptor may have a role in anxiety. Like many other anxiety-related receptor antagonists, anti-Svg-30 treatment in mice does not show significant effects on its own, and requires co-treatment with a stressor to see anxiety-related effects. Infusions of anti-Svg-30 into the lateral septum of mice did not produce effects on the EPM, but blocked both immobilization and CRF-induced reductions in open arm activity [173]. Similarly, i.c.v. administration of anti-Svg-30 did not have significant effects on its own but attenuated CRF-induced behavior in the acoustic startle test [183,203]. However, in rats, i.c.v. infusions of anti-Svg-30 on its own produced anxiolytic effects in the EPM, conditioned freezing test, and defensive-withdrawal test [203]. Therefore, like Ucn 2 and 3 themselves, the effects of anti-Svg-30 may depend on species and administration site.

In summary, Ucn 1 has anxiogenic properties in tests of anxiety and no antidepressant effects, whereas Ucn 2 and Ucn 3 have shown anxiolytic, anxiogenic, and antidepressant-like effects. These results indicate that the CRF_2 receptor may have important, but not necessarily similar, profiles to that of the CRF_1 receptor.

7. Teneurin C-terminal associated peptide (TCAP)

TCAP is a recently discovered peptide that was identified during a homology search for additional members of the CRF family [172]. This peptide shares 20% amino acid identity with CRF, and is located on the C-terminus of the teneurin protein [125], although it is not clear if this peptide has an ancestral relationship with the CRF family. The TCAP family consists of 4 peptides, one associated with each of the four teneurins. *In vitro*, TCAP is neuroprotective against alkalosis-associated necrotic cell death [212] and stimulates neurite outgrowth [2]. *In vivo*, TCAP modulates the acoustic startle response when injected into the BLA [226]. Rats with low baseline startle reactivity showed an increased startle response following TCAP treatment, whereas rats with high baseline startle reactivity showed decreased startle reactivity. Furthermore, intracerebroventricular (i.c.v.) TCAP treatment for five days blocked the increase in startle by an acute i.c.v. injection of CRF [205]. However, the same five day treatment regimen of TCAP resulted in an enhanced effect of CRF in the open field and EPM tests [205]. Five days of intravenous TCAP treatment reduced the anxiety-enhancing effects of i.c.v.-administered CRF in the open field test, but slightly enhanced anxiety following intravenous CRF treatment [3].

Thus, TCAP appears to have differential effects on anxiety depending upon the test, the treatment regimen, and perhaps even the baseline anxiety level of the rats. This is not unlike the results seen with CRF_1 antagonists, which generally do not alter anxiety-like behavior under basal conditions, but rather they block anxiety that is induced by a number of manipulations such as ethanol withdrawal, exposure to stressors, or genetic manipulations [160].

8. Neuropeptide Y (NPY)

Neuropeptide Y is a 36-amino acid peptide that is widely distributed in the central nervous system (CNS). There are currently five identified NPY receptors, which are also widely distributed in the CNS, particularly throughout the frontal cortex and limbic regions [177]. NPY has been implicated in both anxiety and depression (Tables 1 and 2).

8.1. Depression

There is a great deal of evidence, both pre-clinical and clinical, for the role of NPY in depression (for a review, see [132]). Infusion of NPY into the CA3 region of the hippocampus produces an antidepressant-like profile in the learned helplessness model of depression [91]. This antidepressant-like effect was also seen following i.c.v. infusion, but not infusion into the dentate gyrus, highlighting the importance of specific regional differences in the behavioral effects of NPY. The antidepressant effect of NPY was blocked by co-infusion into the CA3 region of a Y1 antagonist (BIBO3304), but not by co-infusion of a Y2 antagonist (BIIE0246). The Y2 antagonist alone had an antidepressant effect, as did infusion of a Y1 and Y5 agonist [Leu(31) Pro(34)]PYY [91].

NPY has an antidepressant response in both the rat [71,201] and mouse [176] FST. Specific Y1 antagonists had no effect in the FST, but do block the antidepressant effects of NPY [176].

Thus, NPY appears to have antidepressant effects when injected i.c.v. in rat and mouse models of depression, and these effects are likely mediated through the Y1 receptor.

8.2. Anxiety

The anxiety-reducing effects of NPY and the anxiety-enhancing effects of antagonists of NPY receptors are fairly well-documented, providing strong evidence for NPY's role in modulating anxiety responses. The amygdala appears to be a key region in this regard.

In the EPM, infusion of NPY, either i.c.v. or into the amygdala, has anxiolytic effects [27,78,95,107,198]. NPY at 0.5 and 1.0 nmol produced anxiolytic-like effects in the light-dark box, and increased locomotor activity in the open field tests at 0.5 nmol [95]. NPY also antagonized the anxiogenic-like behavioral effects of CRF in the EPM [25]. Interestingly, it was noted that i.c.v. infusions of NPY in mice in the EPM test revealed opposing effects on behavior, depending on the doses used. NPY decreased the normal preference for the closed arms of the maze at 700 pmol, indicating an anxiolytic effect; however, at 7 pmol NPY increased the preference for the closed arm, indicating an anxiogenic effect [144]. It was suggested that NPY produces an anxiolytic effect via Y1-type receptors, but also an anxiogenic effect via Y2-type receptors. However, it has been reported that the robust anxiolytic effect of intra-amygdala infusion of NPY is not mimicked by intra-amygdala infusion of specific Y1 agonists, suggesting that the anxiolytic effect in this region is not mediated by Y1 receptors [58]. The time course of NPY effects is also important, as the anxiogenic effect was observed only shortly after i.c.v. NPY injection. A selective antagonist of the Y2 receptor, BIIE0246, increased open arm time in rats in the EPM, [11], consistent with an anxiolytic effect of blocking this receptor. I.c.v. injection of NPY and a specific Y1 and Y5 agonist showed a dose-dependent anxiolytic effect in the EPM and open field tests [198]. I.c.v. injection of a selective NPY Y1 receptor antagonist, BIBP3226 (5.0 μg), caused an anxiogenic-like effect in the EPM [96]. Y1 antagonists have shown mixed effects in the open field test, with both anxiogenic [107] and lack of effect reported [91,96].

Anxiolytic effects of NPY have also been observed using a variety of other behavioral models, such as the conditioned freezing test in mice [95]. NPY dose-dependently increased responding for water in the Vogel conflict test [78] and the punished responding task for food [77], which are consistent with an anxiolytic effect. I.c.v.-administered NPY (1 μg) also antagonized the response-suppressing effects of CRF in the punished responding task to food [25]. In an acoustic startle paradigm, NPY inhibited fear-potentiated startle over the dose-range of 0.23–2.3 nmol [27]. Intra-amygdala injections of NPY decreased the expression of conditioned fear, as measured by the conditioned freezing test and by the fear-potentiated startle test [58].

A recent study has demonstrated a long-lasting anxiolytic effect of NPY injections, which persists up to 8 weeks after injection. NPY was injected into the BLA, and behavior was measured in the social interaction test. NPY had an anxiolytic effect in the social

interaction test that was present even after the first injection, and this effect persisted for 8 weeks after a series of five NPY injections [187]. These NPY injections also made the rats resilient to restraint stress-induced reductions in social interaction. However, similar injections had no effect on behavior in the EPM or locomotor tests. It is interesting also that anxiolytic effects were observed in the social interaction test but not the EPM or locomotor tests, despite other studies reporting anxiolytic effects of NPY injections in these models.

Therefore, it is clear that NPY has anxiolytic properties in many tests, and antidepressant potential as well. Specific agonists of Y1 are anxiolytic, whereas Y2 receptor agonists are anxiogenic and Y2 antagonists have anxiolytic and antidepressant potential.

9. Arginine vasopressin (AVP)

Arginine vasopressin (AVP) is a 9-amino acid peptide that plays a critical role in regulating blood pressure and water balance, but is increasingly being studied for its role in regulating many aspects of emotional and social behavior [31,65]. AVP plays a role in the regulation of aggression, social behavior, memory, stress, anxiety and depression [31]. The synergistic interaction of AVP with CRF in regulating the HPA axis has also led many researchers to suggest a role for AVP in mood and anxiety disorders [65,86,228]. AVP V1b receptors are located throughout the limbic system in key regions of emotional control, such as the lateral septum, amygdala, bed nucleus of the stria terminalis, hippocampal formation, as well as cortical regions [200]. AVP receptor antagonists have, therefore, been suggested as a novel class of therapeutics for stress-related affective illnesses [74,194] (Tables 1 and 2).

9.1. Depression

Mixed results have been obtained in the FST. SSR149415, a V1b antagonist, produced clear antidepressant effects in rats in the FST, and in mice using the chronic mild stress paradigm and 39 days treatment [73]. Infusion of SSR149415 into the lateral septum, or the central, basolateral or medial nuclei of the amygdala decreased immobility time in the rat FST [188,200]. Acute intraperitoneal (i.p.) doses of SSR149415 were inactive in rat and mouse FST, and mouse tail suspension test at doses of 1–30 mg/kg [85]. However, other studies have shown that chronic doses of i.p. SSR149415 decreased immobility in the FST [73,157]. Furthermore, SSR149415 treatment for 14 days reduced immobility in the FST in FSL rats, a proposed animal model of depression, but not in FRL rats [157]. Therefore, it appears that both the injection site and the treatment duration are important in elucidating the effects of AVP receptor antagonists.

9.2. Anxiety

The results of AVP administration in models of anxiety are mixed. An i.p. injection (500 ng, i.p.) or into the septum (200 pg) produced an anxiolytic effect on the EPM [5], whereas another study [123] indicated that an intraseptal infusion of 250 pg of AVP had no effect on EPM behavior. This effect was not blocked by intraseptal administration of the V1/V2 receptor antagonist D-$(CH_2)_5$Thyr(Et)VAVP [5]. However, V1a antagonist D-$(CH_2)_5$Tyr(Me)AVP (5 ng) and intraseptal AVP (250 pg) had an anxiolytic effect as seen by increased open arm time and entries [123]. It is interesting that both AVP and the V1b antagonist, but not the V1/V2 antagonists, have anxiolytic effects in this test. It is also interesting that the V1b antagonists have an anxiolytic effect in the absence of any other stimulation, unlike some other peptides which require a stressor to be present. By infusing D-$(CH_2)_5$Thyr(Et)VAVP into the lateral septum of male Wistar rats, Everts and Koolhaas [54] showed that the antagonist reduced open arm activity in the EPM, which is consistent with an anxiogenic effect.

In rats that have been bred for high-anxiety-like behavior (HAB) and low-anxiety-like behavior (LAB), intraseptal AVP was anxiogenic in LAB rats in the EPM [16]. Furthermore, injection of the V1a antagonist, D-$(CH_2)_5$Tyr(Me)AVP, into the paraventricular nucleus of the hypothalamus was anxiolytic in the EPM in HAB rats, without affecting locomotion [228].

Non-peptide V1b antagonists have been developed, and generally show anxiolytic effects in animal models, however, the results are not always consistent either between models or within the same model. The V1b antagonist SSR149415 is the most characterized of the V1b non-peptide antagonists, and reported to increase social behavior in the social interaction test in rats [193]. In one study, SSR149415 (1–30 mg/kg) was active in the ultrasonic vocalization, EPM, and conditioned lick suppression tests, but inactive in marble burying test of anxiety [73,85]. Intraseptal infusion of SSR149415 had no effect on the Vogel conflict or EPM tests [200]. Microinjection of SSR149415 into the BLA was anxiolytic in the EPM, but there was no effect of injection into central or medial nuclei [188]. SSR149415 treatment for 14 days in FSL rats also increased social interaction in FSL rats, suggesting that it has anxiolytic as well as antidepressant properties [157].

A review of the effects of SSR149415 in tests of anxiety concluded that it can attenuate some, but not all, stress-related behaviors in rodents, and that clear anxiolytic effects were only found in particularly stressful situations [74]. Although SSR149415 had anxiolytic effects in classical models such as the Vogel conflict test, EPM, and light-dark box, the effects were not as pronounced as for the reference anxiolytic, diazepam [73]. However, SSR149415 resulted in clear anxiolytic effects in the social defeat stress-induced EPM test and mouse defence test battery, which are mechanistically different tests involving a social aspect [73]. At 100 mg/kg, another V1a antagonist, JNJ-17308616, significantly reduced anxiety-like behavior in the rat EPM, ultrasonic vocalization test, and the mouse marble burying test [22]. At 30 mg/kg, it was effective in the elevated zero maze and conditioned lick suppression tests. JNJ-17308616 did not impair social recognition or reduce locomotor activity.

10. Oxytocin

Oxytocin is a nonapeptide that is synthesized primarily in the paraventricular nucleus and supraoptic nucleus in the hypothalamus, and plays a key role in social and sexual behavior [145], in addition to its well known roles in females in parturition and lactation. Oxytocin acts through the OTR receptor, which is located in several areas, including the cortex, limbic system, hypothalamus, and brainstem [234]. Oxytocin inhibits stress-induced activity in the HPA axis [147], and has also been shown to play an important role in the response to stress.

10.1. Depression

Oxytocin has not been studied as much for a role in depression as it has for its role in anxiety and social behaviors. However, its close association with CRF and AVP suggest that changes in the oxytocinergic system may in fact play a role (Table 1). Using the FST, oxytocin injected intraperitoneally 60 min prior to testing decreased immobility at doses of 0.25–1.0 mg/kg [8]. This effect was even stronger following a 10-day treatment, indicating an antidepressant effect. Similarly, treatment with 0.5 mg/kg oxytocin (i.p.) for 8 days resulted in an antidepressant-like response in the learned helplessness test [8]. However, in another study, i.c.v. oxytocin did not affect behavior in the FST in male or female HAB or LAB rats, even after a chronic treatment regimen that did affect

anxiety behavior [196]. In the mouse TST, oxytocin administered centrally or systemically decreased immobility time, but this effect was not blocked by a non-peptide OTR antagonist, WAY-162720 [181].

There has been at least one clinical trial showing that daily intranasal oxytocin led to improvements in depressive symptoms [12]. Conversely, it has been reported that oxytocin levels in the cerebrospinal fluid are increased in patients with major depressive disorder, but that there are no differences in plasma oxytocin [217]. Another study found a negative correlation between plasma oxytocin levels and anxiety symptoms in patients with major depressive disorder [189].

Thus, the preclinical and clinical studies suggest that exogenously administered oxytocin may have an antidepressant effect, but the relationship between endogenous oxytocin and depressive symptoms remains unclear.

10.2. Anxiety

The effects of oxytocin on anxiety-like behavior have been studied extensively, particularly in conjunction with effects on social behavior (Table 2). Oxytocin generally has an anxiolytic effect on behavior, although it has been suggested that the effects on anxiety may in fact depend upon changes in social behavior. What is clear is that the effects of oxytocin treatment, similar to what is seen with other neuropeptides, depend upon the dose, duration, route of administration, and test conditions.

In rats that had received chronic injections of phencyclidine, which resulted in a deficit in social behavior, bilateral injections of oxytocin (1 μg) into the central nucleus of the amygdala restored social behavior but did not affect open field behavior [120]. Similarly, oxytocin administration to the central amygdala restored social behavior in rats that had been prenatally stressed [119]. Oxytocin administration (i.p. × 3 days) restored the deficit in locomotor behavior induced by repeated exposure to restraint stress in rats [106]. Interestingly, however, the increased locomotion and rearing was seen only at the low dose (0.3 mg/kg), whereas a higher dose of oxytocin potentiated the stress-induced deficits in exploration. In male mice, both centrally and peripherally administered oxytocin had anxiolytic-like effects in the four-plate test, and centrally administered oxytocin decreased measures of anxiety in the elevated zero maze [180]. Central infusion of a peptide antagonist of oxytocin (des Gly-NH_2 d$(CH_2)_5$ [Tyr$(Me)^2$,-Thr^4]OVT) increased ACTH and corticosterone, but did not affect behavior in the EPM [147]. However, a subsequent study of central oxytocin infusion in rats demonstrated no effect in virgin rats, but an anxiolytic effect in pregnant and lactating rats [146].

The effects of oxytocin treatment also depend upon the duration of administration, and the baseline neuroendocrine status of the animals. Whereas an acute i.c.v. dose of oxytocin did not affect anxiety-like behavior in male or female HAB or LAB rats in the light-dark box, chronic treatment (6 days) decreased anxiety in females but not male HAB rats, and increased anxiety in female but not male LAB rats [196]. This study also illustrates the modulatory nature of peptides reported for several other neuropeptides. The initially low anxiety rats showed an increase in anxiety following treatment, and the initially high anxiety rats decreased their anxiety. This effect was, however, seen in females but not males. Furthermore, in ovariectomized rats, there was no effect of oxytocin in the EPM, but there was an anxiolytic effect in ovariectomized rats given estrogen, and in control rats [135].

Similarly to what is seen with other neuropeptides, the effects of oxytocin also depend upon the conditions under which testing occurs. For example, when rats were tested in the EPM, oxytocin had no effect on behavior in rats that were housed and tested in the same room [232]. However, when the test was made more stressful by testing in a novel environment, the oxytocin-treated rats showed lower anxiety than controls. Additionally, in another study that showed anxiolytic effects of oxytocin in the EPM, there was no anxiolytic effect on the holeboard test [135], demonstrating specificity of the anxiolytic effects to certain tasks.

The effects of oxytocin on behavior have suggested that it could be involved in anxiety disorders, schizophrenia, autism and depression [181]. Clinical trials of intranasal oxytocin have been performed for social anxiety disorder [75]. Although there was a slight effect on patients' subjective feelings, oxytocin treatment did not differentiate from placebo. However, as the authors note, this was only an acute treatment study, and was given as an adjunct to exposure therapy. In a study of the effects of oxytocin on cortisol, mood and anxiety in humans, intranasal oxytocin decreased social stress in the Trier social stress test, and enhanced the protective effects of social support [79]. Evidence of a possible neural substrate of the oxytocin effect was found in a functional magnetic resonance imaging study, which assessed amygdala activation by fear-inducing visual stimuli in 15 healthy males after intranasal application of placebo or oxytocin in a double-blind crossover study [105]. Oxytocin significantly reduced activation of the amygdala and reduced coupling of the amygdala to brainstem fear-related regions as compared to controls.

11. The Tyr-MIF-1 family

The tyrosine melanocyte-stimulating hormone-release inhibiting factor-1 (Tyr-MIF-1) family of 3–4 amino acid residue peptides includes MIF-1 (Pro-Leu-Gly-NH_2), Tyr-MIF-1 (Tyr-Pro-Leu-Gly-NH_2), Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH_2), Tyr-K-MIF-1 (Tyr-Pro-Lys-Gly-NH_2), endomorphin-1 (Tyr-Pro-Trp-Phe-NH_2) and endomorphin-2 (Tyr-Pro-Phe-Phe-NH_2). The first peptide found, MIF-1, was obtained from bovine hypothalamus and originally found to inhibit melanocyte-stimulating hormone [143]. There has been some debate as to whether MIF-1 may result as a degradation product of oxytocin [34,222], as the tripeptide matches the three C-terminal amino acids in oxytocin, but peptidase digests have thus far been unable to produce MIF-1 from oxytocin [30]. Despite its name, the family of peptides have been found to have other functions, such as behavioral and analgesic effects. Members of the Tyr-MIF-1 family are found in the striatum, hypothalamus, hippocampus, thalamus, amgygdala, and cortex. As yet, the receptors for MIF-1 have not been found, whereas Tyr-MIF-1 has its own specific binding site and also binds weakly to μ-opiate receptors. The other members of the MIF-1 family each have unique receptor binding profiles with regard to the Tyr-MIF-1 site and opiate receptors. Tyr-K-MIF-1 binds to its own site, but does not bind to opiate receptors. Tyr-W-MIF-1, endomorphin-1 and endomorphin-2 bind the μ-opiate receptor [161]. The Tyr-MIF-1 family, especially MIF-1, has shown potent effects at low doses in animal models and clinical trials for depression.

11.1. Depression

A growing body of evidence has indicated that the Tyr-MIF-1 family affects behavior in a dose-dependent inverse U-shaped curve that is consistent with the action of other peptides. In the rat FST, MIF-1 has antidepressant effects, with low doses being more effective than higher doses [98,108,171], although one group has reported no effect [7]. In one of these studies, MIF-1 enhanced the effect of tricyclic antidepressants in the FST [108]. MIF-1 increased the number of escape responses in the learned helplessness test [7]. MIF-1 was also effective in the chronic mild stress paradigm, as low doses of MIF-1 (0.1 and 1.0 mg/kg) inhibited the effects of chronic stress in the open field, whereas a high dose (10 mg/kg) potentiated the effects of chronic mild stress [167]. A synthetic

pentapeptide analog of MIF-1, nemifitide (INN 00835), has also shown anti-depressant effects. Chronic treatment of both high and low doses of nemifitide increased swimming in the FST in FSL rats after only 5 days of treatment, while fluoxetine had no effect [158]. Moreover, the effects of nemifitide were long-lasting, as 14 days of treatment increased swimming time both directly after completion of treatment and 5 days later, in contrast to desipramine, which lost its effect 5 days after completion of treatment. Tyr-MIF-1 was also found to be effective in the rat FST, an effect that was abolished by the dopamine blockers, haloperidol or sulpiride [171], suggesting a dopaminergic mechanism of action, consistent with findings that MIF-1 may be an allosteric modulator of the dopamine receptor [63]. I.c.v. administration of endomorphin-1 or endomorphin-2 reduced immobility in the mouse FST and tail suspension test [59].

Small clinical trials have indicated that MIF-1 may have effectiveness as a novel peptide-based therapeutic. Low doses (60–75 mg) but not high doses (150–750 mg) of oral MIF-1 produced improvement in a number of depression scales [51,52,121,216], with one study indicating that MIF-1 was as effective as a reference antidepressant, imipramine [216]. Furthermore, a double-blind, placebo-controlled cross-over study found that a single daily subcutaneous injection of only 10 mg of MIF-1 for 5 days was effective in reducing depression rating scores on all rating scales as compared with placebo [53]. During the second week, the placebo group received MIF-1 and also showed symptom improvement by the end of the 5-day treatment period. Clinical trials with nemifitide have also been promising at low doses [55–57,141,148]. Both MIF-1 and nemifitide were well-tolerated, indicating that both peptides are intriguing new therapeutic targets for depression.

11.2. Anxiety

Very little work has been performed on the effect of the Tyr-MIF-1 family in models of anxiety. A recent study has indicated that members of the peptide family (MIF-1, Tyr-MIF-1, Tyr-W-MIF-1, and Tyr-K-MIF-1) significantly inhibited stressed-induced rises in ACTH and corticosterone [23], and these results suggest that the Tyr-MIF-1 family may have a role in inhibiting the stress response. Injections of MIF-1 decreased drinking in a modified Vogel conflict test [170], although this effect may be due to a suppression of drinking behavior attributed to MIF-1 [153]. Treatment of Tyr-MIF-1 in mice tended to increase the preference for open arms in the EPM [67]. Likewise, i.c.v. injection of endomorphin-1 in mice increased open arm entries in the EPM [10], although this effect could be partially attributed to activation of μ_1- and μ_2-opioid receptors, which enhance locomotion [70,235]. I.c.v. injections of endomorphin-1 [29] and endomorphin-2 [28] increased both locomotion and rearing in the open field test, but these effects were blocked by α-helical $CRF_{9\text{-}41}$, indicating that these locomotor effects may be mediated by CRF. More studies will be required to elucidate whether the Tyr-MIF-1 family of peptides have efficacy in animal models of anxiety.

12. Cholecystokinin (CCK)

Cholecystokinin (CCK) is one of the most abundant neuropeptides in the brain, and is found in high concentrations in cortex and limbic brain regions [17,18]. CCK has been linked to anxiety and panic disorders, but also has a role in satiety, thermoregulation, sexual behavior and memory [185]. There are a variety of biologically active forms of CCK which are derived from the 115-amino acid precursor molecule pro-CCK, and which range from 4 to 58 amino acids in length [225]. The most relevant forms for discussion of depression and anxiety are CCK-8 (sulfated and unsulfated forms), CCK-5 (pentagastrin), and CCK-4. CCK binds to two receptors, CCK_1 and CCK_2 (formerly CCK-A and CCK-B, respectively).

12.1. Depression

CCK_1 antagonists have not shown effects in models of depression [84], whereas CCK_2 antagonists have antidepressant potential in preclinical models (Table 1). The CCK_2 antagonist, L-365,260, showed antidepressant-like effects in mice in the FST [84], whereas chronic blockade of CCK_2 receptors by the specific antagonist CI-988 (1 mg/kg per day for 25 days) in rats normalized immobility time in the FST [15]. Furthermore, this treatment prevented HPA axis hyperactivity, reduction of hippocampal volume and cell proliferation, and decreased sweet water intake normally evoked by repeated social defeat [15].

12.2. Anxiety

A number of anxiogenic effects have been reported for CCK in animal models [185] (Table 2). This increased anxiety has been mainly attributed to activation of the CCK_2 receptor. In the EPM, injection of CCK8S (0.01, 0.05, 0.1 μg) into the dorsal hippocampus (intra-CA1) decreased percent open arm time and percent open arm entries [179], consistent with an anxiogenic profile. I.c.v. administration of CCK-4 in mice (39.5–158 pmol) had an anxiogenic effect in the EPM, and this effect was blocked by a specific CCK_2 antagonist that alone had no effect on anxiety-related behavior [192]. Systemic injections of CCK-4 have an anxiogenic profile in the open field test, and this effect was blocked by CCK_2 but not CCK_1 antagonists [134]. However, CCK_2 antagonists have been shown in other studies to produce anxiolytic-like effects in the EPM test in both rats [195], and mice [90,175]. Other studies have shown that CCK_2 antagonists had no effects on normal behavior, but do attenuate drug withdrawal-induced anxiety [231].

I.c.v. infusions of pentagastrin, a 5-amino acid CCK fragment that preferentially activates CCK_2 receptors, increased acoustic startle responses [66]. The CCK_2 antagonist L-365,260 did not affect baseline acoustic startle responses [93]. However, using the fear-potentiated acoustic startle test, L-365,260 dose-dependently decreased the potentiated startle response [93]. Again, this is consistent with receptor antagonists showing the strongest effects only under potentiated conditions, and not affecting behavior under low stress conditions. Systemic injections of CCK-4 have an anxiogenic profile in the open field test, and this effect is blocked by CCK_2 but not CCK_1 antagonists [134].

Clinical trials in anxiety disorders and CCK antagonists have not been promising. The CCK_2 antagonist CI-988 had no effect in patients with generalized anxiety disorder [1,163], nor did it block the panic-inducing effects of CCK-4 [218]. The CCK_2 antagonist L-365,260 had no effect in patients with panic disorder [111].

In summary, CCK agonists show anxiogenic effects in a number of animal models, but the effects of CCK antagonists often are not seen unless a system is potentiated. The CCK_2 receptor appears to play a key role in anxiety, but it remains to be seen whether efficacious CCK antagonists can be found to treat anxiety disorders or depression.

13. Galanin

Galanin is a 29 or 30-amino acid peptide that has been implicated in a wide range of behaviors such as cognition, memory, feeding, pain, mood regulation and neurological disorders [37,97,127]. Galanin is co-localized with, and modulates serotonin and noradrenaline systems. Galanin receptors (GAL1, GAL2, GAL3)

are located in the hypothalamus, dorsal raphe and locus coeruleus [133]. These receptors are the targets of therapeutic drug development for a variety of neurological and metabolic disorders [139].

13.1. Depression

Galanin administered via the i.c.v. route enhanced depression-like behavior in the rat FST, and this effect was blocked by a non-selective galanin receptor antagonist [116,117] (Table 1). Infusion of galanin into rat ventral tegmental area (VTA) also resulted in increased immobility in the FST [227], indicative of a pro-depressant effect. However, it appears that there are receptor subtype-specific effects of galanin receptor ligands. Stimulation of GAL1 or GAL3 receptors results in a depression-like phenotype whereas stimulation of the GAL2 receptor has an antidepressant-like profile [115,117,151]. Consistent with this, the selective GAL3 antagonist SNAP 37889 decreased immobility and increased swimming in the rat FST [202].

Galnon, a non-selective galanin agonist, has been reported to have antidepressant properties [126], although it also interacts with many other receptors [64,117]. Other studies have shown no effect of galnon in the mouse tail suspension test, or the rat FST [174].

13.2. Anxiety

The effects of galanin and its receptor ligands on anxiety are mixed, and appear to depend upon the test conditions, and the severity of the stress, as well as the ligand used (Table 2). Centrally administered galanin did not affect anxiety in C57BL/6J mice [95]. However, when centrally administered in Balb/C mice, both galanin and the non-selective galanin agonist, galnon, showed anxiolytic-like activity in a number of tests, including the four-plate test and the elevated zero maze [174]. Galanin has been reported to have no effect in the light-dark box [95]. However, it has a robust anxiolytic effect in the Vogel punished drinking test [19]. It is suggested that galanin has no effect on unpunished behavior, such as EPM, but has an anxiolytic effect on punished responding [140], which would be consistent with other peptides showing behavioral effects only under conditions of increased stress.

Intranasal administration of the non-selective galanin antagonist M35 decreased exploration and increased anxiety (freezing and grooming) in the open field test [128]. Centrally administered M35 also eliminated the effects of galanin or galnon in the four-plate test [174].

Acute administration of the GAL3 selective antagonists SNAP 37889 or SNAP 398299 induced anxiety-like behavior in the social interaction test [202]. Furthermore, acute SNAP 37889 was also shown to reduce guinea pig vocalizations after maternal separation in the ultrasonic vocalization test, to attenuate stress-induced hyperthermia in mice, and to increase responding in the Vogel conflict test in rats. Another GAL3 antagonist displayed no effects in the elevated plus maze in mice and did not affect locomotor activity in the open field, indicating no effect on anxiety [14].

An interesting set of studies examining multiple behavioral models indicated that the effects of galanin on anxiety can be facilitating or attenuating, and are region-specific, context-specific and response-specific [50,103,104]. Using the EPM, social interaction, and shock-probe burying tests, and injecting the galanin antagonist, M40, into the amygdala, BnST, or lateral septum, both anxiolytic-like and anxiogenic-like effects were seen.

14. Substance P

Substance P is an 11-amino acid peptide that has received considerable attention as a target for mood and anxiety disorder research [49,133] (Tables 1 and 2). Substance P is the preferred ligand for the neurokinin-1 (NK1) receptor.

14.1. Depression

NK1 antagonists have been extensively tested in preclinical models of depression. In the mouse FST, the NK1 antagonist GR205171 had no effect on its own, but did potentiate the effects of sub-active doses of the SSRIs citalopram and paroxetine, but not the effects of desipramine [36]. Other studies indicate that NK1 antagonists have antidepressant-like properties on their own in the FST [41,130]. A study of selective antagonists for the NK1, NK2, and NK3 receptors (CP-96,345, SR 48968, and SR 142801, respectively), found that all three antagonists decreased immobility time in the FST [41]. However, not all NK1 antagonists induce this effect. Vestipitant and GR-205,171, both selective NK1 antagonists which produce robust anxiolytic effects, failed to have any effect in the mouse FST [26]. Using the chronic mild stress test, administration of the specific NK1 antagonist NKP608, chronically for 5 weeks reduced the decrease in sucrose intake, indicative of an antidepressant effect [164].

Recent clinical trials utilizing NK1 antagonists yielded mixed results in the treatment of depression. L-759274, a selective NK1 antagonist, improved scores on the Hamilton Depression Rating scale relative to placebo [112]. Aprepitant (MK-869), another NK1 antagonist, produced robust antidepressant effects [110], although another study indicated that aprepitant had no effect [102]. Therefore, the substance P system remains an intriguing target for antidepressant effects.

14.2. Anxiety

The effects of substance P in models of anxiety are variable, and seem to depend on the brain area targeted. Anxiolytic effects were observed on the EPM and the open field when substance P was injected into the dorsal, but not the ventral hippocampus [32]. However, injections in rats or mice via the i.c.v. route [46,207–209], or into the medial nucleus of the amygdala (MeA) [48] produced anxiogenic responses on the EPM. Furthermore, substance P injection into the caudal pontine reticular nucleus increased acoustic startle response in rats, indicating an anxiogenic effect [113]. The C-terminus appears to be active in eliciting anxiogenic behavior, as the C-terminal fragment (SP 6–11) retained the anxiogenic properties of the intact peptide, whereas the N-terminal fragment (SP 1–7) did not.

NK1 receptor antagonists have produced anxiolytic effects in preclinical models of anxiety, such as the social interaction test [60], the EPM [220], isolation-induced vocalization in guinea pigs [110], and four-plate test in gerbils [186]. Injection of an NK1 antagonist into the MeA elicited an anxiolytic-like effect in the EPM in rats that received prior immobilization-stress, but had no effect in non-stressed rats [48]. The NK1 antagonists FK888 alone showed an anxiolytic-like profile in the EPM, inhibiting the anxiogenic-like profile of substance P and swimming stress [207].

Vestipitant, an NK1 antagonist, attenuated fear-induced foot-tapping in gerbils, separation-induced distress-vocalizations in guinea pigs, marble burying behavior in mice, and displayed anxiolytic actions in Vogel conflict and fear-induced ultrasonic vocalization procedures in rats [26].

Clinical trials with NK1 antagonists to treat anxiety disorders are currently underway.

15. Concluding remarks

Neuropeptides represent an exciting and potentially valuable class of compounds for drug discovery for anxiety and depression.

However, specific challenges exist for neuropeptides when using and interpreting data from classical animal models that were validated for classic small molecule antidepressants and anxiolytics. First, neuropeptides do not necessarily follow a linear dose-response curve, and therefore, careful analysis of a wide range of doses is required. Furthermore, neuropeptides appear to require higher levels of stress or challenges before behavioral effects are obvious in many tests. This most likely reflects the neuromodulatory nature of peptides, and will most likely be advantageous clinically as normal baseline behaviors will be unaffected, but behaviors associated with higher levels of stress will be targeted. Finally, due to the complexity of the behaviors being modulated, behavioral effects will not be seen in every test of anxiety or depression, but may only be apparent in a subset of such tests. Thus, a new framework for interpretation of behavioral results may be required for peptide-based compounds.

In summary, there are many potential neuropeptide targets for drug development, and design of both preclinical and clinical trials should take into consideration the unique nature of neuropeptides.

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