Cell. Mol. Life Sci. 65 (2008) 1854 – 1863
1420-682X/08/121854-10
DOI 10.1007/s00018-008-8160-9

Cellular and Molecular Life Sciences

Galanin, galanin receptor subtypes and depression-like behaviour

E. Kuteeva, T. Hökfelt, T. Wardi and S. O. Ögren*

Department of Neuroscience, Karolinska Institutet, Retzius väg. 8, S-171 77 Stockholm (Sweden),
Fax: +46 8 302875, e-mail: Sven.Ove.Ogren@ki.se

Online First 27 May 2008

Abstract. The pathophysiology of depression remains unclear, but involves disturbances in brain monoaminergic transmission. Current antidepressant drugs, which act by enhancing this type of transmission, have limited therapeutic efficacy in a number of patients, and not rarely serious side-effects. Increasing evidence suggests that neuropeptides, including galanin, can be of relevance in mood disorders. Galanin is co-expressed with and modulates noradrenaline and serotonin systems, both implicated in depression. Pharmacological and genetic studies have suggested a role for galanin in depression-like behaviour in rodents, whereby the receptor subtype involved appears to play an important role. Thus, stimulation of GalR1 and/or GalR3 receptors results in depression-like phenotype, while activation of the GalR2 receptor attenuates depression-like behaviour. These findings suggest that galanin receptor subtypes represent targets for development of novel antidepressant drugs. (Part of a Multi-author Review)

Keywords. Depression-like behaviour, galanin, galanin receptor, noradrenaline, serotonin.

Introduction

Mood disorders, including the most severe forms such as major depression and bipolar disorder (manic-depressive illness), are among the most prevalent mental illnesses. It is estimated that about 10–20 % of the people in the Western world suffer from depressive episodes during their lifetime [1]. According to the diagnostic criteria, depression is characterised by a number of symptoms, including abnormal lowering of mood (melancholia), low self-esteem and feelings of hopelessness, blunting of brain reward systems (anhedonia), anxiety, irritability, disturbances of sleep, dysfunctions in food intake, sexual dysfunctions and cognitive disturbances [2]. The Global Burden of Disease Study has identified major depressive disorder among the leading causes of disability worldwide, and as an illness representing a growing health, social and economical problem [3, 4].

* Corresponding author.

Depression: monoamine hypotheses

The aetiology of depression is still not well characterised, but involves interactions between genetic and social predisposing factors, including exposure to traumatic (distressing) events [5, 6]. During the past four decades much research has focused on the 'catecholamine hypothesis of depression' [7]. This hypothesis stems from the observation that monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), which both increase noradrenaline (NA) transmission, have antidepressant properties.

The early 'catecholamine hypothesis' proposed that depressive symptoms are related to a deficiency in NA in the brain [7]. Subsequent studies, on the other hand, proposed that brain NA transmission is dysregulated in depressed patients [8]. More recent hypotheses have emphasised the maladaptive nature of catecholamine transmission in depression. Thus, while the basal NA transmission is reduced, the stress-induced NA response is actually amplified in depressed patients [9–11].

The 'indolamine hypothesis of depression', on the other hand, postulates a deficiency in brain 5-hydroxytryptamine (5-HT) activity as a vulnerability factor for mood disorders and suicide, at least in a subgroup of patients [12–15]. In addition, alterations in pre- and post-synaptic 5-HT receptors, e.g. the 5-HT_{1A} autoreceptor, could predispose for depression [16]. In fact, positron emission tomography studies have shown a reduction of both pre- and postsynaptic 5-HT_{1A} receptor binding in depression [17]. Finally, polymorphism in the promoter gene for the 5-HT transporter was found to interact with stressful life events in affective disorders [18, 19].

Current therapy of mood disorders and its limitations

Current pharmacological treatment of depression is dominated by compounds which target the monoamine transporters. These drugs include selective serotonin reuptake inhibitors (SSRIs), NA reuptake inhibitors (NRIs) and combined serotonin-NA reuptake inhibitors (SNRIs) [20]. These drugs increase extrasynaptic NA and/or 5-HT levels and thereby attenuate a postulated deficiency of monoamine transmission. However, the acute increase in monoamine transmission has been difficult to reconcile with the delayed onset of therapeutic efficacy. This led to the search for long-term adaptive changes which could be compatible with clinical evidence. Studies in rodents have shown that long-term treatment with antidepressants produces changes in intracellular signalling mechanisms [21] and multiple alterations in monoaminergic receptors [20, 22], transcription factors [23, 24] as well as an increase in hippocampal neurogenesis [25, 26].

Even if a temporal correlation exists between some of the adaptive changes in monoamine mechanisms and clinical responses, the prolonged changes in monoaminergic signalling cannot explain the major limitations in the therapeutic efficacy of current antidepressant drugs, namely that about 30–40 % of patients do not respond well to current antidepressants. The limited response rate, as well as side-effects related to the mechanism of action of current antidepressant drugs, results in problems with compliance. These limitations have led to an intensive search for novel therapeutic approaches in depression based on a deeper analysis of the behavioural and molecular mechanisms underlying mood disorders.

Peptidergic approaches in development of novel antidepressants

Novel treatment strategies focus on a number of neuromodulators, such as neuropeptides and their receptors, as attractive therapeutic targets for mood disorders [27–30], since they are localised in brain areas (circuits) that mediate behavioural functions related to anxiety and stress. In addition, some of these neuropeptides are co-localised with classical neurotransmitters, such as NA and 5-HT, as well as dopamine (DA), all of which are implicated in mood disorders. An important feature of some neuropeptide systems is that they are activated under stressful or traumatic conditions, when neuronal activity is high. This would result in upregulation of peptidergic transmission and possibly in modulation of the activity and functions of the co-expressing neurons. Neuropeptides mediate their action via multiple receptor subtypes (almost always G-protein-coupled receptors, GPCRs) coupled to differential transduction mechanisms. Genetic manipulation of genes encoding neuropeptides and/or their receptor subtypes have been shown to result in changes in behavioural functions indicative of depression- and anxiety-like behaviour [31–33]. In fact, recently a polymorphism in the galanin gene was shown to be associated with symptom severity in female patients suffering from panic disorder [34].

Galanin and galanin receptors in the brain

Galanin is a 29 (30 in human) amino acid neuropeptide [35] which is widely distributed in the brain, including ventral forebrain, amygdala, hypothalamus and brainstem, in a number of species [36–39].

The potential role of galanin in mood disorders is partially based on its co-localisation in the rat with NA in the locus coeruleus (LC) and with 5-HT in the dorsal raphe (DR) nucleus, and their projection areas in the limbic and cerebral cortex systems [40–42]. In the LC, the majority of the neurons co-express galanin at relatively high levels [41], whereas expression is lower in the DR [42]. However, there exists a distinct species difference, since in the mouse galanin is synthesized in LC, but not at all in DR [43]. Moreover, in the rat DR, galanin is present in numerous nerve endings surrounding, and synapsing on, 5-HT neurons [42]. This arrangement is not obvious in the LC, and here galanin is probably co-released with NA from dendrites and soma [44, 45].

Galanin mediates its multiple physiological functions via three subtypes of GPCRs, GalR1–GalR3 [46]. These receptors are widely distributed in the brain as

demonstrated in ligand binding, immunohistochemical and, in particular, *in situ* hybridisation studies [47]. Expression of galanin receptor mRNA is detected in the regions related to regulation of mood, including LC, DR and their projection areas. However, the exact distribution of galanin receptor protein in the brain is in several cases incomplete due to uncertainty regarding the specificity of available antisera.

Galanin receptors are coupled to several intracellular transduction pathways (see Fig. 2 in the article by Hökfelt and Tatemoto in this issue). Among these receptors, GalR1 and GalR3 mainly activate Gi/o types of G-proteins mediating inhibition via adenylate cyclase [46, 48, 49]. In contrast, the GalR2 subtype transmits either stimulatory effects of galanin, for example, on neurotransmitter release, acting via Gq/11 types of G-proteins, or it inhibits neurotransmission via Gi/o subtypes [46, 50, 51].

Modulatory effects of galanin on NA and 5-HT neurotransmission

Analyses of the role of galanin in the brain have been based on administration of the peptide via a chronic cannula placed in the lateral ventricle (i.c.v.), or directly into a relevant brain regions, or on *in vitro* application to brain slices. The interpretation of the results is hampered by our limited knowledge about the pharmacokinetics and concentrations of the infused peptide. Therefore, it is important to employ antagonists to the different receptor subtypes whenever available.

A number of studies suggests that exogenous galanin can modulate both the LC and DR systems. Electrophysiological recording from rat brain slices has demonstrated that galanin (10^{-7}–10^{-8} M) inhibits LC firing and produces outward current, presumably via activation of G-protein-coupled potassium (GIRK) channels [44, 52, 53]. This inhibitory effect is probably mediated by the GalR1/GalR3 receptors, since application of the mixed GalR1/R2 agonist M961, but not the GalR2 agonist AR-M1896, caused hyperpolarisation of the LC neurons [54]. Importantly, at low concentrations (10^{-9} M) galanin enhanced the hyperpolarisation caused by NA, probably mediated by modulation of the α_2-adrenoreceptor [54]. Also other data indicate that galanin can enhance the α_2-mediated auto-inhibitory action of NA [55].

In agreement, i.c.v. administration of galanin produced a reduction in basal NA release in the ventral hippocampus of the awake rat measured by microdialysis [56]. This effect is probably related to activation of galanin receptors in the LC, since local administration of galanin in the hippocampus failed to alter NA release. Moreover, i.c.v. galanin significantly attenuated the increase of extracellular hippocampal NA levels evoked by systemic administration of the NA reuptake inhibitor desipramine [56]. Thus, the inhibitory action of galanin on NA neurons persists even under conditions where extracellular levels of NA are increased by reuptake blockade.

In the DR there are, functionally, many similarities with LC: (1) galanin (10^{-6} mol/L) inhibits the firing rate of the 5-HT neurons, probably via GIRK channels; (2) galanin (10^{-9} M) enhances the inhibitory action of 5-HT on the DR neurons, hypothetically via interaction with the 5-HT_{1A} receptor [42]; (3) galanin, given i.c.v. or in the vicinity of the DR, inhibits serotonergic transmission, causing a dose-dependent and long-lasting reduction of 5-HT release in the ventral hippocampus of the rat, presumably mediated by galanin receptors on cell bodies in the DR [57]; (4) i.c.v. galanin attenuates the increase in extracellular levels of 5-HT induced by the SSRI citalopram [56], indicating that this inhibitory action persists under conditions of serotonergic activation following reuptake inhibition by an SSRI.

Recent electrophysiological data suggest that the inhibitory action of galanin on 5-HT neurons may be mediated by the GalR3 receptor subtype, since pretreatment with the GalR3 antagonist SNAP 37889 partially blocked the inhibitory action of galanin on 5-HT DR cell firing [58]. In agreement, SNAP 37889 given systemically blocked the reduction of 5-HT release in the hippocampus caused by i.c.v. infusion of galanin [58]. In contrast, infusion of the GalR2 receptor agonist AR-M1896 in the vicinity of the DR increases 5-HT release in the hippocampus [59]. Taken together, these results suggest that the inhibitory action of galanin on 5-HT neurons is mediated by GalR1/R3, while the GalR2 receptor probably activates 5-HT DR neurons, resulting in increased 5-HT transmission in the terminal areas. However, since the exact location of the galanin receptor subtypes on DR 5-HT neurons and/or other types of neurons (GABA, glutamate) is not known, results after exogenous administration of galanin must be interpreted with caution. Nevertheless, the accumulated evidence clearly indicates a predominantly inhibitory role of galanin on ascending 5-HT neurons.

Interaction of galanin and 5-HT_{1A} receptors

The firing rate of the 5-HT neurons (and, therefore, 5-HT release) is controlled by the somato-dendritic 5-HT_{1A} autoreceptors [60, 61]. Given the important role of the 5-HT_{1A} receptors in regulation of 5-HT transmission and their possible involvement in the patho-

physiology of depression [15, 61], the ability of galanin to modulate 5-HT_{1A} receptor functions is intriguing. A number of studies indicate that galanin and the 5-HT_{1A} receptor can interact both at the DR neuronal cell body and terminal levels. Thus, i.c.v. galanin causes a time-dependent reduction in affinity (k_d values) and an increase in the number of 5-HT_{1A} autoreceptors (B_{max}) [62], as well as a decrease of 5-HT_{1A} mRNA levels in the DR [62, 63]. Moreover, the reduction in 5-HT release induced by i.c.v. galanin is partially reduced by pre-treatment with the 5-HT_{1A} antagonist WAY100635 [64]. Also, i.c.v. galanin antagonised 5-HT_{1A} receptor-mediated inhibition of 5-HT release following administration of 8-OH-DPAT. In contrast, pre-treatment with 8-OH-DPAT enhanced the inhibitory effect of i.c.v. galanin on hippocampal 5-HT release [64]. These results suggest the existence of multiple mechanisms underlying reciprocal (antagonistic) interactions *in vivo* between galanin and the 5-HT_{1A} receptor at the DR cell body level.

Both *in vitro* and *in vivo* studies have provided evidence for antagonistic interactions also between the post-synaptic 5-HT_{1A} receptor and galanin. Thus, galanin reduced the affinity of the 5-HT_{1A} receptors in the limbic cortex *in vitro* [65, 66]. Moreover, in various behavioural models, including hypothermia, locomotor activity and passive avoidance, i.c.v. galanin blocked post-synaptic 5-HT_{1A} receptor-mediated functions [57, 67, 68]. However, in contrast to the DR, i.c.v. galanin failed to change the affinity or mRNA levels of the 5-HT_{1A} receptor in limbic cortex and hippocampus [68]. This suggests that galanin may regulate pre- and post-synaptic 5-HT_{1A} receptor functions by different mechanisms.

Galanin and depression: pharmacological evidence

Already at the first galanin meeting in 1990, Fuxe et al. [69] reported a distinct interaction between the galanin and 5-HT systems and suggested that galanin mechanisms may be of relevance for depression. The first pharmacological evidence for involvement of brain galanin in depression-like behaviour was obtained after galanin infusion into the rat ventral tegmental area (VTA), showing an increased immobility time in the forced swim test (FST) [70], a rodent model of depression-like behaviour [71] (Fig. 1). This effect was presumably related to galaninergic inhibition of the activity of the mesolimbic dopaminergic neurons, resulting in reduced dopamine release in the nucleus accumbens and impairment of both motor activity and reward mechanisms [70, 72, 73].

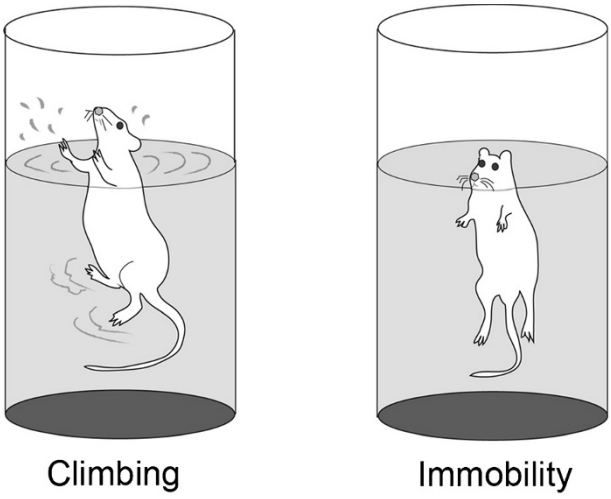

Figure 1. Forced swim test is used to assess depression-like behaviour in rodents. The test is conducted in a cylinder filled with water to a level, which prevents the animal from touching the bottom of the cylinder (30 cm for rats, 16 cm for mice). Animals are pre-exposed to water for 15 or 10 min on day 1, followed on day 2 (24 h later) by a 5-min test. Two types of behavioural activity are quantified: climbing (vigorous attempts to escape) and immobility (passive floating in water). The duration of immobility defines the magnitude of depression-like behaviour and can be decreased by various types of antidepressant drugs.

Also i.c.v. infusion of galanin increases depression-like behaviour in FST [74]. Importantly, an effect of both intra-VTA and i.c.v. infused galanin was blocked by co-administration of the non-selective galanin receptor antagonists M15 [70] and M35 [74], respectively, providing evidence for a receptor-mediated effect. Furthermore, the galanin antagonist M15 infused in the VTA [70, 72], and M35 given i.c.v. [74], decreased immobility time in the FST, suggesting galanin release under stressful conditions, resulting in a behavioural change in response to an inescapable aversive event. Moreover, the decreased immobility time following M15 or M35 infusion gives evidence for antidepressant-like properties of galanin antagonists.

In contrast, a number of other recent studies have suggested that increased galanin signalling may have an antidepressant-like effect. The systemically active, non-peptide galanin agonists galmic and galnon, administered intraperitoneally (i.p.) prior to the FST, were shown to decrease immobility time [75, 76]. A problem here is that galnon is a non-selective compound, also acting via multiple non-galanin receptors [77], and galmic, even though selective for the GalR1 receptor, is a low-affinity compound [75]. At present, there is no information on the role of galanin in human, with exception of one short-term study. Thus, galanin given intravenously (i.v.) was reported to have an antidepressant-like effect, indicated by a

suppression of REM sleep in healthy male volunteers [78].

Galaninergic mechanisms in animal models of depression

Genetic combined in some cases with pharmacological studies have indicated a role for galanin in depression-like behaviour in rodents. Genetically modified mice were tested under various conditions in test models of depression-like behaviour, such as the FST [79] or tail suspension test (TST) [80], which differ functionally. In the TST, the animals are only tested once, while in the modified version of the FST for mice used by Kuteeva et al. [33], mice are exposed to water stress twice. On day 1 animals are exposed for 15 min to forced swimming and on day 2 for 5 min in the FST, recording immobility and climbing (Fig. 1). The results from the modified FST, therefore, represent a measure of the ability of an animal to cope with the previously experienced aversive event. The differences in test procedures may explain some of the contradictory results obtained by use of genetically modified mice.

Mice overexpressing galanin (GalOE) under the platelet-derived growth factor-B (PDGF-B) promoter (GalOE-P mice) displayed an increased immobility in the FST [33], suggesting an increase in depression-like behaviour. Also, i.c.v. administration of galanin (1 nMol/mouse) to NMRI mice increased immobility time in the FST [unpublished observations]. In contrast, mutant mice lacking the GalR1 receptor (GalR1-KO) as well as mice overexpressing galanin under the dopamine-β-hydroxylase promoter (GalOE-D mice) failed to show any signs of altered depression-like behaviour in the TST [81]. Importantly, GalOE-P but not GalOE-D mice showed an augmentation of hippocampal NA and 5-HT release after swim stress as measured by *in vivo* microdialysis [82]. Thus, helpless behaviour in response to inescapable stress sensitises cortical and hippocampal release of NA and 5-HT [83, 84]. Taken together, these results suggest that GalOE-P mice may exhibit a maladaptive reaction to uncontrollable stress, probably related to the exaggerated release of monoamines (cf. [10, 11]).

Rat models of depression also suggest that failure to cope with stress can be related to an abnormal functioning of the brain galanin system. For instance, the Flinders sensitive line (FSL), which displays a high immobility in the FST, shows an up-regulation of the galanin binding sites in the DR [85], as well as a reduction of galaninin in nerve terminals in the hippocampus and the hypothalamus [86]. Antidepressant treatment was found to normalise the galanin levels in the hippocampus and hypothalamus of FSL rats, suggesting that abnormal galanin transmission could, at least partially, be related to depression-like behaviour in this rat strain [86].

Another rat model of depression is based on prolonged decrease in spontaneous locomotor activity after exposure to stress (uncontrollable electric shock). In this model, repeated microinfusions of the galanin antagonists M15 into the VTA significantly accelerated recovery from the depression of locomotor activity [72].

The role of different galanin receptor subtypes

Some of the seemingly contradicting results described above may be related to the fact that galanin signalling in the brain is transmitted via three receptor subtypes, with differential transduction mechanisms and distribution in the brain [46, 47]. Recently, both peptidergic and non-peptidergic compounds with relatively high selectivity for galanin receptor subtypes have been developed [58, 87–89]. Studies using these ligands suggest that GalR1/GalR3-mediated signalling can contribute to pro-depressive effects of galanin. Consistently, the peptidergic GalR1 agonist M617 [90] increased immobility time, similar to galanin itself [63] (Fig. 2). Also, non-peptidergic, systemically active GalR3 antagonists exert an antidepressant-like activity in various models of anxiety- and depression-like behaviour, including an increase in social interaction test and punished drinking in the Vogel test [58] and decreased immobility and increased swimming time in the FST in rats [58, 88].

Stimulation of the GalR2 subtype, in contrast, may produce the opposite (antidepressant-like) effects. Thus, both chronic treatment with the SSRI fluoxetine and electroconvulsive treatment increase galanin mRNA levels in the DR and LC of the rat, accompanied by an increase in GalR2 (but not GalR1) binding sites in these monoaminergic nuclei [76]. Moreover, co-administration of the galanin antagonist M40 blocked the behavioural effect of fluoxetine in the FST, suggesting that the antidepressant action of fluoxetine can (at least partially) be related to an increase in galanin-mediated transmission [76]. An interesting possibility is that antidepressant treatment might result in a shift from the inhibitory GalR1/GalR3 signalling to the excitatory, antidepressive GalR2 signalling, particularly in the DR [58, 76].

In our own experiments, i.c.v. infusion of the GalR2 agonist AR-M1896 to rats decreased the immobility time in the FST, in a manner similar to the antidepressant drug fluoxetine [63] (Fig. 2). The GalR2 antagonist M871 increased immobility in the FST

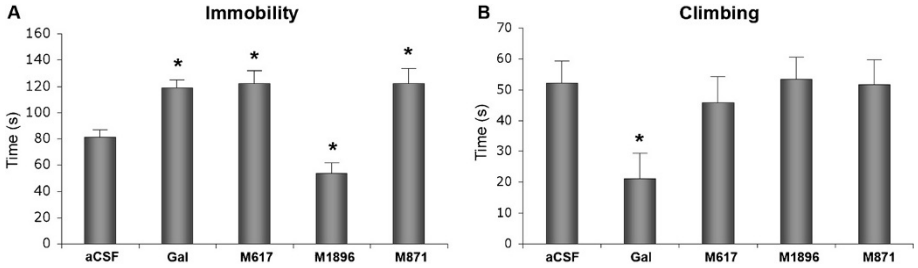

Figure 2. Time of immobility (*A*) and climbing (*B*) in the forced swim test. Rats received i.c.v. infusion of artificial cerebrospinal fluid (aCSF), galanin (Gal), the GalR1 receptor agonist M617, the GalR2 agonist AR-M1896 or the GalR2 antagonist M871 20 min prior to the 5-min test. Data presented as mean ± SEM. *, significant difference from the aCSF-group; $p < 0.05–0.01$; one-way ANOVA, Fisher's PLSD (*A*) or t-test (*B*). (*A*) Both galanin and the GalR1 agonist M617 increase immobility time, suggesting a 'pro-depressive' effect of galanin receptor stimulation. In contrast, the GalR2 agonist decreases immobility time, supporting an 'antidepressant-like' effect of GalR2 receptor stimulation. This view is further supported by the fact that the GalR2 agonist M871 increased immobility. (*B*) Galanin also decreases time of climbing, unlike the receptor-selective peptidergic ligands, suggesting that the native peptide more effectively evokes depression-like behavior. Modified from [63] (© Nature Publishing Group, advance online publication 2 January 2008; doi: 10.1038/sj.npp.1301660).

(Fig. 2), further supporting the evidence for an antidepressant-like effect by stimulation of GalR2 [63]. The findings with the antagonist M871 reveal the existence of a basal galaninergic tone mediated by GalR2, which may counteract the negative consequences of inescapable stress.

Galanin systems in depression: potential mechanisms

The results discussed above support the involvement of brain galanin systems in depression-like behaviour and indicate a differential role of galanin receptor subtypes. The physiological/ pathophysiological mechanisms underlying the action(s) of galanin most probably involve modulation of monoaminergic systems, in particular the LC and DR nuclei. Based on the available results from animal experiments the following hypothetical mechanism for the role of galanin and galanin receptor subtypes in depression-like behaviour can be proposed (Fig. 3).

In the LC, exposure to stressful events upregulates expression of both tyrosine hydroxylase [63, 91, 92], the rate-limiting enzyme in the catecholamine synthesis, and galanin [63, 93]. The increase in the expression of these two biomarkers is likely to reflect compensatory synthesis after increased NA and/or galanin release, possible both from soma/dendrites and nerve terminals [45, 94, 95].

Under conditions of acute stress, in the projection areas of the LC, e.g. the hippocampal formation and also VTA, the increase in NA and galanin transmission could exert a direct or indirect inhibitory effect on post-synaptic neuronal functions, resulting in development of depression-like behaviour [70, 96]. In the LC, galanin can also be released from soma/dendrites of NA neurons, and inhibit their activity, both via GalR1/GalR3 receptors and via interaction with α_2-adrenoreceptors. Over time, prolonged stress will probably lead to a reduction of basal NA transmission, while post-synaptic adrenoreceptors in the LC projection areas will become supersensitive to NA [10]. This situation has been proposed to represent a prodromal stage of depression [10]. In summary, in the hypothesised depressed state, the basal NA transmission would be reduced, while phasic reactivity of NA system in response to stressful events may actually be increased [11] (Fig. 3A–C).

In the DR, the transcript levels of galanin and TPH, the rate-limiting enzyme in 5-HT synthesis, were not affected by exposure to acute stress in our experiments [63], confirming earlier studies on TPH, indicating that this system is less stress-sensitive compared to the LC [97–99]. This is supported by c-Fos experiments showing that only strong acute stress induces expression of this marker [98, 100, 101]. However, galanin transcript levels in the DR might be increased following exposure to prolonged stress or in genetically predisposed animals. The increased galaninergic signalling would probably interfere with 5-HT_{1A}-mediated transmission at both pre- and post-synaptic sites, resulting in impairment of coping mechanisms and development of depression-like behaviour. Moreover, galanin released from soma/dendrites of 5-HT neurons (or from afferent terminals synapsing on the 5-HT or other neurons) could directly (or indirectly) inhibit serotonergic neurons via GalR1/GalR3 receptors. Finally, in the projection areas of the DR galanin could exert a direct inhibitory effect on post-synaptic neurons, further contributing to depression-like behaviour.

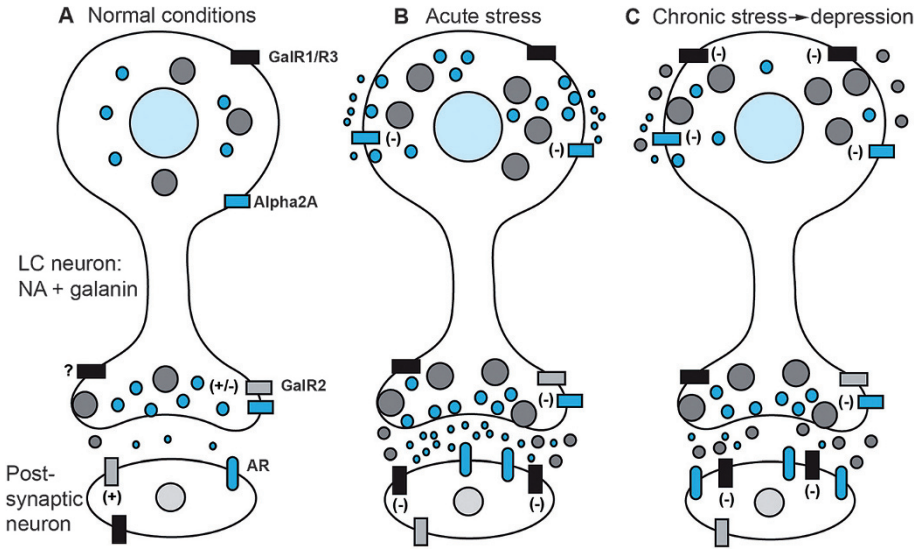

Figure 3. Hypothetical mechanisms underlying involvement of galaninergic system in depression-like behaviour in the locus coeruleus. (*A*) In the LC, NA is mainly stored in small synaptic, granular vesicles (sGVs) (blue), both in the cell bodies and nerve terminals. Galanin is stored in large dense core vesicles (LDCVs) (grey) (which also contain NA). Adrenoreceptors of various types are expressed in the LC neurons, including the somato-dendritic α_{2A}-receptors (Alpha2a). Galanin receptors are also present in these neurons. The inhibitory GalR1/R3 receptors are probably expressed at the cell body level, while the 'excitatory' (alternatively 'inhibitory') GalR2 subtype is a pre-synaptic receptor as well as expressed in post-synaptic neurons, as are adrenoreceptors of different types (AR). Under basal conditions, galanin is primarily released from nerve endings in the forebrain to activate post-synaptic GalR2 receptors, and perhaps presynaptic GalR2 receptors. The post-synaptic GalR2 receptor may mediate i.a. neuroprotective/neurotrophic effects and antidepressant-like action of galanin. (*B*) Under acute stressful conditions, NA as well as galanin releases are increased, as indicated by compensatory elevation of TH and galanin mRNA levels. Initially, primarily NA will be released from nerve endings in the forebrain acting on post-synaptic receptors, and also from soma/dendrites acting on the autoreceptors. The dominant effect of galanin released from the nerve terminals may now be inhibition via the post-synaptic GalR1/R3 receptors. (*C*) The consequences of chronic stress need to be explored. It is possible that with increasing intensity and duration more galanin-ir LDCVs are available for somatic/dendritic release, enhancing autoinhibtion of NA neurons directly via GalR1/R3 and indirectly via the α_{2A} adrenoreceptors, which will inhibit forebrain NA release. The decrease in NA release may lead to development of post-synaptic adrenoreceptor supersensitivity and increased stress reactivity. Such a dysregulation of the noradrenergic system was proposed to represent a prodromal stage for development of depression. LC, locus coeruleus; NA, noradrenaline.

Concluding remarks and perspectives

Integration of both anatomical and functional evidence suggests that modulation of monoaminergic transmission represents the main mechanism by which galanin may be of relevance for stress-related disorders. The observation of the existence of differential functions for galanin receptors in depression-like behaviour implies the possibilities for alternative strategies in drug development. Hypothetically, a GalR1/GalR3 antagonist could prevent the inhibitory action of galanin on the LC and DR neuronal firing rate and counteract its inhibitory action at post-synaptic sites, e.g. hippocampus or VTA. Such a mechanism may prevent the enhanced stress reactivity of the LC NA system and subsequent development of supersensitivity of the post-synaptic receptors. GalR2 receptor stimulation, on the other hand, acting e.g. at the cell body level of 5-HT/DR neurons within the ventral periaqueductal grey, can influence the pathophysiology of the 5-HT systems in depression by enhancing firing rate and 5-HT release in the projection areas. Finally, at the terminal level, activation of the GalR2 receptor may contribute to neurotrophic/neuroprotective processes [102–104]. Taken together, the available data suggest that compounds acting as GalR1/GalR3 antagonists or GalR2 agonists may open new avenues in the treatment of mood disorders.

Acknowledgements. Dr. E. Kuteeva is supported by a post-doctoral fellowship from Hjärnfonden. This work was supported by the Swedish Research Council (11588, 2887), The Marianne and Marcus Wallenberg Foundation, Wallenberg Consortium North, an EC Grant (NEWMOOD; LHSM-CT-2003-503474), Hjärnfonden, Karolinska Institutet Funds, Stiftelsen Ragnhild och Einar Lundströms Minne and Stiftelsen Goljes Minne.

1 Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., Rush, A. J., Walters, E. E. and Wang, P. S. (2003) The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289, 3095–3105.
2 DSM-IV (2000) American Psychiatric Press, Washington, D. C.
3 Wittchen, H. U. and Jacobi, F. (2005) Size and burden of mental disorders in Europe – a critical review and appraisal of 27 studies. Eur. Neuropsychopharmacol. 15, 357–376.
4 Murray, C. J. and Lopez, A. D. (1997) Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 349, 1436–1442.

5 Fava, M. and Kendler, K. S. (2000) Major depressive disorder. Neuron 28, 335–341.
6 Kessler, R. C. (1997) The effects of stressful life events on depression. Annu. Rev. Psychol. 48, 191–214.
7 Schildkraut, J. J. (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am. J. Psychiatry 122, 509–522.
8 Siever, L. J. and Davis, K. L. (1985) Overview: toward a dysregulation hypothesis of depression. Am. J. Psychiatry 142, 1017–1031.
9 Ressler, K. J. and Nemeroff, C. B. (2000) Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress. Anxiety 12 Suppl. 1, 2–19.
10 Harro, J. and Oreland, L. (2001) Depression as a spreading adjustment disorder of monoaminergic neurons: a case for primary implication of the locus coeruleus. Brain Res. Rev. 38, 79–128.
11 Morilak, D. A. and Frazer, A. (2004) Antidepressants and brain monoaminergic systems: a dimensional approach to understanding their behavioural effects in depression and anxiety disorders. Int. J. Neuropsychopharmacol. 7, 193–218.
12 Åsberg, M., Träskman, L. and Thoren, P. (1976) 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? Arch. Gen. Psychiatry 33, 1193–1197.
13 Roy, A., De Jong, J. and Linnoila, M. (1989) Cerebrospinal fluid monoamine metabolites and suicidal behavior in depressed patients. A 5-year follow-up study. Arch. Gen. Psychiatry 46, 609–612.
14 Maes, M. and Meltzer, H. (1995) The serotonin hypothesis of major depression. In: Psychopharmacology: the Fourth Generation of Progress, pp. 933–944, Bloom, F. and Kupfer, D. (eds.) Raven Press, New York.
15 Mann, J. J. (1999) Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior Neuropsychopharmacology 21, 99S–105S.
16 Albert, P. R. and Lemonde, S. (2004) 5-HT1A receptors, gene repression, and depression: guilt by association. Neuroscientist. 10, 575–593.
17 Drevets, W. C. (1998) Functional neuroimaging studies of depression: the anatomy of melancholia. Annu. Rev. Med. 49, 341–361.
18 Collier, D. A., Stober, G., Li, T., Heils, A., Catalano, M., Di Bella, D., Arranz, M. J., Murray, R. M., Vallada, H. P., Bengel, D. et al. (1996) A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol. Psychiatry 1, 453–460.
19 Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A. and Poulton, R. (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389.
20 Millan, M. J. (2004) The role of monoamines in the actions of established and 'novel' antidepressant agents: a critical review. Eur. J. Pharmacol. 500, 371–384.
21 Vetulani, J. and Sulser, F. (1975) Action of various antidepressant treatments reduces reactivity of noradrenergic cyclic AMP-generating system in limbic forebrain. Nature 257, 495–496.
22 Sulser, F. (1989) New perspectives on the molecular pharmacology of affective disorders. Eur. Arch. Psychiatry Neurol. Sci. 238, 231–239.
23 Nibuya, M., Morinobu, S. and Duman, R. S. (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J. Neurosci. 15, 7539–7547.
24 Nibuya, M., Nestler, E. J. and Duman, R. S. (1996) Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. J. Neurosci. 16, 2365–2372.
25 Duman, R. S., Heninger, G. R. and Nestler, E. J. (1997) A molecular and cellular theory of depression. Arch. Gen. Psychiatry 54, 597–606.
26 Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O. et al. (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301, 805–809.
27 Reul, J. M. and Holsboer, F. (2002) Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. Curr. Opin. Pharmacol. 2, 23–33.
28 Hökfelt, T., Bartfai, T. and Bloom, F. (2003) Neuropeptides: opportunities for drug discovery. Lancet Neurol. 2, 463–472.
29 Holmes, A., Heilig, M., Rupniak, N. M., Steckler, T. and Griebel, G. (2003) Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. Trends Pharmacol. Sci. 24, 580–588.
30 Ögren, S. O., Kuteeva, E., Hökfelt, T. and Kehr, J. (2006) Galanin receptor antagonists: a potential novel pharmacological treatment for mood disorders. CNS Drugs 20, 633–654.
31 Timpl, P., Spanagel, R., Sillaber, I., Kresse, A., Reul, J. M., Stalla, G. K., Blanquet, V., Steckler, T., Holsboer, F. and Wurst, W. (1998) Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. Nat. Genet. 19, 162–166.
32 Rupniak, N. M., Carlson, E. J., Webb, J. K., Harrison, T., Porsolt, R. D., Roux, S., de Felipe, C., Hunt, S. P., Oates, B. and Wheeldon, A. (2001) Comparison of the phenotype of NK1R−/− mice with pharmacological blockade of the substance P (NK1) receptor in assays for antidepressant and anxiolytic drugs. Behav. Pharmacol. 12, 497–508.
33 Kuteeva, E., Hökfelt, T. and Ögren, S. O. (2005) Behavioural characterisation of young adult transgenic mice overexpressing galanin under the PDGF-B promoter. Regul. Pept. 125, 67–78.
34 Unschuld, P. G., Ising, M., Erhardt, A., Lucae, S., Kohli, M., Kloiber, S., Salyakina, D., Thoeringer, C. K., Kern, N., Lieb, R. et al. (2008) Polymorphisms in the galanin gene are associated with symptom-severity in female patients suffering from panic disorder J. Affect. Disord. 105, 177–184.
35 Tatemoto, K., Rökaeus, A., Jörnvall, H., McDonald, T. J. and Mutt, V. (1983) Galanin – a novel biologically active peptide from porcine intestine. FEBS Lett. 164, 124–128.
36 Skofitsch, G. and Jacobowitz, D. M. (1985) Immunohistochemical mapping of galanin-like neurons in the rat central nervous system. Peptides 6, 509–546.
37 Melander, T., Hökfelt, T. and Rökaeus, A. (1986) Distribution of galaninlike immunoreactivity in the rat central nervous system. J. Comp. Neurol. 248, 475–517.
38 Kordower, J. H., Le, H. K. and Mufson, E. J. (1992) Galanin immunoreactivity in the primate central nervous system. J. Comp. Neurol. 319, 479–500.
39 Perez, S. E., Wynick, D., Steiner, R. A. and Mufson, E. J. (2001) Distribution of galaninergic immunoreactivity in the brain of the mouse. J. Comp. Neurol. 434, 158–185.
40 Melander, T., Hökfelt, T., Rökaeus, A., Cuello, A. C., Oertel, W. H., Verhofstad, A. and Goldstein, M. (1986) Coexistence of galanin-like immunoreactivity with catecholamines, 5-hydroxytryptamine, GABA and neuropeptides in the rat CNS. J. Neurosci. 6, 3640–3654.
41 Xu, Z. Q., Shi, T. J. and Hökfelt, T. (1998) Galanin/GMAP- and NPY-like immunoreactivities in locus coeruleus and noradrenergic nerve terminals in the hippocampal formation and cortex with notes on the galanin-R1 and -R2 receptors. J. Comp. Neurol. 392, 227–251.
42 Xu, Z. Q., Zhang, X., Pieribone, V. A., Grillner, S. and Hökfelt, T. (1998) Galanin-5-hydroxytryptamine interactions: electrophysiological, immunohistochemical and *in situ* hybridization studies on rat dorsal raphe neurons with a note on galanin R1 and R2 receptors. Neuroscience 87, 79–94.

43 Larm, J. A., Shen, P. J. and Gundlach, A. L. (2003) Differential galanin receptor-1 and galanin expression by 5-HT neurons in dorsal raphe nucleus of rat and mouse: evidence for species-dependent modulation of serotonin transmission. Eur. J. Neurosci. 17, 481–493.
44 Pieribone, V. A., Xu, Z. Q., Zhang, X., Grillner, S., Bartfai, T. and Hökfelt, T. (1995) Galanin induces a hyperpolarization of norepinephrine-containing locus coeruleus neurons in the brainstem slice. Neuroscience 64, 861–874.
45 Landry, M., Xu, Z. Q., Calas, A. and Hökfelt, T. (2005) Galanin, a new candidate for somato-dendritic release. In: Dendritic Neurotransmitter Release, pp. 239–256, Ludwig, M. (ed.), Springer Science and Business Media.
46 Branchek, T. A., Smith, K. E., Gerald, C. and Walker, M. W. (2000) Galanin receptor subtypes. Trends Pharmacol. Sci. 21, 109–117.
47 O'Donnell, D., Mennicken, F., Hoffert, C., Hubatsch, D., Pelletier, M., Walker, P. and Ahmad, S. (2003) Localization of galanin receptor subtypes in the rat CNS. In: Handbook of Chemical Neuroanatomy, vol. 20, pp. 195–244, Quirion, R., Björklund, A. and Hökfelt, T. (eds.), Elsevier, Amsterdam.
48 Habert-Ortoli, E., Amiranoff, B., Loquet, I., Laburthe, M. and Mayaux, J. F. (1994) Molecular cloning of a functional human galanin receptor. Proc. Natl. Acad. Sci. USA 91, 9780–9783.
49 Smith, K. E., Walker, M. W., Artymyshyn, R., Bard, J., Borowsky, B., Tamm, J. A., Yao, W. J., Vaysse, P. J., Branchek, T. A., Gerald, C. et al. (1998) Cloned human and rat galanin GALR3 receptors. Pharmacology and activation of G-protein inwardly rectifying K+ channels. J. Biol. Chem. 273, 23321–23326.
50 Fathi, Z., Battaglino, P. M., Iben, L. G., Li, H., Baker, E., Zhang, D., McGovern, R., Mahle, C. D., Sutherland, G. R., Iismaa, T. P., Dickinson, K. E. and Zimanyi, I. A. (1998) Molecular characterization, pharmacological properties and chromosomal localization of the human GALR2 galanin receptor. Mol. Brain. Res. 58, 156–169.
51 Wang, S., Hashemi, T., Fried, S., Clemmons, A. L. and Hawes, B. E. (1998) Differential intracellular signaling of the GalR1 and GalR2 galanin receptor subtypes. Biochemistry 37, 6711–6717.
52 Seutin, V., Verbanck, P., Massotte, L. and Dresse, A. (1989) Galanin decreases the activity of locus coeruleus neurons in vitro. Eur. J. Pharmacol. 164, 373–376.
53 Sevcik, J., Finta, E. P. and Illes, P. (1993) Galanin receptors inhibit the spontaneous firing of locus coeruleus neurones and interact with mu-opioid receptors. Eur. J. Pharmacol. 230, 223–230.
54 Ma, X., Tong, Y. G., Schmidt, R., Brown, W. A., Payza, K., Hodzic, L., Pou, C., Godbout, C., Hökfelt, T. and Xu, Z. Q. (2001) Effects of galanin receptor agonists on locus coeruleus neurons. Brain. Res. 919, 169–174.
55 Tsuda, K., Tsuda, S., Nishio, I., Masuyama, Y. and Goldstein, M. (1992) Modulation of norepinephrine release by galanin in rat medulla oblongata. Hypertension 20, 361–366.
56 Yoshitake, T., Reenila, I., Ögren, S. O., Hökfelt, T. and Kehr, J. (2003) Galanin attenuates basal and antidepressant drug-induced increase of extracellular serotonin and noradrenaline levels in the rat hippocampus. Neurosci. Lett. 339, 239–242.
57 Kehr, J., Yoshitake, T., Wang, F. H., Razani, H., Gimenez-Llort, L., Jansson, A., Yamaguchi, M. and Ögren, S. O. (2002) Galanin is a potent *in vivo* modulator of mesencephalic serotonergic neurotransmission. Neuropsychopharmacology 27, 341–356.
58 Swanson, C. J., Blackburn, T. P., Zhang, X., Zheng, K., Xu, Z. Q., Hökfelt, T., Wolinsky, T. D., Konkel, M. J., Chen, H., Zhong, H. et al. (2005) Anxiolytic- and antidepressant-like profiles of the galanin-3 receptor (Gal3) antagonists SNAP 37889 and SNAP 398299. Proc. Natl. Acad. Sci. USA 102, 17489–17494.
59 Mazarati, A. M., Baldwin, R. A., Shinmei, S. and Sankar, R. (2005) *In vivo* interaction between serotonin and galanin receptors types 1 and 2 in the dorsal raphe: implication for limbic seizures. J. Neurochem. 95, 1495–1503.
60 Aghajanian, G. K. and Lakoski, J. M. (1984) Hyperpolarization of serotonergic neurons by serotonin and LSD: studies in brain slices showing increased K+ conductance. Brain. Res. 305, 181–185.
61 Barnes, N. M. and Sharp, T. (1999) A review of central 5-HT receptors and their function. Neuropharmacology 38, 1083–1152.
62 Razani, H., Diaz-Cabiale, Z., Fuxe, K. and Ögren, S. O. (2000) Intraventricular galanin produces a time-dependent modulation of 5-HT1A receptors in the dorsal raphe of the rat. Neuroreport 11, 3943–3948.
63 Kuteeva, E., Wardi, T., Lundström, L., Sollenberg, U., Langel, U., Hökfelt, T. and Ögren, S. O. (2008) Differential role of galanin receptors in the regulation of depression-like behavior and monoamine/stress-related genes at the cell body level. Neuropsychopharmacology (in press: doi: 10.1038/sj.npp.1301660).
64 Yoshitake, T., Yoshitake, S., Yamaguchi, M., Ögren, S. O. and Kehr, J. (2003) Activation of 5-HT(1A) autoreceptors enhances the inhibitory effect of galanin on hippocampal 5-HT release in vivo. Neuropharmacology 44, 206–213.
65 Fuxe, K., von Euler, G., Agnati, L. F. and Ögren, S. O. (1988) Galanin selectively modulates 5-hydroxytryptamine 1A receptors in the rat ventral limbic cortex. Neurosci. Lett. 85, 163–167.
66 Hedlund, P. and Fuxe, K. (1996) Galanin and 5-HT1A receptor interactions as an integrative mechanism in 5-HT neurotransmission in the brain. Ann. N. Y. Acad. Sci. 780, 193–212.
67 Misane, I., Razani, H., Wang, F. H., Jansson, A., Fuxe, K. and Ögren, S. O. (1998) Intraventricular galanin modulates a 5-HT1A receptor-mediated behavioural response in the rat. Eur. J. Neurosci. 10, 1230–1240.
68 Razani, H., Diaz-Cabiale, Z., Misane, I., Wang, F. H., Fuxe, K. and Ögren, S. O. (2001) Prolonged effects of intraventricular galanin on a 5-hydroxytryptamine(1A) receptor mediated function in the rat. Neurosci. Lett. 299, 145–149.
69 Fuxe, K., Hedlund, P., von Euler, G., Lundgren, K., Martire, M., Ögren, S. O., Eneroth, P. and Agnati, L. F. (1991) Galanin/5-HT interactions in the rat central nervous system. Relevance for depression. In: Galanin. A New Multifunctional Peptide in the Neuro-Endocrine System, vol. 58, pp. 221–236, Hökfelt, T., Bartfai, T., Jacobowitz, D. and Ottoson, D. (eds.), University Press, Cambridge.
70 Weiss, J. M., Bonsall, R. W., Demetrikopoulos, M. K., Emery, M. S. and West, C. H. (1998) Galanin: a significant role in depression? Ann. N. Y. Acad. Sci. 863, 364–382.
71 Porsolt, R. D., Le Pichon, M. and Jalfre, M. (1977) Depression: a new animal model sensitive to antidepressant treatments. Nature 266, 730–732.
72 Weiss, J. M., Boss-Williams, K. A., Moore, J. P., Demetrikopoulos, M. K., Ritchie, J. C. and West, C. H. (2005) Testing the hypothesis that locus coeruleus hyperactivity produces depression-related changes via galanin. Neuropeptides 39, 281–287.
73 Nestler, E. J. and Carlezon, W. A., Jr. (2006) The mesolimbic dopamine reward circuit in depression. Biol. Psychiatry 59, 1151–1159.
74 Kuteeva, E., Wardi, T., Hökfelt, T. and Ögren, S. O. (2007) Galanin enhances and a galanin antagonist attenuates depression-like behaviour in the rat. Eur. Neuropsychopharmacol. 17, 64–69.
75 Bartfai, T., Lu, X., Badie-Mahdavi, H., Barr, A. M., Mazarati, A., Hua, X. Y., Yaksh, T., Haberhauer, G., Ceide, S. C., Trembleau, L. et al. (2004) Galmic, a nonpeptide galanin receptor agonist, affects behaviors in seizure, pain, and forced-swim tests. Proc. Natl. Acad. Sci. USA 101, 10470–10475.
76 Lu, X., Barr, A. M., Kinney, J. W., Sanna, P., Conti, B., Behrens, M. M. and Bartfai, T. (2005) A role for galanin in

antidepressant actions with a focus on the dorsal raphe nucleus. Proc. Natl. Acad. Sci. USA 102, 874–879.
77 Florén, A., Sollenberg, U., Lundström, L., Zorko, M., Stojan, J., Budihna, M., Wheatley, M., Martin, N. P., Kilk, K., Mazarati, A. et al. (2005) Multiple interaction sites of galnon trigger its biological effects. Neuropeptides 39, 547–558.
78 Murck, H., Held, K., Ziegenbein, M., Kunzel, H., Holsboer, F. and Steiger, A. (2004) Intravenous administration of the neuropeptide galanin has fast antidepressant efficacy and affects the sleep EEG. Psychoneuroendocrinology 29, 1205–1211.
79 Porsolt, R. D., Bertin, A. and Jalfre, M. (1977) Behavioral despair in mice: a primary screening test for antidepressants. Arch. Int. Pharmacodyn. Ther. 229, 327–336.
80 Steru, L., Chermat, R., Thierry, B. and Simon, P. (1985) The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology 85, 367–370.
81 Holmes, A., Li, Q., Koenig, E. A., Gold, E., Stephenson, D., Yang, R. J., Dreiling, J., Sullivan, T. and Crawley, J. N. (2005) Phenotypic assessment of galanin overexpressing and galanin receptor R1 knockout mice in the tail suspension test for depression-related behavior. Psychopharmacology 178, 276–285.
82 Yoshitake, T., Wang, F. H., Kuteeva, E., Holmberg, K., Yamaguchi, M., Crawley, J. N., Steiner, R., Bartfai, T., Ögren, S. O., Hökfelt, T. et al. (2004) Enhanced hippocampal noradrenaline and serotonin release in galanin-overexpressing mice after repeated forced swimming test. Proc. Natl. Acad. Sci. USA 101, 354–359.
83 Jordan, S., Kramer, G. L., Zukas, P. K. and Petty, F. (1994) Previous stress increases *in vivo* biogenic amine response to swim stress. Neurochem. Res. 19, 1521–1525.
84 Petty, F., Chae, Y., Kramer, G., Jordan, S. and Wilson, L. (1994) Learned helplessness sensitizes hippocampal norepinephrine to mild restress. Biol. Psychiatry 35, 903–908.
85 Bellido, I., Diaz-Cabiale, Z., Jimenez-Vasquez, P. A., Andbjer, B., Mathe, A. A. and Fuxe, K. (2002) Increased density of galanin binding sites in the dorsal raphe in a genetic rat model of depression. Neurosci. Lett. 317, 101–105.
86 Husum, H., Van Kammen, D., Termeer, E., Bolwig, G. and Mathe, A. (2003) Topiramate normalizes hippocampal NPY-LI in flinders sensitive line 'depressed' rats and upregulates NPY, galanin, and CRH-LI in the hypothalamus: implications for mood-stabilizing and weight loss-inducing effects. Neuropsychopharmacology 28, 1292–1299.
87 Lundström, L., Sollenberg, U., Brewer, A., Kouya, P. F., Zheng, K., Xu, X.-J., Sheng, X., Robinson, J. K., Wiesenfeld-Hallin, Z., Xu, Z. Q. et al. (2005) A galanin receptor subtype 1 specific agonist. Int. J. Peptide. Res. Therapeutics 11, 17–27.
88 Barr, A. M., Kinney, J. W., Hill, M. N., Lu, X., Biros, S., Rebek, J., Jr. and Bartfai, T. (2006) A novel, systemically active, selective galanin receptor type-3 ligand exhibits antidepressant-like activity in preclinical tests. Neurosci. Lett. 405, 111–115.
89 Sollenberg, U., Lundström, L., Bartfai, T. and Langel, U. (2006) M871 – a novel peptide agonist selectively recognizing the galanin receptor type 2. Int. J. Peptide Res. Therapeutics 12, 115–119.
90 Lundström, L., Elmquist, A., Bartfai, T. and Langel, U. (2005) Galanin and its receptors in neurological disorders. Neuromolecular Med. 7, 157–180.
91 Biguet, N. F., Buda, M., Lamouroux, A., Samolyk, D. and Mallet, J. (1986) Time course of the changes of TH mRNA in rat brain and adrenal medulla after a single injection of reserpine. EMBO J. 5, 287–291.
92 Berod, A., Biguet, N. F., Dumas, S., Bloch, B. and Mallet, J. (1987) Modulation of tyrosine hydroxylase gene expression in the central nervous system visualized by *in situ* hybridization. Proc. Natl. Acad. Sci. USA 84, 1699–1703.
93 Holmes, P. V., Blanchard, D. C., Blanchard, R. J., Brady, L. S. and Crawley, J. N. (1995) Chronic social stress increases levels of preprogalanin mRNA in the rat locus coeruleus. Pharmacol. Biochem. Behav. 50, 655–600.
94 Schalling, M., Stieg, P. E., Lindquist, C., Goldstein, M. and Hökfelt, T. (1989) Rapid increase in enzyme and peptide mRNA in sympathetic ganglia after electrical stimulation in humans. Proc. Natl. Acad. Sci. USA 86, 4302–4305.
95 Landry, M. and Hökfelt, T. (1998) Subcellular localization of preprogalanin messenger RNA in perikarya and axons of hypothalamo-posthypophyseal magnocellular neurons: an in situ hybridization study. Neuroscience 84, 897–912.
96 Mongeau, R., Blier, P. and de Montigny, C. (1997) The serotonergic and noradrenergic systems of the hippocampus: their interactions and the effects of antidepressant treatments. Brain Res. Rev. 23, 145–195.
97 Wilkinson, L. O. and Jacobs, B. L. (1988) Lack of response of serotonergic neurons in the dorsal raphe nucleus of freely moving cats to stressful stimuli. Exp. Neurol. 101, 445–457.
98 Takase, L. F., Nogueira, M. I., Bland, S. T., Baratta, M., Watkins, L. R., Maier, S. F., Fornal, C. A. and Jacobs, B. L. (2005) Effect of number of tailshocks on learned helplessness and activation of serotonergic and noradrenergic neurons in the rat. Behav. Brain Res. 162, 299–306.
99 Abumaria, N., Rygula, R., Hiemke, C., Fuchs, E., Havemann-Reinecke, U., Ruther, E. and Flugge, G. (2007) Effect of chronic citalopram on serotonin-related and stress-regulated genes in the dorsal raphe nucleus of the rat. Eur. Neuropsychopharmacol. 17, 417–429.
100 Martinez, M., Phillips, P. J. and Herbert, J. (1998) Adaptation in patterns of c-fos expression in the brain associated with exposure to either single or repeated social stress in male rats. Eur. J. Neurosci. 10, 20–33.
101 Takase, L. F., Nogueira, M. I., Baratta, M., Bland, S. T., Watkins, L. R., Maier, S. F., Fornal, C. A. and Jacobs, B. L. (2004) Inescapable shock activates serotonergic neurons in all raphe nuclei of rat. Behav. Brain Res. 153, 233–239.
102 Mahoney, S. A., Hosking, R., Farrant, S., Holmes, F. E., Jacoby, A. S., Shine, J., Iismaa, T. P., Scott, M. K., Schmidt, R. and Wynick, D. (2003) The second galanin receptor GalR2 plays a key role in neurite outgrowth from adult sensory neurons. J. Neurosci. 23, 416–421.
103 Mazarati, A., Lu, X., Kilk, K., Langel, U., Wasterlain, C. and Bartfai, T. (2004) Galanin type 2 receptors regulate neuronal survival, susceptibility to seizures and seizure-induced neurogenesis in the dentate gyrus. Eur. J. Neurosci. 19, 3235–3244.
104 Pirondi, S., Fernandez, M., Schmidt, R., Hökfelt, T., Giardino, L. and Calza, L. (2005) The galanin-R2 agonist AR-M1896 reduces glutamate toxicity in primary neural hippocampal cells. J. Neurochem. 95, 821–833.