Galanin, galanin receptor subtypes and depression-like behaviour

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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 therapeutical 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].

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].

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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-HT₁A autoreceptor, could predispose for depression [16]. In fact, positron emission tomography studies have shown a reduction of both pre- and postsynaptic 5-HT₁A 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 antidepressants, 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