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Review

The neuropeptide galanin as an *in vivo* modulator of brain 5-HT$_{1A}$ receptors: Possible relevance for affective disorders

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Abstract

The neuropeptide galanin is widely distributed throughout the central nervous system with multiple and diverse biological functions mediated by different receptor subtypes. In the rat, galanin-like immunoreactivity is expressed in a population of 5-hydroxytryptamine (5-HT, serotonin) neurons in the dorsal raphe with extensive projections to the forebrain areas, *e.g.*, hippocampus. This review summarizes results from experimental studies in rodents showing that *in vivo* galanin is a potent modulator of brain 5-HT transmission, and in particular 5-HT$_{1A}$ receptor-mediated functions. Galanin, given intracerebroventricular (i.c.v.), was demonstrated to have strong inhibitory interactions with 5-HT$_{1A}$ receptor functions, particularly in the dorsal raphe but also in the hippocampus. Since pre- and postsynaptic 5-HT$_{1A}$ receptors in the dorsal raphe and hippocampus are implicated in the action of antidepressant drugs and in depressive disorders, it is suggested that galanin receptors may be an important target for development of novel antidepressant drugs. This view is supported by a recent study in the rat showing that the galanin antagonist M35, given i.c.v., could block the depression-like behavior in the forced swim test induced by galanin, while M35 produced an antidepressant-like effect on its own.

Keywords: Galanin; Raphe nuclei; Serotonin; 5-HT$_{1A}$ receptors; Depression

Contents

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1. Introduction

1.1. Serotonin in affective disorders

A large body of evidence implicates hypofunctions of brain monoaminergic transmission in the symptoms of depression [1]. Major depression has been linked to decreased serotonergic activity or disturbed serotonin (5-hydroxytryptamine; 5-HT) metabolism [2]. Studies aimed at investigating the mechanisms underlying depression have focused on the role of ascending 5-HT neurons derived from cell bodies in the dorsal (DR) and median raphe nuclei (MR) [3]. These neurons innervate the entire cortex cerebri and forebrain limbic systems such as the hippocampus, septum, amygdala and hypothalamus; areas of the brain, which have a role in the perception and assessment of emotional stimuli as well as in regulation of the behavioral expression of mood and emotion [4,5].

Serotonergic transmission in the central nervous system (CNS) is regulated by the brain levels of the amino acid precursor tryptophan and by the rate-limiting enzyme in the 5-HT synthesis, tryptophan hydroxylase. In the CNS, 5-HT modulates neuronal activity *via* a seven-member family of receptors comprising 14 receptor subtypes [6]. The 5-HT receptors are G-protein coupled receptors with the exception of the 5-HT_3 receptor, which is a ligand-gated channel receptor. The 5-HT_{1A} receptor has an important physiological role since it is the major somatodendritic autoreceptor in the raphe neurons regulating raphe neuronal signaling. Thus, the 5-HT_{1A} receptors mediate the negative feedback inhibition that controls raphe 5-HT neuronal activity [7]. Intracellular recordings have indicated that local application of 5-HT_{1A} agonists on serotonergic DR neurons reduces the firing rate of these neurons by triggering a hyperpolarization *via* an increased K^+ conductance and a decreased Ca^{2+} conductance [8]. Postsynaptic 5-HT_{1A} receptors, localized on pyramidal cells and interneurons in the cortex and limbic systems also have an inhibitory role mediated *via* coupling to Gi/Go proteins to block cAMP functions, to inactivate calcium channels or to increase K^+ conductance [9]. Changes in the regulatory role of both pre- and postsynaptic 5-HT_{1A} receptors will, therefore, have profound effects on brain serotonergic transmission and influence neuronal activity in the transmitter systems innervated by 5-HT terminals.

1.2. Role of 5-HT_{1A} receptors in the action of antidepressant drugs

Multiple lines of evidence have implicated 5-HT_{1A} receptors in the mechanism of action of antidepressant drugs and in the pathophysiology of affective disorders. The 5-HT_{1A} receptors appear to play a critical role in the therapeutic effect of currently used antidepressant drugs, *e.g.*, the selective serotonin reuptake inhibitors (SSRIs). SSRIs are believed to act by enhancing 5-HT function through inhibition of the reuptake of 5-HT [1,7]. Although SSRIs immediately increase 5-HT neurotransmission in the synaptic cleft, typically 2–3 weeks of drug treatment is required for a clinically significant antidepressant effect. The delayed onset of the therapeutic action of antidepressant drugs has been attributed to the powerful negative feedback regulation *via* the somatodendritic 5-HT_{1A} autoreceptors [7,10]. Thus, the acute 5-HT reuptake blockade by *e.g.*, SSRIs, will result in a powerful inhibition of raphe cell firing due to activation of 5-HT_{1A} autoreceptors as a consequence of the increase in 5-HT concentrations at the raphe nuclei. Following chronic treatment with SSRIs, the prolonged exposure to 5-HT at the raphe level desensitizes the somatodendritic 5-HT_{1A} autoreceptors. The recovery of the initial reduction of raphe cell firing, in combination with maintained 5-HT uptake inhibition, will result in enhanced 5-HT release and neurotransmission at nerve terminal areas [7,11]. On the contrary, electrophysiological studies indicate that long-term treatment with SSRIs appears not to change postsynaptic 5-HT_{1A} receptor signaling [7]. Thus, the antidepressant effect of SSRIs seems to mainly involve adaptive changes in 5-HT_{1A} autoreceptor signaling in the serotonergic raphe nuclei. The changes in 5-HT_{1A} receptor mechanisms involve multiple mechanisms including alterations in receptor occupancy (desensitization and internalization) and also changes in transduction processes and gene transcription [10].

Studies using positron emission tomography also support a role for changes in 5-HT_{1A} receptor function in depressive disorders. A reduction of pre- and postsynaptic 5-HT_{1A} receptor binding potential has been reported in depressed patients [12], suggesting a reduced 5-HT_{1A} autoreceptor function and a blunted postsynaptic 5-HT_{1A} receptor signaling in depression. On the other hand, studies in postmortem brains of depressive patients committing suicide indicated an increase in 5-HT_{1A} autoreceptors in the midbrain areas, suggesting an increased 5-HT autoreceptor function, and thereby a reduction in 5-HT activity [12]. Interestingly, the transcriptional regulation of 5-HT_{1A} receptor gene may be disturbed in depression, as it was shown that a 5-HT_{1A} polymorphism of C(1019)G, which blocks repression of 5-HT_{1A} receptor by the repressor NUDR, may predispose to depression [10]. However, the mechanisms responsible for the observed changes in 5-HT_{1A} autoreceptor function are presently not known.

In this context, the neuropeptide galanin is of particular interest given the distribution of the peptide and its receptors, which allows for multiple regulatory actions of 5-HT raphe signaling and of 5-HT_{1A} receptors. Recent findings have indicated that galanin can modulate 5-HT_{1A} receptor function at both pre- and postsynaptic receptors sites [13,14]. This paper will review the evidence, based on *in vivo* studies in the rat, for a modulatory role of galanin on 5-HT transmission with focus on 5-HT_{1A} receptor function in the dorsal raphe nucleus and the hippocampus. The possible relevance of galanin/5-HT_{1A} receptor interactions for affective disorders such as depression will be discussed.

2. Anatomical and physiological basis for galanin/5-HT interactions

Galanin, isolated from the porcine gut by Viktor Mutt and co-workers in 1983, is a 29 (30 in human) amino acid neuropeptide [15]. The anatomical distribution of galanin studied with immunohistochemistry and *in situ* hybridization, led to the suggestion that this neuropeptide might be involved in a variety of physiological and behavioral processes [16]. Galanin-like immunoreactivity (galanin-IR) was demonstrated in many brain transmitter and neuropeptide systems as shown