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Possible role for interactions between 5-lipoxygenase (5-LOX) and AMPA GluR1 receptors in depression and in antidepressant therapy

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Summary

Emerging evidence suggests that 5-lipoxygenase (5-LOX) plays a role in central nervous system functioning. It has been shown that 5-LOX metabolic products can decrease the phosphorylation of the glutamate reseptor subunit GluR1, and that this effect can be antagonized by 5-LOX inhibitors. Recent concepts about the pathobiological mechanisms of depression and the molecular mechanisms of antidepressant activity postulate a significant role for glutamatergic neurotransmission and the GluR1 receptor. Regulation of GluR1 phosphorylation, i.e., enhancement of this phosphorylation, may be a part of antidepressant activity. On the other hand, reduced GluR1 phosphorylation may be a pathobiological mechanism contributing to depression. Since 5-LOX inhibitors, along with antidepressants share the capacity to increase GluR1 phosphorylation, we hypothesize that they may also have antidepressant properties. Furthermore, we postulate that increased brain 5-LOX expression may lead to decreased GluR1 phosphorylation and favor the development of depression. For example, brain 5-LOX expression is stimulated by stress hormone glucocorticoids, and stress is a known as a contributing factor to depression.

Keywords

glutamate GluR1 receptor; phosphorylation; 5-lipoxygenase; antidepressant

Introduction

Recent clinical research has provided evidence of an association between depressive symptoms and the progression of subclinical atherosclerosis [1]. We have proposed that the pro-atherosclerotic 5-lipoxygenase (5-LOX) pathway may be one of the biological mechanisms linking atherosclerosis and cardiovascular pathology to depression [2]. Numerous studies have investigated the 5-LOX-mediated mechanisms of atherosclerosis [3]. Although animal behavioral studies indicate the possible antidepressant consequences of 5-LOX inhibition [4], the molecular mechanisms of neuronal 5-LOX actions are not well understood [5].

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Here we hypothesize that an action of 5-LOX on a subtype of the AMPA glutamate receptors, the GluR1 receptor, may support a role for 5-LOX in depression.

Implications of GluR1 phosphorylation

Ionotropic glutamate receptors are ligand-gated ion channels that can be subdivided on the basis of agonist pharmacology and sequence homology into three classes: NMDA (N-methyl-D-aspartate), kainate, and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors. AMPA subtypes (GluR1-GluR4) of ionotropic glutamate receptors participate in fast excitatory neurotransmission in the mammalian brain and contribute to both neuroplasticity and neurodegeneration. The composition of AMPA receptors, in particular the ratio between different subunits, i.e., GluR1-GluR4, determines the permeability of these receptors to calcium. A number of post-transcriptional and post-translational modifications are important for AMPA receptor functioning. Particularly well studied is the role of GluR1 phosphorylation in synaptic plasticity [6,7]. This subunit is phosphorylated at Ser 845 [by protein kinase A (PKA)] and at Ser 831 [by protein kinase C (PKC) and calcium/calmodulin-dependent kinase II (CaMKII)]. Dephosphorylation of GluR1 is achieved by an action of phosphatases, for example, protein phosphatase 1 (PP1). It has been established that phosphorylation of GluR1 is required for synaptic plasticity, i.e., LTP (long-term potentiation) and LTD (long-term depression), and that alterations in GluR1 phosphorylation status significantly impact on LTP and LTD [8].

The statuss of GluR1 phosphorylation may change channel open probabilities and conductance (low when both sites are dephosphorylated) [9]. Increased GluR1 phosphorylation is associated with increased membrane expression of this subunit [8] and may lead to an increase in receptor function. It is believed that the GluR1 subunit is crucial for activity-dependent synaptic delivery of AMPA receptors.

AMPA receptors in depression

Based on pharmacological studies, AMPA receptor dysfunction has been primarily associated with schizophrenia. Supporting this concept is the finding that AMPA-potentiating drugs produce improvements in this disorder [10]. In preclinical tests such as the forced swim test, AMPA receptor potentiators exhibit antidepressant-like activity and they also enhance the antidepressant-like activity of biogenic amine-based antidepressants [11]. Genome wide gene expression studies in mood disorders point to alterations of glutamate-related genes in depression and suicide [12]. Furthermore, recent studies in post-mortem human brain indicate major alterations in glutamate receptor mRNA levels in psychiatric disorders including depression; GluR1 mRNA expression was reduced in the perirhinal cortex [13]. These findings and preclinical data suggest that increasing AMPA (GluR1)-mediated neurotransmission might be useful for the treatment of depression.

GluR1 and antidepressants

Most effective antidepressants are known to increase serotonergic neurotransmission (e.g., Prozac), but this mechanism cannot fully explain their therapeutic effects. In 2002, Svenningsson et al. [14] proposed that the underlying mechanism of antidepressant action may involve the antidepressant-stimulated phosphorylation of the AMPA GluR1 receptor. Subsequent work by others provided additional support to this concept [15–19]. Thus, chronic but not acute administration of the antidepressants desipramine and paroxetine increased GluR1 levels in the rat hippocampal membrane fraction, with no significant change in the total extract, suggesting a trafficking of this receptor from intracellular pools to synaptic sites [15]. It appears that these changes were region-specific since no change in AMPA receptor subunit trafficking was found in the frontal cortex. Drugs with a predominantly antidepressant profile

were shown to be capable of significantly increasing the surface expression of GluR1 in cultured hippocampal neurons [16]. It was suggested that mechanisms involved in the antidepressant-increased trafficking of AMPA receptors may include the brain-derived neurotrophic factor (BDNF) [17] and the protein stargazing [18].

5-LOX and GluR1

Recently, it was suggested that 5-LOX may participate in the regulation of brain (e.g. hippocampal) GluR1 phosphorylation [20]. In these experiments, acute rat hippocampal slices were incubated with the 5-LOX inhibitor MK-886. Phosphorylation at both Ser831 and Ser845 of GluR1 was increased by preincubating slices with MK-886, whereas inhibitors of 12-lipoxygenase and cyclo-oxygenases were ineffective. Furthermore, the effect of MK-886 was selective for GluR1; it did not alter the phosphorylation of the glutamate NMDA subunit NR1 (Ser896/Ser897). In addition, 5-LOX-dependent modification of GluR1 phosphorylation was not observed in the phosphorylation of GluR2/3 AMPA subunits. Using the ^{3}H-AMPA binding assay, these authors concluded that 5-LOX metabolite-regulated phosphorylation of GluR1 subunits might selectively influence the number of membrane receptors in the rat hippocampus. The stimulating effects of MK-886 on GluR1 phosphorylation were recently confirmed in a model of primary neuronal cultures in-vitro [21]. Furthermore, chronic but not acute intraperitoneal administration of MK-886 to mice in-vivo increased the phosphorylation of GluR1 in the brain [21].

GluR1 receptors play a major role in various forms of synaptic plasticity including LTD [8]. 5-LOX metabolites also influence this type of GluR1-related neuroplasticity; application of a 5-LOX inhibitor to hippocampal slices increased GluR1 phosphorylation and reduced LTD [22]. On the other hand, it was shown that LTD is increased in an animal model of depression [23]. Hence, it appears that 5-LOX inhibitors, by increasing GluR1 phosphorylation, might normalize LTD in depression and produce antidepressant effects.

To date, there are no clinical data available on a putative antidepressant activity of 5-LOX inhibitors. Indications for such an effect can be found in preclinical studies. Caffeic acid, a naturally occurring phenolic compound, has been characterized as a 5-LOX inhibitor [24]. Administration of caffeic acid to mice produced an antidepressant-like effect in a forced swim test and prevented a swim test-induced decrease in cortical BDNF mRNA content [25].

Conclusion

Recent concepts about the pathobiological mechanisms of depression and molecular mechanisms of antidepressant activity postulate a significant role for glutamatergic neurotransmission and AMPA receptors, particularly the GluR1 receptor subunit. Regulation of GluR1 phosphorylation, i.e., enhancement of this phosphorylation, may be a part of antidepressant activity. On the other hand, reduced GluR1 phosphorylation may be pathobiological mechanism contributing to depression. Evidence is emerging suggesting that 5-LOX metabolite may decrease GluR1 phosphorylation and that this effect can be antagonized by 5-LOX inhibitors. 5-LOX inhibitors, along with antidepressants, share the capacity to increase GluR1 phosphorylation and may also have antidepressant properties. Furthermore, we hypothesize that increased brain 5-LOX expression [5] may lead to decreased GluR1 phosphorylation and favor the development of depression. For example, brain 5-LOX expression is stimulated by stress hormone glucocorticoids [26,27], and stress is a known contributing factor in depression.

Acknowledgments

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