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Neuroprotective effects of agmatine and hippocampal neuron loss in the depression

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Abstract

Agmatine is an endogenous polyamine and potential neurotransmitter in the brain. This article reviewed the neuroprotective effects of agmatine on hippocampal neurons against glutamate and glucocorticoids-induced neuronal damage. As neuronal loss in the hippocampus is a characteristic of depression, the neuroprotective activity of agmatine may play important role in the pathophysiology of major depression.

The hippocampus plays a vital role in learning and contextual fear conditioning. While it influences autonomic and vegetative functions such as corticotropin secretion [1], it also is one of the most vulnerable brain regions to various insults (seizures, hypoxia-ischemia, hypoglycemia etc.). Based on these characteristics, the hippocampus is likely to be an important brain structure in the pathophysiology of depression, a disorder in which both cognitive deficits and hypercortisolemia are found [2]. Considerable evidence has revealed that morphological changes occur in the hippocampus of subjects with chronic Major Depressive Disorder (MDD) [3]. For example, postmortem brains of patients with MDD showed smaller hippocampal volumes [4,5]. Brain imaging (MRI) studies revealed the hippocampal atrophy in chronically depressed patients [6,7].

The exact reason for hippocampal volume loss in depression remains speculative. There are several possibilities. Given neurogenesis continues in the hippocampus, especially the dentate gyrus throughout adulthood in humans and other mammalian species [8,9], a decreased neurogenesis has been considered to be one factor underlying the hippocampal atrophy observed in MDD [10]. Nevertheless, chronic stress may be one important cause for such reduced neurogenesis in the hippocampus. Animals exposed to various stressors exhibit overt loss of hippocampal neurons and potently suppressed adult neurogenesis in the dentate gyrus [7]. Prolonged stress causes atrophy and death of CA3 pyramidal neurons in the rat hippocampus [11,12], which was confirmed in adult monkeys [13]. Stress also suppresses the gene expression of brain-derived neurotrophic factors (BDNF), an important neurotrophin for neurogenesis, in hippocampus [14]. Both chronic stress and elevated glucocorticoids inhibit proliferation of granule cell precursors in the dentate gyrus [15,16].

Apoptosis is likely another important mechanism responsible for hippocampal volume loss in depression. As mentioned above, a reduction in numbers of neuronal and/or glia cells has been reported [17] in the hippocampus of MDD. Alternatively, such a reduction in neuronal and glia cells would occur in the face of apoptosis [18]. Support for this contention comes from recent observations demonstrating that glucocorticoid receptor activation induces apoptosis of granule cells in the hippocampus [19], where glucocorticoid receptors are enriched [20]. It has been reported that glucocorticoid receptor occupation stimulates apoptosis within the granular and hilar cell populations of the dentate gyrus [21]. Moreover, increased apoptosis has been found in peripheral blood cells in patients with MDD [22]. Many studies have demonstrated that glutamate and its NMDA Receptor (NMDA-R) are important factors for apoptosis [23]. Glutamate-mediated apoptosis involves an increase in intracellular Ca^{2+} concentrations above the buffering capacity of neurons, leading to toxic conditions such as oxidative and nitrosative stress. Cytotoxicity, as a result of massive Nitric Oxide (NO) formation through NO donors [24] or a Ca^{2+}-independent and inducible form of NOS by astrocytes or microglia [25], has been established in apoptosis.

It should be noted that NO-induced cell death can be entirely blocked by agents that directly or competitively block NMDA-R channel [26]. Therefore, blocking either the NMDA-R channel or NO Synthase (NOS) to reduce excitoxicity, or reducing neuronal Ca^{2+} overload and thereby inhibiting cysteine proteases, would attenuate apoptosis. Taken together, agents which antagonize the NMDA-R and NO formation have potential neuroprotective and anti-apoptotic effects. Agmatine, as a novel neurotransmitter in mammals, is such an endogenous agent that blocks the NMDA Receptor (NMDA-R) channels and inhibits NOS [27]. Agmatine is an endogenous polyamine derived from enzymatic decarboxylation of L-arginine [28] and preponderantly localized in neurons [29]. Immunocytochemical studies have demonstrated that agmatine is widely distributed in brain but enriched in subcortical regions [29]. Agmatine exerts neuroprotective action by reducing the size of ischemic infarctions or the loss of cerebella neurons after focal or global ischemia *in vivo*. It has also been reported that agmatine fully prevents neurotoxicity produced by glutamate in cultured cerebellar granule cells. In the CA1 region of hippocampus, agmatine-like immunoreactivity primarily is present in the perikarya and dendritic profiles of pyramidal cells and in punctate processes preponderantly in stratum radiatum [30]. CA3 pyramidal cells also contain agmatine-

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immunoreactivity, which indicates that CA3 might be the source of agmatine-containing terminals found in CA1. Subcellularly, agmatine-immunoreactivity is affiliated primarily with tubular vesicles and mitochondria. In the hippocampal regions, agmatine is found primarily in nerve terminals forming excitatory synapses on pyramidal cells, implicating that agmatine is possibly released as a co-transmitter with l-glutamate. These cellular and subcellular localizations of agmatine provide an important structural basis for the possible involvement of agmatine in the pathophysiological alteration of hippocampus in depression.

Although the study of the possible physiological functions of agmatine in the brain is still in its infancy, accumulating evidence indicates several levels of pharmacological and physiological importance. One of the most important facts is that agmatine selectively blocks NMDA-R channels in hippocampal neurons in a concentration- and voltage-dependent manner [31]. Agmatine is also a competitive inhibitor of all isoforms of NOS [32]. As already mentioned, both the NMDA-R and NO are involved in neurotoxicity and apoptosis [24,25], which might contribute to hippocampal atrophy in major depression. In addition, there is a growing body of preclinical research showing that NMDA-Rs are altered in MDD and normalized by antidepressant treatments [33]. This is based on observations that various antidepressant treatments change the characteristics of NMDA-R subunits [34]. NMDA-R antagonists, like eliprodil and MK-801, have been shown to robustly decrease depressive symptoms in animal models of depression and in patients with MDD [35,36].

Actually, the neuroprotective action of agmatine has been observed in various neuronal injuries beyond major depression. For example, agmatine attenuates the extent of neuronal loss following excitotoxic spinal cord injury [37] and reduces tissue damage following spinal cord injury [38]. Agmatine exerts neuroprotection by reducing the size of ischaemic infarctions, as well as the loss of cerebellar neurons after focal or global ischemia [39,40]. Olmos et al [41] have reported that agmatine fully prevents neurotoxicity produced by glutamate in cerebellar granule cells. The studies from our laboratory demonstrated that agamtine protected cultured hippocampal neurons against cell damage induced by NMDA, glutamate [42], and glucocorticoids [43]. Furthermore, *in vivo* studies demonstrated that while chronic administration of glucocorticoids resulted in rat morphologic damage in the hippocampus, same treatment caused a parallel reduction of endogenous agmatine and arginine decarboxylase levels in rats, indicating the modulatory effects of stress hormones on endogenous agmatine [44]. This result was confirmed in the stress animal models [45], which can be protected by administration of exogenous agmatine [46]. Taken together, agmatine has neuroprotective role for the damaged hippocampal neurons.

It is noteworthy that agmatine also binds α_2-adrenoceptors and is an endogenous ligand at imidazoline receptors [47]. So far there is no single report about the relationship between agmatine's neuroprotective effects and its α_2-adrenoceptor properties, but an increased density of brain and platelet α_2-adrenoceptor agonist binding sites has been reported in major depression and suicide [48-51]. The experimental paradigms previously performed in our laboratory and others have indicated that imidazoline binding sites are upregulated in platelets of patients with MDD and in brains of suicide victims [52,53]. In addition, agmatine has been reported to prevent the development of opioid tolerance [54] and alleviate pain associated with excitotoxic lesions in the spinal cord [37]. Although these functions may not be related to hippocampal neuronal damage in MDD, they indicate that agmatine has broad biochemical and physiological implications.

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