ISSN : 0974 - 7532 Volume 5 Issue 2

Trade Science Inc.

Research & Reviews in

BioSciences

Review

RRBS, 5(2), 2011 [78-80]

Imbalance in chloride homeostasis in substantia nigra reticulata: A novel pathogenesis of hepatic

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Received: 6th June, 2011 ; Accepted: 15th July, 2011

BACKGROUND

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome, that frequently occurs in chronic liver disease. Its clinical manifestations range from minor sleep disturbances, changes in personality and motor activity, to overt deterioration of cognitive functions, motor coordination, decreased consciousness and coma[1]. The pathogenesis of HE is not been fully understood and many factors may affect its development[2].

Several lines of evidences have suggested that disturbances in GABAergic neurotransmission are an essential factor of HE development[3,4]. GABA is the predominant inhibitory neurotransmitter in the mammalian central nervous system. GABAergic neurotransmission is mediated by GABA which mainly activates the postsynaptic $GABA_A$ receptor complex. It was shown in the early 1980s that in rabbits succumbing to galactosamine induced fulminant hepatic failure the visual evoked response patterns resembled those of animals treated with various allosteric modulators of the $GABA_A$ receptor complex such as muscimol, pentobarbital, and diazepam[5-7]. Furthermore, it was shown that $GABA_A$ receptor complex agonists were more potent depressors of spontaneous electrophysiological activity of neurons from animals with HE compared to those of normal animals[8]. Subsequent observations consistent with increased GABAergic tone include reports of a beneficial effect in HE patients of flumazenil, a highly selective $GABA_A$ receptor complex antagonist[9]. Together these findings suggest that increased GABAergic tone could be the consequence of either increased brain GABA content, altered $GABA_A$ receptor complex integrity, or increased brain concentrations of endogenous $GABA_A$ receptor.

However, the role of GABAergic neurotransmission in the pathogenesis of HE remains controversial. GABA concentrations were found to be unaltered[10] or increasedin the brain of HE patients[11]. Comparably, $GABA_A$ receptor densities were reported to be up-regulated[12] in cerebral cortex in some studies, but were unaltered in others[13-16]. Additionally, the mRNA expression of the GABA transporter GAT-2 was increased in the cerebral cortex of rats with portocaval shunts, whereas the genes for the $GABA_{B1D}$ receptor and for the β2 subunit of the $GABA_A$ receptor were downregulated[17]. These results indicate that several important issues about the biochemical basis of dysfunction of GABA-mediated neurotransmission in pathogenesis of HE remain unsolved. We therefore moved our focus to the role of alterations of chloride (Cl^-) homeostasis in the pathophysiology of HE, based on the fact that the $GABA_A$ receptor complex is a specific ligand-gated ion channel selective for Cl^-.

Presentation of the hypothesis

In view of the evidence above, we hypothesize that reduced motor activity in HE is a consequence of altered GABAergic neurotransmission produced by an imbalance of chloride homeostasis in the substantia ni-

gra reticulata (SNr), and that this results from a mutation or dysfunction of the K^+-Cl^- cotransporter 2 (KCC2) and the Na^+-K^+-$2Cl^-$ cotransporter 1 (NKCC1). We also hypothesize that intracerebral injections into the SNr of bumetanide, an agent that is uniquely sensitive to NKCCl and is considered to be the prototypic agent for pharmacologic investigations of the role of NkCCl, may produce improvements in HE patients by restoring depolarizing GABAergic signaling in the SNr.

Theoretical foundation of the hypothesis

KCC2 and NKCC1 determine Cl^- homeostasis

Cation–Cl^- cotransporters have been considered to play pivotal roles in controlling the intracellular Cl^- concentration ([Cl^-]i) of neurons, and, further, in modulating their GABAergic functions. To date, seven electroneutral cation-Cl^- cotransporters have been described in mammals: a thiazide-sensitive Na^+-Cl^- cotransporter (NCC), two loop diuretic-sensitive Na^+-K^+-$2Cl^-$ cotransporters (NKCC1 and 2), and four K^+-Cl^- cotransporters (KCC1–4) [18]. Among these, KCC2 and NKCC1, functioning in opposite directions, affect GABAergic neurotransmission through regulation of [Cl^-]i of neurons[18]. The KCC2 plays a dominant role in determining [Cl^-]i and the GABAergic hyperpolarization in mature neurons, while the NKCC1 is a major source of Cl^- influx in immature neurons. A precise balance between NKCC1 and KCC2 activity is necessary for inhibitory GABAergic signaling in the adult central nervous system, and for excitatory GABAergic signaling in the developing central nervous system and in the adult peripheral nervous system.

Altered Cl^- homeostasis is inolved in the pathogenesis of several diseases

Altered chloride homeostasis, resulting from mutation or dysfunction of NKCC1 and/or KCC2, causes neuronal hypoexcitability or hyperexcitability; such derangements have been implicated in the pathogenesis of seizures[19] and neuropathic pain[20]. [Cl^-]i is also regulated to maintain normal cell volume. Dysfunction of KCC2 or NKCC1 has been implicated in the damaging secondary effects of cerebral edema after ischemic and traumatic brain injury, as well as in swelling-related neurodegeneration[21]. KCC2 and NKCC1 represent attractive therapeutic targets in neurological disorders the pathogenesis of which involves deranged cellular chloride homoestasis.

The SNr, one of the components of the basal ganglia, is intimately involved in the movement disorder of HE

The motor symptoms of HE have been shown to be a consequence of basal ganglia dysfunction, including alterations in the basal ganglia, in the neuronal circuits linking the basal ganglia and the prefrontal cortex, or in altered functional connections within the basal ganglia-thalamo-cortical loop[22,23]. The above reports have suggested that the function of the neuronal circuits by which basal ganglia modulate motor function are altered in HE and that this alteration would be responsible for some of the motor alterations in patients with HE.

A main neuronal circuit modulating motor function involves the basal ganglia, thalamus and cerebral cortex and this is modulated by the SNr[25,26]. To modulate motor activity, the basal ganglia send messages that go via the ventral pallidum to the thalamus which, in turn, sends messages to cerebral cortex to modulate movement execution. The signals from basal ganglia are modulated by SNr, which sends inhibitory signals to the ventro-medial nucleus of the thalamus[24]. Furthermore, the predominant neurons to the SNr are GABAergic and neurons in SNr express $GABA_A$ receptors[27,28].

Importantly, it has been indicated that substantia nigra neurons of rats express KCC2 mRNA and NKCC1 mRNA, and respond to $GABA_A$ receptor activation[29,30], although the morphological distribution of both KCC2 and NKCC1 in the SNr remains to be demonstrated.

Testing the hypothesis

Animals will/should be randomly divided into five groups: normal group, thioacetamide induced HE animal group[31], the group of thioacetamide induced HE animal followed by unilateral infusion of KCC2 or NKCC1 antisense into the SNr, the group of thioacetamide induced HE animal followed by bilateral infusions of KCC2 or NKCC1 antisense into the SNr, and sham operation group. The expression level of NKCC1/KCC2 in the SNr in these groups will/should be analyzed by semi-quantitative single cell multiplex RT-PCR, western blotting, in situ hybridization and immunofluorescence double labeling. Whole-cell voltage-clamp recordings will/should be used to measure the reversal potential of GABA-evoked currents and intracellular chloride estimation will be performed by Cl^- imaging [32]. Moreover, behavioral tests, liver hematoxylin eosin staining, liver function, blood ammonia and Nissl staining of the brain stem will/should be added.

Review

Implication

We expect to gain a deeper insight into the pathophysiology of HE, with the purpose of identifying potential new treatments. Studies on the association between KCC2 or NKCC1 in SNr and HE have shown that KCC2 or NKCC1 may play the leading role in patients with HE[33]. If so, normalizing intracellular Cl- concentration may be a new therapeutic approach to improve motor functions in patients with HE.

Conflict of interest statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. There is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, this manuscript.

ACKNOWLEDGEMENT

This work is supported by grants from the National Natural Science Foundation of China (Nos. 30600176, 30700811, and 30971174).

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