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Pharmacological Targets for Neurorehabilitation

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Editorial

For almost a quarter of century D-cycloserine, a second line tuberculostatic agent [1], was proposed as a drug to potentiate the glutamatergic receptor function [2] and was introduced to act as a partial agonist at the N-methyl-D-aspartate (NMDA) receptor [2,3].

In respect to the functional activities of D-cycloserine scientists suggested anticonvulsive activities [4,5] and furthermore the application seems to improve memory and cognitive function. Recently we discovered that D-Cycloserine has the ability to block kynurenic acid synthesis [6]. Kynurenic acid, a metabolite along the kynurenine pathway of tryptophan degradation blocks the glycine sites of NMDA glutamatergic receptors [7] and also the nicotine cholinergic receptors [8] and exerts anticonvulsive activities [7].

An animal experimental study gives significant evidence that an increased level of kynurenic acid in the brain enhances memory impairment [9]. On the other hand the plus maze retest paradigm shows an enhancement of memory consolidation after D-cycloserine treatment [10]. This and other significant accumulated experimental findings allowed us to suggest that an increased kynurenic acid level in the CNS of brain disorders might play a role in the impairment of memory and cognition. Subsequently, this consideration challenged neuroscientists and clinicians to find pharmacological and/or therapeutic approaches for better output in neurorehabilitation.

Increased kynurenic acid synthesis in the brain has been found in neuropsychiatric disorders, such as Alzheimer's, Downs Syndrome, [11,12], Schizophrenia [13], HIV encephalopathy [14] and stroke [15-17] or during the aging process [18] and kynurenic acid's involvement in memory and cognition impairment has been suggested.

An improvement of memory in Alzheimer patients has been described after D-cycloserine treatment [19]. Furthermore, in patients with schizophrenia D-cycloserine enhanced learning significantly [20] and D-cycloserine improves memory consolidation and facilitation of behavioural therapy for delusions in patients with schizophrenia [20,21]. Notably, the positive effect of D-cycloserine was enhanced in the presence of neuroleptic drugs [22], confirming that both pharmacological approaches, thus lowering of dopamine neurotransmission by neuroleptic drugs and lowering of kynurenic acid levels due to D-cycloserine treatment are significant therapeutic paradigms in patients with schizophrenia.

D-cycloserine dose-dependently and significantly blocked kynurenine aminotransferase I, II and III (KAT I, II and III) activities in rat liver, and in rat and human brain homogenates [6]. In our further work on the mechanism of D-cycloserine action we demonstrated that lowering of kynurenic acid involves lowering of pyridoxal-5-phosphat levels [23]. D-cycloserine lowers significantly levels of pyridoxal-5-phosphat which acts as a cofactor in many biochemical reactions involving transamination. Interestingly, Dengler et al. 1962 [24] demonstrated that D-cycloserine inhibits glutamic acid- and dopamine- decarboxylase activities. Dopamine decarboxylase which synthesizes dopamine is - beside kynurenine aminotransferase - a further enzyme which requires pyridoxal-5-phosphat, as well. Therefore it is reasonable to believe that lowering of dopamine and kynurenic acid synthesis due to D-cycloserine action can result in the positive effect of this drug in schizophrenia patients.

It is important to mention one study demonstrating that D-cycloserine did not enhance motor learning or motor skill generalization in neurologically intact adults or in adults after stroke [25], however, authors stated that likely the tasks selected for motor training were not challenging enough. Currently there are several clinical trials ongoing to evaluate the effect of D-cycloserine in different neurological and psychiatric disorders and with different approaches and variable results [26-28].

An improvement of cognition as well as lowering of kynurenic acid synthesis in an in vitro study has been described by using Cerebrolysin [29]. Cerebrolysin is a peptidergic drug, a mixture of low-molecular-weight peptides and amino acids derived from pigs' brain tissue, exhibiting neuroprotective and neurotrophic effects in experimental and clinical studies [30-32]. Interestingly, Cerebrolysin is described to be effective in preventing cognitive impairment in different experimental animal models [33-35]. Also human studies indicate that Cerebrolysin improves dementia symptoms and cognitive performance in patients with Alzheimer's disease and in other types of senile dementia [36-38], and also in elderly control subjects [39]. Treatment of stroke patients with Cerebrolysin provided positive effect, too [40].

Although, D-cycloserine and Cerebrolysin lower kynurenic acid content [6, 29] and the effect of both drugs lo lower kynurenic acid is additive, at least in an in vitro study (Baran observation), the mechanism of their actions is not elucidated yet.

Tryptophan metabolites are significantly enhanced in the serum and CSF of stroke patients [15-17,41] and increased kynurenic acid levels might have an impact on the impairment of memory and cognition as well as on the development of post-stroke depression which might involve also deficiency of serotonergic activities. Therefore, it is reasonable to believe that lowering of dopamine and also of serotonine synthesis due to D-cycloserine could even promote the progression of depression. And, this could be also one explanation for the lacking positive effect of D-cycloserine treatment in stroke patients.

Movement disturbance up to immobility is a very common condition in stroke patients and might be in part responsible for the increase of kynurenic acid levels in the serum. On the other hand exercise by using stochastic resonance therapy (SRT) and also running activities significantly lowered kynurenic acid levels in the serum of healthy human subjects [42] and of animal experimental model [43]. It is possible that due to forced movement and/or exercise in stroke rehabilitation the kynurenic acid metabolism in the brain could be affected similarly. The importance of exercise for the improvement of chronic stroke patients has been already reported [44].

Rehabilitation of stroke patients by applying repetitive transcranial magnetic stimulation (rTMS) yielded also promising data concerning recovery of sensomotoric and cognitive functions [45,46]. In good correlated with other researches [47-50] and also our study [42] demonstrated the improvement of motor ability in stroke patients after rTMS. Augmentation of motor performance and a moderate reduction of spasticity could be seen [42] and this was in the line with previously published data [51].

We found that the effect of rTMS had a notable impact on the output of occupational therapy if these trials were performed immediately after rTMS. An increase of finger dexterity and amelioration of Barthel Index was observed [42]. Importantly, in patients with high nursing needs less service was required if occupational therapy was performed right way after rTMS [52]. These are important observations for optimizing post stroke rehabilitation.

Furthermore, we could show that rTMS affects L-TRP metabolism in the serum of stroke patients significantly [42]. Among revealed alterations a significant increase of the anthranilic acid/kynurenic acid ratio value due to rTMS was revealed and this change might be important with respect to neuro-modulatory activities and could be involved in the improvement of motor performance too, and this finding need to be further investigated.

The effect of D-cycloserine to act as anticonvulsant has been shown in chemically or electrically induced epileptic models in rats and mice [4,5]. The anticonvulsive activity has been suggested due to action as a partial glycine agonist at the NMDA receptor [3]. A notable enhancement of kynurenic acid levels in the brain regions and in the plasma have been observed in kainic acid induced epilepsy model [53], therefore the mechanism of D-cycloserine to act as an anticonvulsant drug remains questionable.

The mechanism of D-cycloserine action as a partial agonist at the NMDA receptors sites is still unclear. We suggested that lowering of kynurenic acid synthesis due to D-cycloserine is responsible for the drug to act quasi as a partial agonist at the glycine site of the NMDA receptor [6]. Furthermore, since D-cycloserine blocks also decarboxylation of glutamate [24] and experimental study has revealed an enhancement of glutamate levels in the rat brain after D-cycloserine treatment [54], therefore lowering of kynurenic acid and increasing of glutamate levels might result an activation of glutamate receptors. Besides that, diminishing of kynurenic acid synthesis due to D-cycloserine affects cholinergic neurotransmission [8], which has a significant impact on the improvement of memory and/or cognition, too.

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