

Basic Neuroscience Research Inspires Neurorehabilitation and Vice Versa

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Starting in 1980 with basic neuroscience and neuropharmacology research on the kainic acid model for human temporal lobe epilepsy in Oleh Hornykiewicz's Lab in Vienna and later with research work on Tryptophan metabolism in Robert Schwarcz's Lab in Baltimore and now in my Lab at the Karl Landsteiner Research Institute Mauer I experienced and still enjoy the fruitful connection with clinical neuroscientists. Particularly the cooperation with Berth Keplinger the past Chief of Neurological Departments of Hospitals in Mauer and Amstetten, Austrian provided a convincing strategy for the integration of both, basic neuroscience and neurorehabilitation research.

In 1880 Jean-Martin Charcot introduced the first therapeutic indication of exercise by using a shaking chair in Parkinson patients which lowered tremor and improved stability [1]. A marked deficit of dopaminergic neurotransmission and its significance with Parkinson's symptoms was discovered by Oleh Hornykiewicz in 1963 [2] and his suggestion to use L-DOPA for therapy became later a standard for Parkinson treatment [3].

Interestingly, 100 years after Charcot's suggestion it has been shown in experimental animal studies that dopamine synthesis and metabolism in the striatum is increased significantly in rats exposed to exercise [4]. Scientists have suggested that physical exercise might contribute to adjust extracellular dopamine levels within an adequate range. Running activities applied to animal model of Parkinson's disease showed also improvement of motor symptoms and caused less degeneration of the dopaminergic system [5].

Stochastic resonance therapy (SRT), a whole body vibration, is a novel method for rehabilitation of patients with various neurological and psychiatric disorders e.g. Parkinson disease [6,7], Alzheimer's [8], Multiple Sclerosis [9], post stroke spasticity [10], post traumatic brain damage [11], depression and schizophrenia [12,13], and also with low back pain [14]. The effectiveness of SRT in the treatment of these diseases or conditions is significant however the mechanism is still widely unknown.

Keplinger et al. demonstrated that treadmill running significantly lowered serum kynurenic acid in rats [15]. A recent study on influence of SRT on tryptophan metabolism in the serum of healthy human subjects revealed lowered L-tryptophan, L-kynurenic acid and kynurenic acid levels, as well [16].

With respect to dopaminergic neurotransmission scientists described an enhancement of dopamine levels in the plasma after exercise in rat and healthy human subjects [17]. Revealed data are in correlation with the observation that endogenous kynurenic acid can control the extracellular levels of dopamine at least in rat striatum [18] and the interaction between increased kynurenic acid and lowered dopamine levels in the striatum has been indicated [18].

Interestingly, comparison between L-DOPA treatment and the physical exercise in patients with spinal injury revealed similar positive effect in both types of treatment [11] supporting an enhanced dopamine function during exercise. Consistent with this data, application of exercise to Parkinson's patients treated with L-DOPA increased significantly therapeutic efficiency [19]. The improvement of Parkinson symptoms due to SRT is transient, nevertheless the positive effect would confirm an advantage of SRT and suggest its therapeutic

significance in the rehabilitation process. The combination of SRT with L-DOPA medication might have an impact on reducing L-DOPA medication and preventing dyskinesia, as observed by Parkinson's patients after 5 to 6 years of L-DOPA therapy.

Kynurenic acid aminotransferases which are responsible for kynurenic acid synthesis are widely distributed in the mammalian body. Lowering of kynurenic acid levels after SRT could be due to an activation of glia depressing factor (GDF), which has the ability to block kynurenic acid aminotransferases activities, as we described recently [20]. Since kynurenic acid is increased and GDF is reduced in CSF of Multiple Sclerosis patients, we speculate that application of SRT ameliorates clinical symptoms of Multiple Sclerosis patients due to GDF activation.

But, there are also data demonstrating discrepancies in respect to neurochemical changes after exercise, and these discrepancies are probably due to different kinds of exercise (running vs. sinusoidal vibration vs. vibration with stochastic resonance), different kind of parameters (amplitude, frequency) and duration of exercise and this gives a reason to further study experimentally and clinically for better output of exercise methods.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique has been suggested to be effective for treatment of depression [21] and might reduce spasticity. In the last decade rTMS gained more attention and significance for neurorehabilitation. Our study on the influence of rTMS on patients with stroke, with central neuropathic pain and with major depression revealed clinical improvements, data presented in part [22]. Parallel to clinical investigation we performed measurement of tryptophan metabolites in the serum to find correlations between clinical outcome and neurochemical findings. Furthermore, our data suggest that the localisation and pattern of stimulus as well as the time period between rTMS and occupational therapy seems to be important for the clinical outcome, at least for stroke patients.

Increased kynurenic acid formation in the brain has been found in patients with neurodegenerative and neuroinflammatory disorders and certain psychiatric conditions, such as Alzheimer's, Parkinson's [23], HIV-1 encephalopathy [24] and Schizophrenia [25] or during the aging process [26]. These and also other accumulated data strongly suggest that increased kynurenic acid in the brain plays a role in the impairment of cognition and memory.

Kynurenic acid is a well-known endogenous antagonist of the

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glutamate ionotropic excitatory amino acid receptors N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate [27] and of the nicotine cholinergic subtype 7α receptors [28] and exerts anticonvulsive and neuroprotective activities, at least in animal models of neurodegenerative diseases [27]. Therefore it is reasonable to believe that pharmacological approaches which influence kynurenic acid synthesis can affect neurotransmission in the brain and have an impact on cognition and memory.

Indeed, Cerebrolysin, a porcine brain extract with neurotropic activities is used for the treatment of Alzheimer's to improve brain activities, memory and cognition, and it blocks cerebral kynurenic acid synthesis, at least in an *in vitro* study [29]. Interestingly, D-Cycloserine, an anti-mycobacterial drug, also blocks markedly kynurenic acid synthesis, what we discovered recently [30]. Importantly, this drug shows improvement of dementia in Alzheimer's patients and amelioration of cognition and/or delusion in schizophrenia [31].

Summarizing, new physical and pharmacological trials for neurorehabilitation are challenges for basic scientists to help clearing the mechanism(s) of action and to find possible clues for more successful applications. On the other hand the knowledge of neurochemical and neuropharmacological findings are fruitful for professionals of rehabilitation to provide more understandings of rehabilitative interventions, which may guide to reasonable selection of treatment options.

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