[5] Shoval, G., Shbiro, L., Hershkovitz, L., Hazut, N., Zalsman, G., Mechoulam, R., Weller, A., 2016. Prohedonic effect of cannabidiol in a rat model of depression. Neuropsychobiology 73 (2), 123–129.

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P.566 Sumatriptan binds to central 5-HT1B receptors in migraine patients

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Background: Migraine is a severe, common headache disorder which has excruciating consequences for those suffering from it as well as for the society in general. The pathophysiology is still poorly understood but serotonin is known to be of importance. This is underlined by the fact that triptans, the most effective acute treatment for migraine attacks, are 5-HT1B/1D receptor agonists. However, the exact role of serotonin and the precise mechanism of action of triptans in migraine are not completely understood. Further, the extent to which triptans enter the central nervous system and bind to 5-HT1B receptors in the brain is unknown. Here we investigated the occupancy of sumatriptan to central 5-HT1B receptors, as well as changes in brain serotonin levels during migraine attacks.
Methods: We used the sensitive and validated method of positron emission tomography imaging of the 5-HT1B receptor radiotracer [11C]AZ10419369 to determine the occupancy of sumatriptan to central 5-HT1B receptors and to investigate changes in brain serotonin levels during migraine attacks. Eight otherwise healthy, episodic migraine patients without aura were scanned three times: 1) during an experimentally induced migraine attack, 2) after a subcutaneous injection of 6 mg sumatriptan, and 3) on an attack-free day. Migraine attacks were induced using cilostazol, a PDE3 inhibitor which is a validated and potent migraine inducer. The primary outcome was the non-displaceable binding potential of [11C]AZ10419369 across 7 brain regions involved in pain modulation. The binding potential reflects receptor density, and changes in binding potential reflect displacement of the radiotracer. The binding potential was calculated using the simplified reference tissue model with cerebellum as a reference region. The occupancy of sumatriptan was estimated from the two scans before and after sumatriptan administration.
Results: Eight patients with migraine were included in the study. Of these participants, seven (87%) were women. The mean (SD) age of participants on study day 1 was 29.5 (9.2) years and 30.0 (8.9) years on study day 2. We found that sumatriptan significantly reduced 5-HT1B receptor binding across pain-modulating regions (mean [SD] 1.20 [0.20] vs 1.02 [0.22]; $P = 0.0001$, one-tailed, paired t-test). This corresponded to a mean (SD) drug occupancy rate of 16.0% (5.3%). Furthermore, during migraine attacks, as compared with outside of attacks, 5-HT1B receptor binding was significantly reduced in pain-modulating regions (mean [SD] binding potential, 1.36 [0.22] vs 1.20 [0.20]; $P = 0.019$, one-tailed, paired t-test).
Conclusion: Treatment with sumatriptan during migraine attacks was associated with a decrease in 5-HT1B receptor binding. This indicates that sumatriptan crosses the blood-brain barrier and binds to central 5-HT1B receptors. Whether this is an integral part of the pain-relieving effect of sumatriptan remains unknown. Further, migraine attacks are associated with an increase in brain serotonin levels, indicating that migraine attacks may be triggered by increases in endogenous serotonin.

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P.567 The study of excitability of motor cortex with motor imagery and simultaneous electrical stimulation

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Background: It is known that the kinesthetic presentation of the movements leads to an increase in the excitability of the motor cortex, which can have a positive effect during the post-stroke rehabilitation due to the activation of plastic rearrangements in the target cortical regions. Non-invasive stimulation techniques that can modulate short spinal excitability are also promising. Moreover, the combination of the various methods of modulating the excitability of the motor cortex at different levels of the central nervous system, and the creation of new rehabilitation programs based on them may help in the fight with the disappointing statistics of the post-stroke motor recovery.

In this work, the excitability of the corticospinal tract was studied during motor imagery (MI) and cortical activation by neuromuscular stimulation of an imaginary hand simultaneously. The aim of the study is to evaluate the modulating effect of functional neuromuscular stimulation on corticospinal excitability when imagining movements. The hypothesis was that peripheral stimulation of the forelimb, while imagining this limb, can increase excitability, which can be measured directly after neuromuscular stimulation.
Methods: The study involved 18 healthy volunteers who had different experience in motor imagery. The subjects were asked to imagine the right hand grasping, alternating with the reference state of motor rest. The duration of each trial was 9 seconds. At the same time a current stimulation was applied on the 4th second, activating the FDS muscle contraction, which lasted for 3 seconds. Evaluation of the corticospinal excitability was carried out via transcranial magnetic stimulation (TMS) of the left motor hand area and registration of the MEPs from the right FDS muscle. TMS was applied during the resting state, and also before and after neuromuscular stimulation. Performed statistical analysis (N=18) on a group level included paired comparisons between before/after conditions. Changes in MEPs amplitude were assessed using Wilcoxon signed-rank tests.

Results: Statistically significant changes (p values <0.05, Wilcoxon signed-rank test) in the MEP amplitude of the right FDS during MI before and after neuromuscular stimulation were obtained (N = 18). Also, one part of the group (N = 11) demonstrated an increase in the MEP amplitude during rest state immediately after neuro-muscular stimulation compared to the pre-state.
Discussion: Our results suggest a direct effect of the peripheral neuromuscular stimulation on the excitability of the corticospinal tract, which is especially expressed in combination with the mental representation of movements. Moreover, the effect of such stimulation can be measured immediately after muscle stimulation.
Conclusion: Thus, it can be assumed that the potentiating effect of the peripheral stimulation on motor circuits may be prolonged. A more detailed study of this issue may light up the question of activating plastic rearrangements during post-stroke motor recovery. Moreover, the data obtained has a methodological potential, since it shows that the effect due to the effects of neuromuscular stimulation on excitability can be measured immediately after the stimulation itself, which can greatly simplify the experimental setup (avoiding artefacts).

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P.570 Effects of ginseng and ginsenosides on mutant huntingtin aggregation, cellular apoptosis, mitochondrial dysfunction and motor impairment of Huntington's disease model

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Background: Huntington's disease (HD) is a hereditary neurodegenerative disease characterized by chorea, dementia and depression due to neuronal death caused by long CAG repetition in mutant huntingtin (mHtt) gene [1]. HD patients show a decrease in cognitive function and motor function with involuntary movement. There are currently no cure and effective drugs to delay or prevent HD. The aggregation of extended polyglutamine is a common mechanism of glutamine repeat disease, including HD, and the mutant Htt aggregation induced by extended glutamine repetition is involved in the pathology of HD. Recent reports suggest that mitochondrial dysfunction induced by mHtt contributes significantly to the progression of HD [2]. Ginseng is a popular herb used in oriental countries for over 2,000 years and has grown to be one of the best-selling herbs in the world [3]. These popularity and global consumption indirectly explain its efficacy, and scientific evidences have shown that ginseng has a wide range of beneficial pharmacological effects in cardiovascular, endocrine, immune, obesity, atopic dermatitis, and central nervous system. This study was conducted to investigate the effects of ginseng extract (GE) and ginsenosides on HD phenotypes including mitochondrial function molecules, neuronal cell apoptosis, toxic protein aggregation and motor impairment of HD.
Methods: To investigate the effect of GE and ginsenoside on HD, neuronal stem cells from the R6/2 mice, exhibiting typical cellular HD phenotypes, were used. Changes of mHtt aggregation of HD cell were measured by immunocytochemistry. The expressions of apoptotic and mitochondrial biogenesis molecules were investigated by western blot. We use transgenic mice of the R6/2 line and their WT littermates. The R6/2 mice were randomly divided into two equivalent groups, one administered vehicle and the other KRG. The animals were orally fed with a dose of 40 mg using zonde needle once daily for six weeks. For vehicle-treated WT or R6/2 mice, the same volume of 0.5% carboxymethyl cellulose-sodium solution was administered once daily for six weeks.
Results: Aggregation of mHtt is the main cause of HD pathology, and mHtt aggregation in the nucleus was clearly observed in our in vitro HD model. The number of mHtt aggregates positive cells has significantly decreased by ginsenoside Rg3 and Rf treatment in in vitro HD model. Apoptotic molecules including cleaved caspase-3 were decreased by treatment of ginsenoside Rg3 or Rf. Mitochondrial function related molecules such as p-CREB, p-Akt and PGC-1α were significantly increased by ginsenoside Rf. These in vitro data suggests that HD neuronal cells undergo apoptosis by mHtt aggregation, and KRG treatment normalize the apoptotic pathway of HD possibly by attenuating toxic protein aggregation. In addition, oral administration of GE improves motor function of R6/2 mice, which is impaired by HD progression.
Conclusion: These results demonstrate that RG can improve motor function with a decrease in mHtt protein aggregation and apoptotic molecules and an increase in mitochondrial activation. Our finding suggests that GE and its ginsenosides are possible active compounds for treating HD phenotypes.

References

[1] Landles, C., Bates, G.P., 2004. Huntingtin and the molecular pathogenesis of Huntington's disease. Fourth in molecular medicine review series. EMBO Rep. 5 (10), 958–963.
[2] Panov, A.V., Gutekunst, C.A., Leavitt, B.R., Hayden, M.R., Burke, J.R., Strittmatter, W.J., Greenamyre, J.T., 2002. Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. Nat Neurosci 5 (8), 731–736.
[3] Qi, L.W., Wang, C.Z., Yuan, C.S., 2011. Ginsenosides from American ginseng: chemical and pharmacological diversity. Phytochemistry 72 (8), 689–699.

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P.571 Transgenic mouse, carrier of human CYP2C19 gene, as an animal model for hyperdopaminergism-induced hyperkinesia

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