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Effects of simvastatin and 6-hydroxydopamine lesion on histaminergic H1 receptor binding in rat brains

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POS-MON-205

N-ARACHIDONYL-GLYCINE INHIBITS GLYCINE TRANSPORT IN RAT SUPERFICIAL DORSAL HORN

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The arachidonyl amino acid N-arachidonyl glycine (NAGly) is expressed at high levels within the spinal cord and produces analgesia following spinal delivery, via mechanisms which differ to the related endocannabinoid arachidonyl ethanolamide (anandamide). It has recently been demonstrated that NAGly inhibits the cloned glycine transporter GLYT2. Here, we examined the actions of NAGly on neurons in lamina II of the superficial dorsal horn, a key site for the actions of many analgesic agents. NAGly prolonged the duration of GlyR-mediated currents induced by exogenous application of glycine, but not by β-alanine. NAGly and the GLYT2 inhibitor ALX-1393, but not the GLYT1 inhibitor ALX-5407 produced an inward current and an increase in noise which was abolished by strychnine. ALX-5407 and ALX-1393, but not NAGly prolonged the decay phase of GlyR-mediated spontaneous miniature IPSCs. By contrast, NAGly, ALX-5407 and ALX-1393 all prolonged the decay phase of GlyR-mediated evoked IPSCs. The effect of NAGly on evoked IPSCs was increased during rapid train stimulation. NAGly had no effect on IPSC rise-time, or amplitude. These findings suggest that NAGly enhances inhibitory glycinergic synaptic transmission within the superficial dorsal horn by blocking glycine uptake via a transporter, possibly GLYT2, which is located outside the glycine synaptic cleft.

POS-MON-206

THE INTRA-CORTICAL ORIGIN OF ABSENCE-LIKE SEIZURES IN THE GAERS MODEL IS LOCATED IN THE SOMATOSENSORY S2 CORTEX

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Introduction: The intra-cortical localisation of the seizure generator in the Genetic Absence Epileptic Rats from Strasbourg (GAERS) is still unknown. This study localised and characterised the site of seizure initiation within the somatosensory cortex at the cellular and network level. Methods: Depth EEG recordings were performed in freely moving GAERS (n=6) and non-epileptic control rats (NECs, n=3). In a separate set of experiments, single-cell juxtacellular recordings of cortical neurons were made along with EEG recording of the related sensorimotor cortex *in vivo* under neurolept-anaesthesia in adult male GAERS (n=19) and NEC rats (n=5). Results: In freely moving animals, depth multi-site recordings revealed that seizures were initiated within the somatosensory S2 cortical region. The 5-9 Hz oscillations in S2 preceded the S1 by up to 3 seconds (n=6). Furthermore, typical SWD events were evoked by delivering a electrical stimulus train (7 Hz, 2 seconds) to the somatosensory cortical regions of the GAERS. A significantly smaller current was required to initiate SWD events in the S2 vs. the S1 Ulp region (mean±s.e.m., 146±31μA vs 257±56μA, n=7, p=0.025). Stimulation train induced oscillations but not SWDs in the NEC rats (n=3). Juxtacellular recordings from both the GAERS and NECs revealed a population of cells within S2 and immediate adjacent cortical regions that fire rhythmically during both ictal and interictal periods at similar frequencies (6-15Hz, GAERS, 37 of 178 cells, 21%; NEC rats 13 of 78 cells, 17%). Conclusions: These results extend the "cortical theory" of absence seizures by localising the S2 region as the likely generator of SWD events. A population of inherent rhythmically firing cortical cells were identified in and around the S2 region. These cells may be acting as the initiators of the 5-9 Hz somatosensory rhythm which subsequently triggers absence seizures in epileptic animals.

POS-MON-207

INHIBITION IN THE LATERAL VESTIBULAR NUCLEUS

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The lateral vestibular nucleus (LVN) projects to all regions of spinal cord for innervation of axial and limb muscles to maintain posture and balance. The LVN consists predominantly of large Deiters neurons. Inhibition of Deiters neurons arises predominantly from cerebellar Purkinje cells and is GABAergic in origin. A recent study has shown a glycinergic projection from fastigial nucleus. This study investigates inhibition onto large Deiters neurons and interneurons of the LVN. **Immunofluorescence:** Mice (approx. 3 weeks old) were anaesthetised with Ketamine (100mg/kg) and transcardially perfused with saline, followed by 4% paraformaldehyde. Brains were removed and postfixed for 1 hour. Immunolabelling of $GABA_A$, glycine receptors, and anchoring protein, gephyrin, showed immunofluorescence in LVN. **Electrophysiology:** Mice were anaesthetized as above and decapitated. Brains were removed and the region containing the LVN was sectioned (300 μm). Approximately 73% of Deiters neurons are tonically active, and have comparable discharge rate (mean 9.69 Hz, n = 6) to nearby medial vestibular nucleus neurons (mean 9.71 Hz, n = 27). $GABA_A$ergic and glycinergic mIPSCs were recorded in the presence of TTX (1 μm) and CNQX (10 μm) and their respective antagonists, strychnine (1 μm) and bicuculline (10 μm). Recordings from 45 neurons showed a differential inhibitory input to Deiters and interneurons. Deiters neurons received predominantly $GABA_A$ergic inhibitory input, of very high frequency (mean frequency = 13.25 Hz, n=7), while interneurons received both $GABA_A$ergic and glycinergic inputs. Preliminary results also show a rostrocaudal difference in the degree of $GABA_A$ergic and glycinergic input onto Deiters neurons.

POS-MON-208

EFFECTS OF SIMVASTATIN AND 6-HYDROXYDOPAMINE LESION ON HISTAMINERGIC H1 RECEPTOR BINDING IN RAT BRAINS

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Statins have been widely used for the treatment of a variety of medical conditions including neurological disorders beyond their original role in lowering cholesterol. The histamine receptors play an important role in neural regulation. However, it is yet unknown whether statins act on histamine receptors, particularly for their neuroprotective effects. METHODS: After pre-treatment with simvastatin (saline, or 1 or 10mg/kg/day, n=14-16) for 5 days, a half of each group were treated with 6-hydroxydopamine (6-OHDA) and the other half with sham-treatment, followed by 3-week treatments of simvastatin as mentioned above. Histamine H1 receptors (H1R) were detected by [3H]pyrilamine binding autoradiography. RESULTS: Compared to the saline group, simvastatin (1mg/kg/day) significantly decreased H1R bindings in the primary motor cortex (M1), ventromedial hypothalamic nucleus (VMH), caudate putamen (CPu), accumbens core (AcbC), prefrontal cortex (PF) (all $p<0.05$); however 10mg/kg/day simvastatin increased H1R density in the medial amygdaloid nucleus ($p<0.05$), but no significant effect in other regions detected. 6-OHDA lesion did not alter H1R binding density in most brain areas, except a decrease in the cingulate cortex ($p=0.05$). No interacted effect between simvastatin and 6-OHDA was observed. CONCLUSION: Simvastatin has different effects on the H1R in various brain regions of rats, which was not interacted with 6-OHDA lesion. These results suggest that simvastatin can modulate histaminergic neurotransmission in the brain, and support the role of H1 receptors in neurodegenerative disorders.