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HISTAMINE H1 RECEPTOR AGONIST AND CONTROL OF OLANZAPINE-INDUCED OBESITY

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The atypical antipsychotic drug olanzapine is widely used to treat the symptoms of schizophrenia, however, it also induces serious metabolic side-effects, such as obesity. An antipsychotic drug's antagonistic affinity to histamine H1 receptors (H1R) is one of the main indicators of weight gain/obesity side-effect. This study aimed to investigate whether a combined treatment of betahistine (a H1R agonist and H3 receptor antagonist) with olanzapine could reduce the body weight/obesity side-effects induced by olanzapine. **Methods:** Female Sprague Dawley rats (n=12/group) were administered orally with either olanzapine (3mg/kg/day, 3 times/day), betahistine (8mg/kg/day), olanzapine plus betahistine (O+B), or vehicle (control) for 2-weeks. **Results:** Rats treated solely with olanzapine exhibited significant body weight gain and increased food intake (all $p<0.001$). However, sole betahistine treatment had no effect on weight gain and food intake. The O+B co-treatment group exhibited significantly reduced feeding efficiency and body weight (~50% net decrease) compared to the sole olanzapine-treated group ($p=0.015$). Olanzapine treatment reduced locomotor activity and increased white fat mass; however sole betahistine had no influence on these parameters. **Conclusion:** These findings revealed that olanzapine-induced body weight gain could partially be reduced by co-treatment with betahistine. Betahistine has H3 receptor antagonistic effects to increase histamine release, which may augment its direct agonistic effects on H1 receptors. These findings further support the important role of H1R in olanzapine-induced obesity, and have important implications for clinical trials using betahistine to control antipsychotic-induced obesity side-effects.

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THE INVOLVEMENT OF THE KYNURENINE PATHWAY IN NEUROINFLAMMATION AND NEURODEGENERATION OF MULTIPLE SCLEROSIS PROGRESSION

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Purpose: The kynurenine pathway (KP) has increasingly drawn awareness in multiple sclerosis (MS), for which abnormal levels of KP metabolites have been found. The KP may be involve in neurological deficit from two aspect: firstly, it has been shown that the first rate limiting enzyme of the KP, Indoleamine, 2-3 dioxygenase (IDO) is involve in immune regulation of inflammatory process in the brain; and/or secondly, metabolites from the KP are associated with neurodegeneration. Despite earlier studies showing that the KP may be activated and also the neuroprotective metabolite kynurenic acid (KYNA) production is increased. However, these data do not explain the detrimental effects of the KP in the neuropathology of MS. We hypothesize that this is associated with increased production of the downstream excitotoxin metabolite, quinolinic acid (QUIN). **Methods:** Our studies involve quantifying levels of tryptophan and several KP metabolites in the serum and cerebrospinal fluid of MS patients with early (n=50) and late (n=37) stages diagnosis using HPLC and GC/MS. These patients had not received any recent corticosteroid treatment or other medications known to interfere with the KP at the time of sample collection. **Results:** We found that IDO is upregulated at all the stages of MS compare to healthy controls. We also observed an increased production of excitotoxin, QUIN in MS patients compared to controls implying abnormal alteration to the KP metabolism. Furthermore, we found QUIN to be present in active lesion of human MS postmortem brain tissue suggesting their involvement in neurodegeneration. Interestingly, we found that the profiles of neuroprotective KP metabolites, KYNA and QUIN are unique across various stages of MS progression. **Conclusion:** All the above data suggests the significant involvement of KP metabolism in MS progression and the potential use of these metabolites as biomarkers to assess severity of MS progression.

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DEEP BRAIN STIMULATION OF THE POSTERIOR SUBTHALAMIC AREA MODULATES SACCADIC EYE MOVEMENTS

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Deep brain stimulation (DBS) of the caudal zona incerta (ZI) in the posterior subthalamic area (PSA) is being trialled as a refined treatment for movement disorders using a new precise surgical technique. The ZI may influence saccadic eye movements in animals but its role in humans is unknown. **PURPOSE:** To measure the effects of electrical stimulation on head-fixed horizontal predictive saccades in patients with Parkinson's disease or essential tremor. **METHODS:** Patients (n=8) undergoing PSA DBS underwent testing at pre-operative baseline and with four randomized post-operative stimulation settings (nil, 1 volt low frequency stimulation (LFS), 1V high frequency (HFS), and 3V HFS) on day six after surgery. For each condition, 20 trials of 30° saccades were carried out in darkness with infrared video eye movement monitoring and direct current electro-oculography to generate saccade latency, duration, velocity and amplitude data in each gaze direction. **RESULTS:** Saccade velocity was successively reduced by 16.4%, 4.9% and 9.5% by electrode insertion, 1V and 3 V HFS respectively ($p < 0.05$ for each). Saccade duration was similarly increased but there was no change in latency. HFS at 3V reduced saccade amplitude by 16.7% compared to the pre-operative state ($p<0.0001$). LFS (10 Hz, 1V) did not alter saccades. **CONCLUSION:** Saccades had normal latency but were slow and hypometric with PSA DBS. This contrasts with the reduced saccade latency, increased velocity and increased amplitude reported with HFS of the adjacent subthalamic nucleus. We provide the first evidence that human eye movement control structures may lie within the region of the caudal ZI.

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A NOVEL VISUAL DISCRIMINATION TASK TO INVESTIGATE THE DORSAL VISUAL FIELD IN RODENTS

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Purpose: The visual system of the rodent is a highly studied brain region, yet many of its fundamental functional characteristics are yet to be described. Here, we detail a novel behavioural task that can be used to measure discrimination at varying dorsal regions of the rodent visual field. **Methods:** A modified version of the aquatic visual discrimination task (Prusky, G.T. et al., 2000) was used. Visual stimuli were projected onto a matte surface at one end of the tank and the surface of the pool was agitated. Groups of male and female mice were first pre-trained to associate a single stimulus with an escape platform in blocks of 10 trials and 2 blocks per day. Upon achieving three consecutive scores ≥80% the mice were then made to discriminate between a vertical and horizontal grating at water level, again associating 1 of the 2 orientations with an escape platform. Upon achieving ≥80% in 4 consecutive blocks of trials, the stimulus was then raised dorsally in increments of 5cm per block. In order for the stimulus to be raised further, mice had to score ≥70% correct per block. Once performance dropped <70% in a given block of trials, the stimulus was lowered to the water level and their discrimination at gradually more dorsal positions was re-tested identically to determine an upper threshold. **Results:** The ability of wildtype mice to correctly discriminate visual stimuli decreased dramatically at stimulus positions exceeding 20 cm above water level. **Conclusions:** Mice have an upper limit in their dorsal visual field at which they can discriminate static visual stimuli above chance.