Pramipexole decreases locomotor activity in the spontaneously hyperactive chakragati mouse

Matthew O’Callaghan¹, Roynston Albert¹, Gavin Dawe², Anil Ratty³. ¹Cerca Insights, Penang, Malaysia, ²National University of Singapore, Singapore, Singapore, ³Chakra Biotech, Singapore, Singapore.

The chakragati (ckr) mouse has been proposed as an animal model of psychosis. These mice display a number of behavioural and anatomical characteristics supporting this proposal. These include spontaneous circling, hyperactivity, hyper-tone of the dopamine system, reduced social interactions, enlarged lateral ventricles and deficits in both pre-pulse and latent inhibition. Previous work has demonstrated that antipsychotic drugs dose dependently suppress the hyperactivity in these mice (Dawe et al., 2010). This observation suggests that these mice may provide a useful tool in the screening of compounds for antipsychotic activity. However, the selectivity and mechanism of action of this attenuation is not fully understood. The aim of this study was to further examine pharmacological control of this effect using the dopamine D3 receptor preferring agonist, pramipexole. Group housed 3-6 month old female mice (19-24g) with ad libitum access to food and water were used. All testing was performed during the light phase of the light/dark cycle. The mice (n=6-8 per group) were placed in a circular Perspex box for ten minutes habituation time after which they received an intraperitoneal injection of (10ml/kg) either test drug or the appropriate vehicle and left for 30 minutes before a 60 minute test session. The sessions were recorded on video and locomotor activity was then analysed using Ethovision video tracking software and distance moved (cm) calculated for the sessions. The drugs tested were imipramine (20mg/kg), pramipexole (5mg/kg), clozapine (5, 15 and 30mg/kg) and haloperidol (0.4, 0.8 and 1.6mg/kg). The distance moved following treatment with clozapine at 5, 15 and 30mg/kg was 6138cm +/-1020, 2443cm +/-257 and 182 +/-416cm respectively. The distance moved following haloperidol treatment at 0.4, 0.8 and 1.6mg/kg was 20265cm +/-1860, 179221cm +/-2110 and 8073cm +/-1493 respectively. Analysis showed a significant effect of treatment (F6,72=33.1 P<0.0001) and post-hoc analysis revealed that both haloperidol (at 1.6mg/kg) and clozapine (at all doses) significantly reduced (P<0.01) distance moved in these mice compared to the acidified saline vehicle (19806cm +/-1803). The distance moved by mice treated with pramipexole (31255cm +/-10517) was significantly reduced (P<0.05) when compared to vehicle treated mice (77521cm +/-17597). These data demonstrate a reduction in activity in these mice by clozapine and haloperidol in agreement with previously reported data. Imipramine a norepinephrine and serotonin reuptake inhibitor has been reported to attenuate locomotor activity but did not attenuate the hyperactivity in these mice. The dopaminergic agonist pramipexole reduced locomotor activity in these mice, producing an effect similar to that seen after the administration of drugs that can act as D2 receptor antagonists. It is possible that pramipexole reduced activity through the dopamine D3 receptor, as it has been reported that the activation of the D3 receptor reduces stimulant induced locomotor activity (McNamara et al., 2006).