Further characterisation of the rat model of Tourette-related striatal disinhibition

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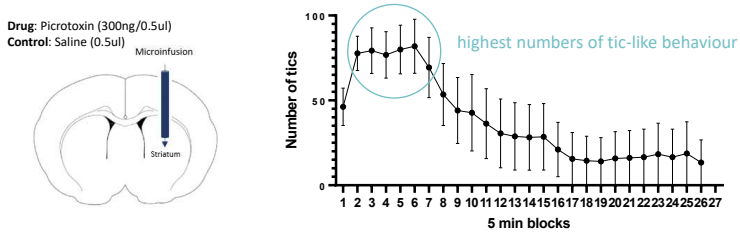
Striatal disinhibition model

- Abnormalities of the cortical-striatal-thalamic-cortical circuit have been suggested to play a central role in Tourete Syndrome (TS) (Albin & Mink, 2006). Specifically, it was suggested that motor tics arise from neural disinhibition, i.e. loss of GABAergic inhibition, in the striatum, which in turn leads to disinhibition of the thalamus and hyperexcitability of the motor cortex, leading to tics (Gilbert, 2006).
- The effects of neural disinhibition in the striatum have been investigated directly through the use of microinjections of GABA-A antagonists, including picrotoxin and bicuculline, in rodents (e.g. Israelashvili & Bar-Gad, 2015; Klaus & Plenz, 2016) and non-human primates (e.g. Worbe et al., 2009). Such striatal disinhibition produced tic-like movements on the contra-lateral side to the disinhibited area that manifested several minutes after injection and lasted up to two hours (Israelashvili et al., 2015).
- Depending on the somatotopic location of the striatal infusion, the tic-like behaviours involved forelimb or hindlimb movements (Bronfeld, Israelashvili, et al., 2013).

Aims

- To confirm and extend previous studies of the impact of striatal disinhibition in rats, we examined the impact of unilateral picrotoxin infusion (300 ng in 0.5 ul of saline) into the anterior dorsal striatum of young adult male Lister hooded rats.
- We measured tic-like movements (1) and took automated photo-beam measurements of open field locomotor activity and fine movements (2) following striatal disinhibition.
- We examined the impact of striatal disinhibition on prepulse inhibition (PPI) of the acoustic startle response (3). PPI has shown to depend on the striatum and to be disrupted in TS (Koch, 1999; Swerdlow et al., 2001).
- We examined the effects of striatal disinhibition on neural activity in the vicinity of the infusion site, using multi-unit and local field potential (LFP) recordings under isoflurane anaesthesia (methods adapted from Pezze et al.,2014) (4 and 5).

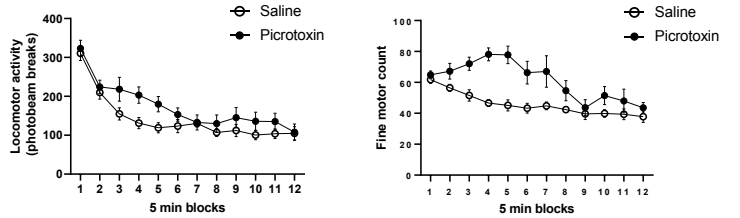
1: Robust induction of tic-like behaviour



15/16 picrotoxin infusions led to tic-like behaviour in the left forelimb.

2: Increased locomotor activity and fine motor counts

Within-subjects design
n=13



Striatal disinhibition increased locomotor activity ($F_{(1,12)}$=7.01, p=0.02). Locomotor activity reduced across 5-min blocks, reflecting locomotor habituation ($F_{(11,132)}$=31.50, p<0.001), regardless of infusion condition (infusion X 5-min block interaction: $F_{(11,132)}$=1.69, p<0.08).

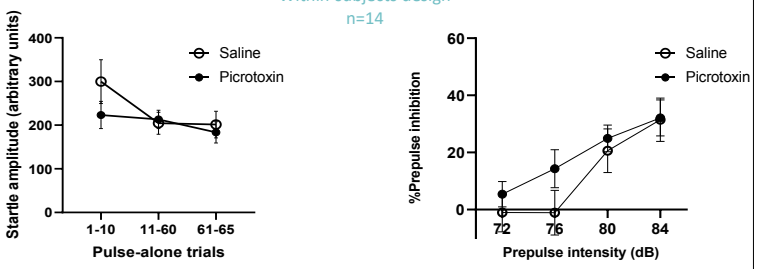
Striatal disinhibition markedly increased fine motor counts, mainly during 5-min block 2 to 8 after infusion (main effect of infusion: $F_{(1,12)}$=20.04, p<0.001; main effect of time: $F_{(11,132)}$=8.34, p<0.001; infusion X 5-min block interaction: $F_{(11,132)}$=3.12, p<0.001).

Conclusions

- Striatal disinhibition by picrotoxin reliably induced tic-like movements (in 15/16 infusion). We found a slight increase in locomotor activity after striatal disinhibition - This may reflect that the dorsal striatal neural activity facilitates locomotor activity (e.g. Barbera et al., 2016) and indicates that striatal disinhibition may contribute to hyperactivity, which is a common comorbidity of TS (El Malhany et al., 2015).
- We found an increase in fine motor counts after picrotoxin infusion which shows a similar time course to tic-like movements, suggesting an automated method to quantify these movements.
- Striatal disinhibition tended to reduce startle reactivity, but did not affect PPI. The latter contrasts with reduced PPI in TS (Swerdlow et al., 2001). This does not support a direct contribution of striatal disinhibition to PPI deficits in TS, but may also reflect the difference between acute striatal disinhibition (in our rat model) and chronic striatal disinhibition (in TS).
- Our electrophysiological findings under anaesthesia showed that striatal disinhibition causes marked striatal spike-wave discharges, consistent with previous findings in freely moving rats (e.g. Israelashvili & Bar-Gad, 2015; Klaus & Plenz, 2016), and enhances neuronal burst firing, consistent with findings on neural disinhibition in prefrontal cortex and hippocampus (Bast et al., 2017).

3: Reduced startle - Prepulse inhibition (PPI) not affected

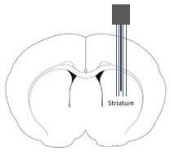
Within-subjects design
n=14



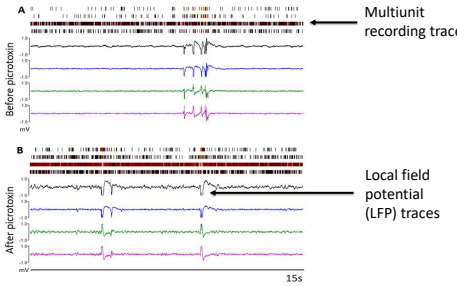
Striatal disinhibition tended to reduce startle during the first test block, before habituation led to similarly low startle responses in both infusion conditions. There was a significant effect of pulse-alone trials ($F_{(2,26)}$=5.54, p=0.01), no significant main effect of drug ($F_{(1,13)}$<1) and a strong trend for an interaction infusion X pulse-alone trials ($F_{(2,26)}$=3.18, p=0.058).

Striatal disinhibition in rats did not affect PPI (main effect and interaction involving striatal infusion condition: F<1.4, p>0.27). There was only a significant effect of prepulse intensity ($F_{(3,39)}$=19.15, p<0.001).

4: Large LFP spike-wave discharges and intensified multiunit burst-firing



Between-subjects design
Picrotoxin n=9
Saline n=10

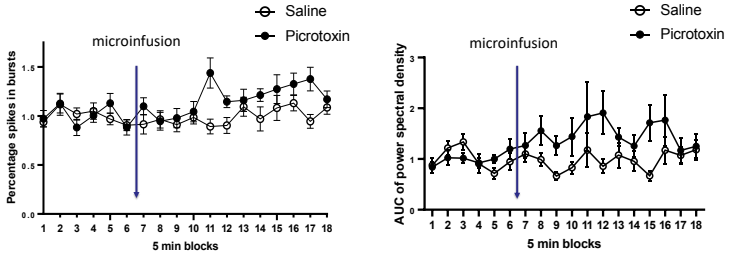


Striatal disinhibition caused marked changes in the striatal multi-unit firing and LFP pattern. There were large LFP spike-wave discharges and sharp multi-unit bursts during the spike.

5: Enhanced burst firing and LFP spike discharges

Between-subjects design

Picrotoxin n=9 , Saline n=10



Picrotoxin increased percentage spikes in burst compared to saline. This was supported by an ANOVA of a significant interaction of infusion X 5min block ($F_{(17,289)}$ = 1.89, p=0.019).

Overall LFP power was numerically markedly increased in the picrotoxin compared to the saline group, although the interaction infusion group X time did not reach significance ($F_{(17,289)}$ =1.586, p=0.067).

Values are normalised to the average of the 6 baseline 5 minute blocks.

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