

Effect of chemogenetic modulation of hippocampal neurons on depression and spatial memory impairment in a rat model for temporal lobe epilepsy.

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Rationale

Major depression and spatial memory impairment are the most common comorbidities in patients with temporal lobe epilepsy (TLE). For these patients, treatment options are limited highlighting the need for innovative treatments such as Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). Studies investigating the effect of DREADDs on these comorbidities are lacking.

In the present study, we evaluated whether activation of hM4Di DREADDs with clozapine affects anhedonia (i.e. the inability to experience pleasure) and spatial memory in the intraperitoneal kainic acid (IPKA) rat model for TLE.

Method

Status epilepticus (SE) was elicited by i.p. kainic acid (KA) injections in male Sprague Dawley rats. A control group was injected with saline (SAL). Three months post-SE, animals received bilateral intrahippocampal adeno-associated viral vector injections (2x0.5µL) carrying the hM4Di DREADD or a SHAM construct, yielding four experimental groups: KA-DREADD (n=8), KA-SHAM (n=6), SAL-DREADD (n=5) and SAL-SHAM (n=5). Anhedonia was evaluated using the saccharin preference test (SPT) and the novel object test (NOL) to assess spatial memory impairment. Following hM4Di DREADDs activation by clozapine (0.1 mg/kg, s.c.), the SPT and NOL were repeated.

Results

The KA group showed a significant reduction in preference towards saccharin compared to the SAL group (66.25% vs 96.96% respectively, $p < 0.001$). In the NOL, a trend towards spatial memory impairment was observed in the KA group. DREADDs activation with clozapine increased preference towards saccharin in the KA-DREADD group, while spatial memory was not affected compared to SHAM groups.

Conclusion

The IPKA rat model displays anhedonic-like behavior whereas enlargement of sample size is required for characterization of spatial memory impairment. Although activation of hM4Di DREADDs did not alter spatial memory, an increased preference towards saccharin was present in the IPKA rat model containing hM4Di DREADDs, suggesting a potential antidepressant effect.