KAINATE RECEPTORS CONTROL GABA RELEASE IN LAYER III OF THE ENTORHINAL CORTEX

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We have shown that GABA release in the entorhinal cortex (EC) may be modulated by a number of presynaptic receptors including NMDA, metabotropic glutamate and $GABA_B$ receptors (Jones et al, 2005). In the hippocampus, kainate receptors (KAr) have also been shown to regulate GABAergic transmission (e.g. Cossart et al, 2001) but, currently, little is known about their role in the EC. In the present study we have looked at the effect of a GluR5 selective kainate receptor agonist, ATPA, on GABA release in layer III of the rat EC *in vitro.*

Spontaneous inhibitory postsynaptic currents (sIPSCs), mediated by $GABA_A$ receptors, were recorded using whole cell patch clamp (in the presence of AMPA and NMDA antagonists) in EC slices from male Wistar rats (50-60g), and used as a monitor of presynaptic GABA release. To compare data under control and drug conditions, we determined mean values for inter-event interval (IEI) and amplitude for events in each cell, using a paired t-test for statistical comparison. All error values refer to the standard error.

ATPA (0.5µM) significantly decreased the mean IEI of the sIPSCs in layer III neurones (from 117±48 ms to 84±34 ms, $P<0.01$, n=10) reflecting an increase in frequency of events. Concurrently, there was a decrease in amplitude (from 40.2±3.3 pA to 33.2±3.0 pA, $P<0.05$). These results indicate that KAr can promote GABA release in layer III of the EC, either via excitation of interneurones, or via a direct effect on the GABAergic terminals. To distinguish between these possibilities, experiments were conducted in the presence of TTX (1 µM). Under these conditions, ATPA (0.5 µM) still decreased the IEI of miniature IPSCs (mIPSCs; from 278±96 ms to 223±77 ms, $P<0.001$, n=10), but had no effect on amplitude (29.8±2.0 pA *v* 31.3±2.8 pA). Comparison of the changes in IEI showed that it decreased on average by about 30% in the absence of TTX compared to only 20% in its presence. In a further 9 neurones we applied Cd^{2+} (50 µM) in addition to TTX. In these experiments, ATPA had no effect on IEI (252±29 ms *v* 251±31 ms) or amplitude (27.8 ± 3.2 pA *v* 27.4 ± 2.0 pA) of mIPSCs.

The increase in frequency of sIPSCs by ATPA may reflect excitation of GABAergic interneurons in layer III via activation of KAr on the cell bodies. However, the partial persistence of this effect in TTX indicates that KAr may also be present on GABAergic terminals, acting to facilitate quantal GABA release. The blockade of this effect in the presence of Cd^{2+} suggests that KAr activation may directly depolarize the terminals leading to activation of voltage gated Ca channels. Thus, KAr appear to modulate GABAergic transmission on at least two levels in the EC.

Cossart R *et al.* (2001) *Neuron*. **29:** 497-508.
Jones RSG and Woodhall GL. *et al.* (2005). *J Physiol.* **562:** 107-120.

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