TITLE

The effect of perforant path mediated GABAb inhibition on CA1 activity.

ABSTRACT

Direct perforant path input activates GABAb receptors in CA1 which inhibit pyramidal cells from firing. We use an integrate-and-fire model of EC and CA1 to show how this GABAb inhibition controls CA1 activity. It orthogonalises successive activity patterns, and it orthogonalises representations of the same place in different paths. This increases the capacity of CA1 as an associative memory network, by reducing the width of the cell usage distribution. It also allows the hippocampus to distinguish between representations at different times of the same location, as required by CA1-dependent temporal spatial memory tasks.

INTRODUCTION

What is the function of the perforant path direct input to CA1 in hippocampal information processing? Interestingly, when the perforant path afferents are stimulated 40 ms before the CA3 Schaffer Collateral afferents, the probability of the CA1 pyramidal cell spiking increases, but when they are stimulated 400 ms before, the probability decreases (Remondes and Schuman, 2002). These results are found in adult rat slices at room temperature, with CA3 and EC removed, and with a stimulation of 10 pulses at 100 Hz. The spike probability decreasing effect is impaired or blocked by GABAb antagonists. The GABAb activation is not mediated by individual interneurons, rather it is a result of cooperative inhibition (Vida et al. 1998).

This study investigates the effects of the GABAb response on the neural coding in CA1. The long time course of GABAb inhibition provides a memory trace of activity, which may be helpful in hippocampal tasks with a temporal component. As a first stage in understanding the effects, only the activity in CA1 as a result of perforant path input is modelled.

NETWORK

The network consists a population of entorhinal cortex cells, of CA1 pyramidal cells, and of CA1 interneurons. In each case, conductance-based integrate-and-fire neurons are used. The rat explores an 1m x 1m environment which is randomly and evenly mapped to the entorhinal cells with realistically large Gaussian place fields. The entorhinal cells' projections to both CA1 populations are sparse and topographically organised along the septo-temporal axis (Naber et al. 2001). The interneurons also project topographically and sparsely to both the pyramidal cells and to each other. When the inhibitory input to a cell exceeds a fixed threshold, a postsynaptic GABAb current is activated with a time constant of 100 ms (Molyneaux and Hasselmo, 2002). The parameters are set as guided by analysis (Treves, 1993) such that the mean activity for all populations is 50 Hz. When GABAb is included, we reduced the coupling between the

interneurons and CA1 excitatory cells to maintain activity rates. The effects of theta-rhythm inhibition have not been included, and no attempt has been made to model the theta phase-precession of activity (O'Keefe and Recce, 1993).

The results are contingent on the successful formation of CA1 place fields. When no place fields are present in CA1, each pyramidal cells has equal probability of firing, and GABAb has little effect on the activity. Models of place field formation have used the computational properties presented by the recurrent collaterals in CA3. Lesion studies have demonstrated that CA1 place field sizes are statistically unaltered for rats without CA3 input (Brun et al., 2002). A spike-time-dependent plasticity rule was used to introduce competition to form the place fields (Song et al. 2000).

RESULTS

The CA1 pyramidal cells which were active in a given theta cycle, and which received strong inhibition, are inhibited from firing in the next theta cycle. By inhibiting cells which have been active in the previous cycle, the GABAb input makes successive ensemble representations of contextual place more orthogonal. Additionally, the GABAb input orthogonalises representations of the same location in different paths. The strength of this effect is increased by differences in the paths. When the paths are in opposite directions, the orthogonalisation of the activity is the greatest, because the activity in the previous cycles is most likely to be different.

Meanwhile, the cells active in the previous cycle which receive less strong focal inhibition are more likely to be active both in successive representations of place, and in representations of the same place at different times. Preliminary results indicate that the resultant correlation in the activity of overlapping place fields is consistent with experiments (McHugh et al., 1996).

DISCUSSION

Orthogonalising the successive activity representations of place, and orthogonalising different representations of the same place depending on the preceding path, both reduce the variance in the cell usage distribution. This dramatically increases the storage capacity of the network as an associative memory network (Graham and Willshaw, 1997). This result supports the body of hippocampal modelling work which has proposed that the role of CA1 in hippocampal processing is to recode CA3 activity to ensure efficient transmission of information to the neocortex.

The CA1 ensemble place code is accurate to less than 2 cm for populations greater than 40 neurons (Wilson and McNaughton, 1993). This distance is covered in one theta cycle by a rat running at ~20 cm/s. A place traversed twice during two different paths is therefore only likely to be ambiguous for one theta cycle. By temporally orthogonalising place representations on the timescale of one theta-cycle, perforant path mediated inhibition increases the probability of downstream brain areas being able to distinguish between different temporal examples of the same place. This effect is strong enough to explain evidence from lesion studies and NMDAr knock-out studies suggesting that CA1 has a

specific role in spatial and non-spatial tasks with a temporal component (Huerta et al. 2000; Rondi-Reig et al. 2000; Gilbert et al., 2001).

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