Influence of the decay time of GABAergic postsynaptic currents on the spatial spread of network activity

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The subunit composition of the $GABA_A$ receptor determines the decay time of GABAergic inhibitory postsynaptic currents (IPSCs). In mice in which the $\alpha 1$ subunit is deleted, the decay time is longer than in wild type mice, while the spatial spread of activity in the visual cortex following local stimulation is smaller. Using a simple network model of the visual cortex, we show that this reduced spread of activity could be accounted for by the longer IPSC decay time. After local stimulation of the network, a patch of activity develops, the equilibrium size of which depends on the IPSC decay time.

The $GABA_A$ receptor is the main inhibitory receptor in the mammalian brain. GABA synapses are omnipresent in all layers of the neocortex and are present on virtually all types of neurons. GABAergic inhibition prevents excessive firing, is crucially involved in the timing of action potentials and the synchronization of firing patterns, and plays an important role in the fine tuning of synaptic efficacies. Impaired GABAergic transmission has been reported to be associated with several pathological conditions, such as epilepsy and anxiety.

The $GABA_A$ receptor is composed of five subunits, which can be of different classes. The α, β, γ, and δ classes are the most abundant ones. Each class consists of a number of different types; for example, there are six types of the α subunit ($\alpha 1$ through $\alpha 6$). In the neonatal visual cortex, the most abundant α subunit in layers II and III is $\alpha 3$. During postnatal development, between postnatal days 6 and 21 (around the time of eye opening), $\alpha 1$ expression is highly upregulated, so that in adult neurons, $\alpha 1$ is the most abundant α subunit.

The subunit composition of the $GABA_A$ receptor determines the deactivation and desensitization times, and therefore also the synaptic responses. The naturally occurring upregulation of the $\alpha 1$ subunit during development is correlated with faster inhibitory postsynaptic receptor currents (IPSCs)(refs). In line with this, the decay time of the IPSCs is longer in mice in which the $\alpha 1$ subunit is deleted ($\alpha 1$ -/- mice) than in wild type mice ($\alpha 1$ +/+ mice) (Bosman et al., 2003). In $\alpha 1$ -/- mice, the ability of neurons in the visual cortex to fire synchronously at γ-frequencies is significantly reduced. Furthermore, the spatial spread of network activity following stimulation of the cortex is much smaller in $\alpha 1$ -/- mice than in $\alpha 1$ +/+ mice (as observed with voltage-sensitive

dyes.

To test whether the reduced spatial spread of network activity in $\alpha 1$ -/- mice could be the result of the longer decay time of the IPSCs, we constructed a network model with integrate-and-fire neurons and roughly the same connectivity pattern as that in the cortex. The network is composed of 30% inhibitory (i) cells and 70% excitatory (e) cells, which are randomly placed on a two-dimensional grid. For each cell, the target cells onto which it makes connections are randomly chosen with uniform probability within a circular field, the radius of which depends on the type of connection. The e to e connections are short range, the e to i connections are long range, and the i to e and i to i connections are medium range. The strength and number of connections also depend on the type of connection. In accordance with the experimental data, GABA inhibition is modeled as shunting inhibition.

A small patch of cells in the network is stimulated for a number of time steps, after which stimulation is stopped. The strengths of the connections are such that the network can remain active without external stimulation. After stimulation, activity in the network spreads out until an equilibrium state is reached in which a patch of cells is active that does no longer expand. The size of this patch depends on the decay time of the IPSCs. The longer the decay, the smaller the size of the patch of active cells, in accordance with what has been found experimentally.

When excitatory cells are stimulated, they recruit other cells in their neighborhood (the e to e connections are short range), so that activity expands. But at the same time, inhibitory cells farther away become activated (the e to i connections are long range), which in turn project back to excitatory cells (the i to e connections), inhibiting them. Thus, the active patch of cells becomes surrounded by a ring of inhibited excitatory cells (and active inhibitory cells), which, if the ring is "closed", prevents further expansion of activity. The shorter the decay time of the IPSCs, the farther activity can expand before it is eventually stopped by a ring of inhibited excitatory cells. Essential in this mechanism are thus the presence of short-range e to e connections, long-range e to i connections, and medium-range i to e connections. The latter should be numerous and strong enough to build up a ring of inhibited excitatory cells that at some point can prevent further expansion of the patch of active cells.

In conclusion, we have shown that the length of the decay time of the IPSCs can determine the spatial spread of network activity. To test if the mechanism suggested by the model is indeed operative in the cortex, we are planning experiments in which we can monitor whether the patch of active cells becomes surrounded by a ring of strongly inhibited excitatory cells.

References

Bosman, L., Lodder, J. C., Heinen, K., Spijker, S., Rosahl, W., Brussaard, A. (2003). Impaired development of fast GABAergic neurotransmission in $\alpha 1$ -/- mice reduces γ-oscillations in the visual cortex. In preparation.