

# **NEURONAL MECHANISMS UNDERLYING THE MODULATION OF THE GRANULE CELLS IN THE DENTATE GYRUS**

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The functional organisation of the anatomical elements whereby the hippocampal formation gains its main excitatory input, whose signals are processed in it and its output is being sent toward other brain areas is largely referred to as trisynaptic circuit (TC). The first element of this neurocircuit

is the perforant path (PP), originating in the layers II-III of the entorhinal cortex. These axons form the first excitatory synapse on the dendrites of the second element. This is the granule cell (GC), which relays the signal by means of the mossy fibres through the second excitatory synapse onto the CA3 pyramidal cells. Further, the information is processed in the CA (Cornu Ammonis) areas (the hippocampus proper). The GC-s are located in the dentate gyrus (DG). This consists of trilaminar cortex (archicortex). The perykaria of the GC-s form the granule cell layer (GCL). Their spiny dendrites form the molecular layer (ML), whereas the axons are confined within the hilus of the DG. As a member of a group of researchers I studied the internal circuitry of the DG. Here I review our data in a context of the literature.

In the ML of the DG there is a very strict further lamination of the PP fibres. These are located only in the outer 2/3-s of the ML, and they target the distal dendrites of the GC-s. They form symmetric synapses mainly on dendritic spines. The inner third of the ML receives axons emerging from the contralateral hippocampus, the commissural path (CP) and axons originating in different septotemporal levels of the ipsilateral hilus (associational fibres). These axons form both symmetric and asymmetric synapses on the proximal dendrites of the GC-s. The anatomy of the hilus is much more complicated. Classical Golgi studies of *Cajal* and *Lorente de Nó* followed by later ones of *Blackstad* and *Amaral* (for review see *Amaral*, '78) revealed that, in addition to the already listed elements, the hilus contains non-pyramidal - non-granule neurones as well. Due to technical limitations of the Golgi method, the axonal arbours usually remained largely unidentified. Thus, attempts for classifying these cells based on the morphological properties of their dendrites remained inconclusive. However, two distinct cell types were described. First, the basket cell, with its soma in the polymorphic layer (PL) of the hilus, is subjacent to the GCL. Its smooth dendrites extend vertically in the ML, others ramify in the hilus. The axon was largely confined to the GCL. Second, the chandelier cell, whose soma can be located in the PL, GCL or ML. The recovered dendrites were smooth, ascending in the ML. Its axon has been shown to be very characteristic, forming vertically oriented rows between the bundles of the initial segments of the GC-s. (*Kosaka*, '83, *Soriano* and *Frotscher*, '89). Recent intracellular recording and labelling techniques allowed us to correlate electrophysiological and morphological data on hippocampal interneurons. (The reader is referred to the article by *Han* et al., '93, where the methods are described in details. Subsequently, the same material underwent EM processing, in order to study the fine structure, synaptic connections and the nature of the neurotransmission by *Halasy* and *Somogyi*, '92).

Three newly discovered interneuron types were described. First, the interneuron with soma located in the ML associated with the PP input

(MOPP cell) Its smooth dendrites were located in the outer 2/3 of the ML, suggesting the same PP input as to the distal dendrites of the GC. The MOPP cell's axonal arbor was strictly confined to the outer 2/3 of the ML, to the very same zone providing its input. Subsequent postembedding immunocytochemistry on EM sections revealed that its GABA containing axons made symmetrical synapses onto dendritic shafts. These findings strongly suggest that the MOPP cell is involved in the inhibition of GC-s in feedforward manner. It probably modulates the PP input onto GC dendrites. This will be more effective if the activation threshold of the MOPP cell is lower than the GC's one. Further, it seems to be ineffective in the neurocomputation that is going on the more proximal dendrites, in the zone of the CP and associational fibres. The dendrites of the MOPP cell received both symmetrical and asymmetrical synapses.

Another type of interneuron had its soma in the PL, and its sparsely spiny dendrites were confined to the hilus, where they may be contacted by recurrent collaterals of the mossy fibres. An extensive axonal arborization was located in the outer 2/3 of the ML, also in relation with the innervation zone of the PP. (Hence its name derives: HIPP cell). Its axon terminals formed symmetric synapses both on dendritic shafts and spines (most probably of GC's). Although technical limitations made difficult to unambiguously establish whether its boutons contained GABA, there is little doubt regarding its inhibitory postsynaptic effect. This cell is presumably involved in a feedback inhibitory local circuit as its dendrites may be contacted by the hilar mossy fibre collaterals.

The third type of hilar interneuron is characterized by sparsely spiny dendrites which extend from the hilus to the outer ML. Interestingly, a dendritic shaft upon entering the ML became densely covered with spines. The axonal arbor was confined to the inner third of the ML, the termination zone of the CP and associational fibres. These features are summarised in the acronym HICAP cell. Although the axon terminals formed mainly symmetric synapses, a few asymmetric synapses were also observed. The synapses on both dendritic shafts and spines were strongly immunopositive for GABA. The dendrites of this cell also received symmetrical and asymmetrical synapses. These findings suggest that the HICAP cell is involved in both feedback and feedforward inhibition.

As shown in the introduction, previous Golgi studies have dealt with a category called the basket cells. As this group increased, its members finally shared only one feature, namely that they all were non-principal neurons. It is important to notice, that the group of basket cells became quite heterogeneous as it comprised very different types of interneurons regarding their location, dendritic and axonic patterns. (Amari '78, Ribak and Seress, '83). There came the need to divide the vast category of basket cells in

distinct classes, to define what a "basket cell" is. In our opinion, a basket cell proper is a cell making synapses onto perikarya and proximal dendrites. All other interneurons, terminating on different parts of the target cells should be classified using names which express their morphology properly.

We made an attempt to establish morphological criteria for the newly discovered neurons and create a specific nomina. As a support to these principles, a hilar basket cell (proper) was described as well, but only its axonal arbor was recovered for morphological analysis.

Further, one hilar chandelier cell was recorded and filled. Its dendrites were only partially labelled, and only those were visualised which travelled to the extreme border of the ML. Unexpectedly, there was a copious amount of chandelier terminals in the hilus as well, in addition to the curtain-like plexus in the lower GCL.

In a recent study *Soriano and Frotscher* ('93) reported another new type of DG interneuron. The cell body was located in the inner part of the ML, the dendrites ramified in the hilus, although one dendrite descended to the ML. The authors suggest that the axonal arbor fills the entire ML, although in their figure 1-B, C, D, it is apparent that a narrow band in the inner ML remains almost free of axon collaterals. As the authors didn't trace the hippocampal fissure, it remains to appreciate the ratio, but it appears that the axonal arbor is much denser in the outer 2/3 - 3/4. The axon terminals established symmetrical synapses on both dendritic shafts and spines, which presumably belong to GC-s, and subsequently they were shown to contain GABA. Thus, this cell is an inhibitory neuron involved in both feedback and feedforward inhibition.

As seen above, in the DG the afferent fibre systems terminate in a laminated fashion. Our data, viewed in conjunction with the results in the literature show that intrinsic modulatory circuits within the DG exhibit a striking selectivity regarding the types of interneurons involved in different forms of inhibition in addition to a high target specificity of their terminals (for review see *Frotscher*, '91). The fact that a neuron, as in the case of the HIPP cell, can form both symmetrical and asymmetrical contacts suggests that on the postsynaptic membrane may be different types of receptors facing the same presynaptic cell and neurotransmitter. Consequently, the postsynaptic effects of a neuron seem to depend to a large extent on the receptors and receptor mechanisms of the postsynaptic membrane.

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The dentate gyrus, part of the hippocampal formation, receives its input in a strictly laminated fashion. In addition to the basket and chandelier cells (known to send their output selectively to different input sites of the granule cells) a group of researchers with the participation of the author described three new types of interneurons. These are the MOPP, the HICAP and the HIPP cells, showing a high target selectivity for the granule cell's input sites according to the lamination of main excitatory inputs. Electrophysiological and anatomopharmacological data show that these are GABA-ergic inhibitory interneurons.

The activity of the granule cells can be regulated very selectively by means of intrinsic inhibitory neurocircuits formed by these neurons.

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