**The Mossy-fiber synapse – the detonator synapse of the trisynaptic pathway**

The hippocampus has long been recognized as a key region for the formation and long-term storage of memories. According to the ‘trisynaptic pathway’ model, the hippocampus is roughly divided into three sub-regions – the dentate gyrus (DG) and Cornu Amonis 1 and 3 (CA1 and CA3 respectively) which are connected by unidirectional pathways to form a closed loop with the cerebral cortex. The mossy-fibers are the axons sent by the granular cells of the DG to the CA3 sub region, where they form large and complex synapses onto CA3 pyramidal cells (hereafter MF-synapses). Traditionally, the MF-synapse is considered to be a ‘detonator synapse’ because of the unique ability of a single MF-synapse to induce spiking in its post-synaptic target, when activated in short bursts of high-frequency. This ability of the MF-synapse is largely attributed to its special short-term plasticity – namely, its extremely high facilitation.

**The Mossy-fiber synapse – STP and its hypothesized computational role**

The high facilitatory nature of the MF-synapse is also integrated into computational theories that ascribe a central role for this synapse in ‘pattern separation’ – the cognitive process that allows the memory system to orthogonalize highly overlapping mnemonic representations (Ref). According to these theories the high-facilitation of the MF-synapse makes it a suitable neuronal substrate to perform pattern-separation because it acts as a high-pass filter (Why???).

The large efficacy of the MF-synapses had led researchers to view the MF pathway as the main excitatory input to the CA3 region. However, recent studies provide evidence that the view of the trisynaptic pathway information flow, entorhinal cortex (EC) 🡪 DG🡪 CA3🡪 CA1, is overly simplified, and direct excitatory input provided by the EC to the CA3 is stronger than this provided by the MF pathway (Urban, Henze & Barrionuevo, 2001).

**The Mossy-fiber synapse – Unique LTP and changes in STP**

In addition to these unique properties, the MF-synapse also exhibits a special form of long-term potentiation (LTP) which forms in response to prolonged activity of the synapse at a high frequency and manifests as a sustained increase in the probability of neurotransmitter release (Pr). Because, the Pr of a given synapse is inversely related to its short-term facilitation, MF synapses that undergo LTP also show decrease in facilitation. This raises the question about the implications of such a deterioration of the high-pass filter properties of the MF-synapse as a result of LTP processes.

**The Mossy-fiber synapse – Unique LTP non-associativity and a bit of HSP**

Another non-trivial property of the MF-LTP is that it does not require any post-synaptic coordinated activity, as is the case in NMDA-dependent LTP which is the prevalent form of LTP in the hippocampus and is generally considered to be expressed post-synaptically as an increase in AMPA receptors responses (Ref, but see Jaffe & Johnston, 1990). The fact that the MF-LTP is non-associative suggests that it is not a suitable process to underlie memory storage, as it does not obey the hebbian learning rules (Ref). This is consistent with a recent study in which the researchers provided evidence that homeostatic plasticity processes are prevalent in the MF-synapse, and in-light of these observations, suggested a new role for this synapse as a gain-control device that helps keeping excitation levels in a certain physiological range (Lee et al., 2013).

**The Mossy-fiber synapse – LTP open questions**

Any connection between impairment of MF-LTP and any cognitive or behavioral deficit has yet to be demonstrated. Knock-out mice in which MF-LTP or MF long-term depression (MF-LTD) are eliminated have shown to be unimpaired in learning tasks (Silva et al., 1992, Chapman et al., 1995, Mayford et al., 1995). Therefore, the role of MF-LTP remains enigmatic to this day,

**Review of the traditional experimental approach to MF-LTP**

In-order to elucidate the physiological role of LTP, it is crucial to study it under conditions that resemble those present in-vivo. However, mainly due to technical constraints, most of the researches done on MF-LTP used non-physiological induction protocols to induce it. These protocols usually involved the simultaneous activation of multiple MF-axons; some of them converge on the same post-synaptic CA3 pyramidal cell. The probability of such an event, when taking into account the endogenous firing patterns of DG granular-cell (basal firing frequency of approx. 0.1 Hz) and their low connectivity to CA3 pyramidal cell, is very low (Unpublished data). Moreover, most researchers used the paired-pulse recording approach in-order to measure MF responses and to verify the pre-synaptic origin of LTP. However, there is ample evidence that the first two responses in a stimulation burst are unable to propagate their post-synaptic target, and thus are irrelevant to the information transfer through the hippocampal circuitry. This was shown in a seminal study in which the researchers tested the ability of one granular cell to induce spiking in its post-synaptic targets in the CA3, using *in-vivo* patch-clamp of DG granular cell combined with multi-unit activity measurements in the CA3 sub region. Consistent with the view of the MF-synapse as a high-pass filter, it was shown that only bursts of action-potentials, but not single action-potentials could induce spiking in the CA3 pyramidal cells. Furthermore, the researchers have shown that for a given number of presynaptic APs, the higher the frequency of their introduction, the higher their chances to induce spiking in the post-synaptic targets (Henze, Wittner & Buzsaki, 2002). In another study in which researchers used a setup closely resembles the conditions of physiological activity …utilized organotypic slices and performed double-patch between DG granular-cell and CA3 pyramidal cell they observed that …, When they used high-frequency bursts that according to other e studies is capable of inducing LTP, they saw an initial decrease in failure rates of neurotransmission is response to single AP, but later, failure rates returned to baseline levels, which suggests that no significant LTP processes are evident under these conditions (Mori et al., ).