Review of: "Cell-Type Specific Neuromodulation of Excitatory and Inhibitory Neurons via Muscarinic Acetylcholine Receptors in Layer 4 of Rat Barrel Cortex"

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The study from Qi and Feldmeyer investigates the modulatory role of acetylcholine (ACh) on rat sensory cortex, showing ACh receptor-specific effects on distinct types of layer 4 interneurons.

Previous studies using *in vivo* electrophysiology and behavioral protocols have shown an important role of ACh on consolidation and retrieval of memories linked to sensory inputs; the present work provides new data to explain the underlying neural circuits and cellular mechanisms.

Some previous literature (Ego-Stengel *et al*., 2001; Oldford & Castro-Alamancos, 2003; Shulz *et al*., 2003) has not been discussed here, making difficult for readers to reconcile results from other research groups that used different techniques and different experimental conditions. However, with respect to previous studies, the present one is much more detailed and represents a considerable advancement under many aspects: ACh was tested at doses (in the low micromolar range) closer to physiological synaptic concentrations; the location of recorded neurons was precisely identified within layer 4 and their morphology was reconstructed; the authors pharmacologically identified the ACh receptor types mediating distinct effects.

Results show that ACh inhibits layer 4 excitatory interneurons by activation of M4 receptors and activates inhibitory interneurons (mostly co-releasing Vasoactive Intestinal Polypeptide, VIP) by activation of M1, M3, M5 and nicotinic receptors. These results are very interesting with respect to the function of each neuronal type. As reported by the same authors in a previous publication, L4 excitatory neurons distribute sensory signals within and beyond the sensory cortex, whereas L4 inhibitory interneurons might regulate intracortical excitatory transmission and shape its “temporal” characteristics”(Emmenegger *et al*., 2018).

Thus, from a functional point of view, the present results might suggest that ACh reduces excitatory transmission to neighbouring sensory cortex and enhances modulatory inhibition to other cortical areas, opening questions about the physiological consequences of ACh multifaceted action.

Starting from these data, it would be interesting to identify the projection sites of layer 4 neurons respectively inhibited and activated by ACh. In a previous study, the same laboratory investigated in details non-fast spiking inhibitory interneurons in layer 4 and identified 5 different types with distinct projections, suggesting a different physiological role for each type of interneurons: for example trans-columnar projecting interneurons might be responsible for lateral or “surround” inhibition of adjacent barrels (Emmenegger *et al*., 2018). In future studies, it might be interesting to test the effects of M4, M1/3/5 and nicotinic agonists on layer 4 interneurons followed by immunohistochemical staining of the recorded neurons, and

biocytin labeling reconstruction of neuronal projections. It would be also interesting to correlate ACh responsiveness of layer 4 interneurons with input specificity (interneurons receiving either sensory input from thalamus or intracortical projections). A possible development might be a selective pharmacological modulation of distinct ACh-mediated functions. Future studies might also investigate the role of the arousal state on the activity of sensory cortex layer 4 neurons. In physiological conditions of increased arousal, higher levels of ACh released in sensory cortex might exert either a stronger or a different modulation. The effects observed in this study might be different at higher endogenous ACh levels: for example, since nicotinic receptors have lower affinity for ACh with respect to muscarinic receptors, nicotinic effects might prevail at high ACh concentrations, although this suggestion is purely speculative.

It would also be interesting to investigate if the expression level of different ACh receptors in sensory cortex (thus global ACh action) changes during development and/or in pathologies, for example in Alzheimer's Disease (AD), involving a disruption of brain cholinergic transmission. Interestingly, observations on patients indicate abnormal sensory and pain transmission in dementia states including AD, suggesting altered sensory processing (Scherder *et al*., 2009).

Finally, this study underlines an important role of VIP-ergic interneurons in the modulation of sensory cortex circuitry. VIP and its related Pituitary Adenylate Cyclase Activating Peptide (PACAP) are endogenous neurotrophic factors that also behave as neuromodulators of synaptic transmission and plasticity in physiological conditions (Ciranna & Cavallaro, 2003; Di Mauro *et al*., 2003; Costa *et al*., 2009) and in animal models of cognition deficit (Costa*et al*., 2018; Ciranna & Costa, 2019). VIP, PACAP and their receptors are widely distributed in brain areas involved in learning and memory (Borbely *et al*., 2013). A possible use of VIP and PACAP in the therapy of cognition impairment is currently being investigated, especially since several peptides (including PACAP) were shown to reach the brain after intranasal administration (Meredith *et al*., 2015; Reglodi *et al*., 2018). The present results add new information about ACh-VIP interactions in sensory cortex and open interesting perspectives for future studies.

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