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Review

Biophysical modifications underlying complex learning

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ABSTRACT

Rats that are trained in a particularly difficult olfactory-discrimination task demonstrate a dramatic increase in their capability to acquire memories of new odors, once they have learned the first discrimination task ('rule learning'). Such rule learning is accompanied by a series of cellular modifications which share three major traits: First, they are widespread throughout the relevant cortical networks. Both physiological and morphological modifications are found in most of the studied neurons. Second, the time course in which these modifications appear and disappear is strongly correlated with the time course in which the skill is acquired and decays. However, memories for specific odors outlast these modifications by far. Thus, the identified modifications are related to rule learning (learning how to learn), rather than to long-term memory for the specific odors for which the rats are trained. Third, at the cellular level, learning-induced long-term modifications occur in the three components controlling neurons activation: The excitatory synaptic drive, mainly mediated by glutamate receptors, the intrinsic neuronal excitability, and synaptic inhibition, mediated by $GABA_A$ receptors. Such profound, whole network modifications are not the mechanism by which memories for specific sensory inputs or sequences of events are stored. Rather, they may be the mechanism that enables neuronal ensembles to enter into a state which may be best termed "*learning mode*". This state lasts for up to several days, and its behavioral manifestation is a general enhancement in learning capabilities in tasks that depend on these particular neuronal ensembles. The transition in and out of learning mode may be well described as a beyond-hebbian phenomenon, based on the facts that it results with a dramatic change in the animal's behavior, and requires modifications in biophysical properties in most elements of the neuronal ensemble.

KEYWORDS: complex learning, olfactory discrimination, intrinsic excitability, synaptic enhancement

INTRODUCTION

Rule learning

The ability to extract general rules from specific experiences is a fundamental attribute of higher cognitive functioning. In the example of learning olfactory discrimination (OD) tasks, two different types of learning can be distinguished: acquiring the knowledge of how to perform a discrimination task (procedural memory), and acquiring the knowledge of the specific discriminative stimuli within the task (declarative memory). However, while our understanding of procedural and declarative memory (often referred to as implicit and explicit memory, respectively) has developed substantially over the past 30 years, the neurobiology of elaborate forms of memory - such as rule learning - is not well understood [1]. Thus an animal model that would allow a comprehensive study of the biological bases of rule learning is of utmost importance.

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Olfactory discrimination learning in rodents as a model for rule learning

Olfactory discrimination tasks in rodents provide an excellent framework to investigate rule learning [2, 3]. Rats, for which olfaction is a dominant sensory modality, can efficiently learn to discriminate between positive and negative cues in pairs of odors. Furthermore, rats demonstrate capability for rule learning in odor discrimination, which enables them to acquire large amount of olfactory information in discrimination tasks in a relatively short time [3].

OD training is known to induce changes in encoding of the learned odor in the olfactory bulb [4, 5, 6] piriform cortex [7, 8, 9], orbitofrontal cortex [10, 11, 12], amygdala [13 10, 11, 12] and hippocampus [14].

Odor learning displays characteristics typically associated with higher order learning, such as: object oriented perception [15], pattern completion [16], rule learning [2, 3], and transitive inference [17]. We have shown that learning of a particularly difficult OD task opens a period of accelerated learning of other odors, manifested as a dramatic increase in the rats' capability to acquire memories of new odors once they have learned the first discrimination task, implying that rule-learning has taken place. This increased learning capability has a restricted time window, generally lasting up to 7-8 days [3, 18, 19] (Figure 1). Notably, the memory for specific odors, as indicated by "reversal test", in which the rat has difficulty to acquire learned odors when presented with reversed meaning, outlast these neural modifications by far. Thus, the above identified modifications are related to rule learning itself, rather than to long-term memory for the specific trained odors [20].

Basic synaptic circuitry in the piriform cortex

The piriform cortex contains three layers that are distinct in their neural components (Figure 2). Layer I includes pyramidal cell apical dendrites along with afferent and intra-cortical axons, and a small number of interneurons. The afferent inputs

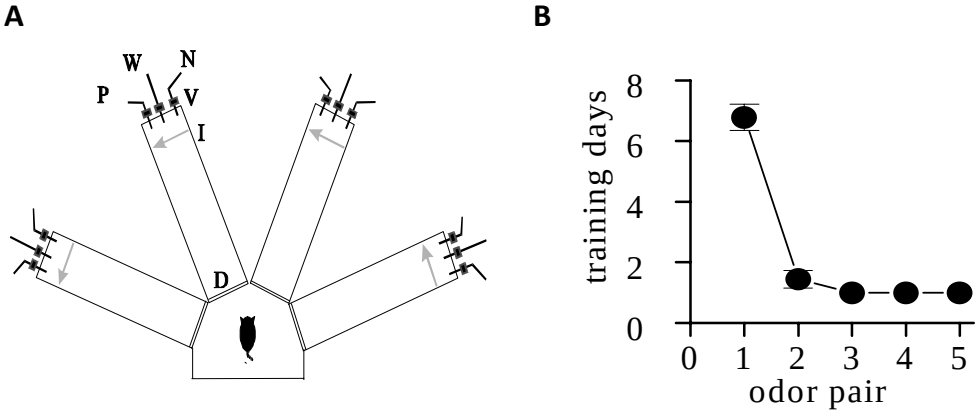

Figure 1. Olfactory-discrimination training: apparatus and rule learning. A. Schematic description of the 4-arm maze. Protocols for trained and pseudo- trained rats are similar**:** an electronic 'start' command opens two random valves out of eight (V), releasing a positive-cue odor (P) into one of the arms and a negative-cue odor (N) into the other. Eight seconds later, the two corresponding guillotine doors (D) are lifted to allow the rat to enter the selected arms. Upon reaching the far end of an arm (90 cm long), the rat body interrupts an infrared beam (I, arrow) and a drop of drinking water is released from a water hose (W) into a small drinking well (for a trained rat - only if the arm contains the positive-cue odor, for pseudo- trained rat- randomly). A trial ends when the rat interrupts a beam, or in 10 seconds, if no beam is interrupted. A fan is operated for 15 seconds between trials, to remove odors. **B.** Trained rats demonstrate acquisition of rule learning. Criterion for discriminating between the first pair of odors (80% correct choices) was reached after 7 consecutive days of training. Discrimination between any new pair of odors, starting from the third pair and forth, could be reached within one day. Values represent mean $\pm$ SE. n = 11 rats.

from the olfactory bulb terminate within superficial Layer I (Ia) while the deeper Layer Ib contains mostly intra-cortical association fibers. Layer II contains pyramidal cell bodies, the superficial lamina; IIa, contains the somata of semilunar pyramidal neurons, and the deeper lamina; IIb, contains densely packed pyramidal cell bodies. Layer III contains basal dendrites and axons of Layer II pyramidal neurons, as well as deep pyramidal neurons that extend apical dendrites into Layer I, and local interneurons. The piriform cortex contains several classes of GABAergic interneurons, distinguished both on morphology and laminar location [21]. The GABAergic interneurons include horizontal cells within Layer Ia and with long dendrites parallel to the cortical surface. Additional multipolar cells (without dendritic spines) lie within Layer II and III, mediating classic inhibitory feedback functions, and a class of small bipolar or bitufted cells have somata in Layer IIa and dendrites extending into both Layers I and III. The major elements of the piriform cortex circuit are shown schematically in Figure 2.

Physiological manifestations of rule learning

Learning-induced enhancement of neuronal excitability

Learning induced enhancement in neuronal excitability has been shown in hippocampal neurons following classical conditioning of the trace eyeblink response [22, 23] and the Morris water-maze task [24], and in piriform cortex neurons following operant conditioning [3, 19, 25]. In hippocampal and piriform cortex neurons, this enhanced excitability is manifested in reduced spike-frequency adaptation in response to prolonged depolarizing current step injections [22, 19, 23]. Olfactory-discrimination learning also results in enhanced neuronal excitability in CA1 hippocampal neurons [14].

Neuronal adaptation in neocortical, hippocampal and piriform cortex pyramidal neurons is modulated by medium and slow after-hyperpolarizations (AHPs) (Figure 3A), generated by potassium currents, which develop following a burst of action potentials [19, 26, 27, 28]. Indeed, it was shown in hippocampal and piriform cortex pyramidal neurons, that the post-burst AHP amplitude is reduced after learning [3, 22].

Functional significance of post-burst AHP reduction

Several findings suggested that AHP reduction enables the neuronal ensembles to enter into a state which may be best termed "*learning mode*". It is likely that enhanced neuronal excitability sets a time window in which most neurons in the relevant neuronal network are more excitable, and thus activity-dependent synaptic modifications are more likely to occur [3, 22]. The main evidences supporting this notion are:

a. The averaged AHP amplitude in neurons from hippocampus and piriform cortex is modified in most, if not all, sampled neurons, and tends to return to its initial value within days, when training is suspended (Figure 3B, C). This recovery is not accompanied by memory loss. However, rule learning (manifested as the enhanced ability to acquire new memories rapidly and efficiently) is strongly correlated with reduced post-burst AHP; return of AHP to its initial value is accompanied by reduced learning capability.

b. Before olfactory training, application of a cholinergic agent reduces the post-burst AHP and blocking cholinergic activity delays rule learning. However, once rule learning is established, acetylcholine's ability to affect the AHP is abolished and it also does not affect further acquisition of memories [19].

c. Learning impairment in aged animals is accompanied by enhanced post burst AHP [29].

d. Application of apamin, venom that reduces the AHP by blocking the I_{AHP} current, enhances hippocampal-dependent memory encoding, but not retention [30].

e. Finally, in the process of olfactory-discrimination learning the post burst AHP is reduced and neuronal excitability is transiently enhanced in CA1 pyramidal neurons. Such olfactory learning-induced increased excitability in hippocampal neurons enhances the rats' learning capability in another hippocampus-dependent task, the Morris water maze [14]. These evidences suggest that enhanced excitability of CA1 neurons may serve as a mechanism for generalized enhancement of hippocampus-dependent learning capability.

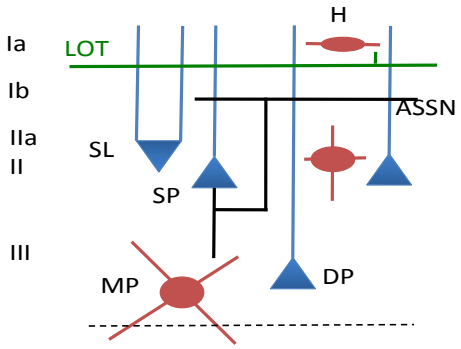

Figure 2. Major local circuit components of the piriform cortex. Pyramidal cell bodies are located mainly in layer II, and also in layer III. Layer Ia entails afferent axons arriving from the lateral olfactory tract (LOT), and layer Ib entails intracortical axons arriving from neighboring pyramidal cells (association fibers). Local GABAergic inhibitory interneurons are located in all layers. Abbreviations: H = horizontal cell interneuron; MP = multipolar interneuron; SL = semilunar pyramidal cell; SP = superficial pyramidal cell; DP = deep pyramidal cell; ASSN = association fibers.

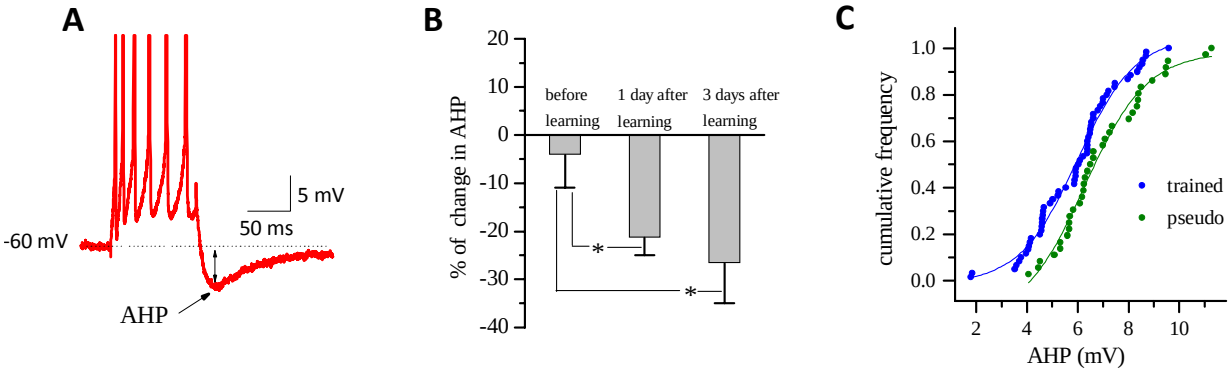

Figure 3

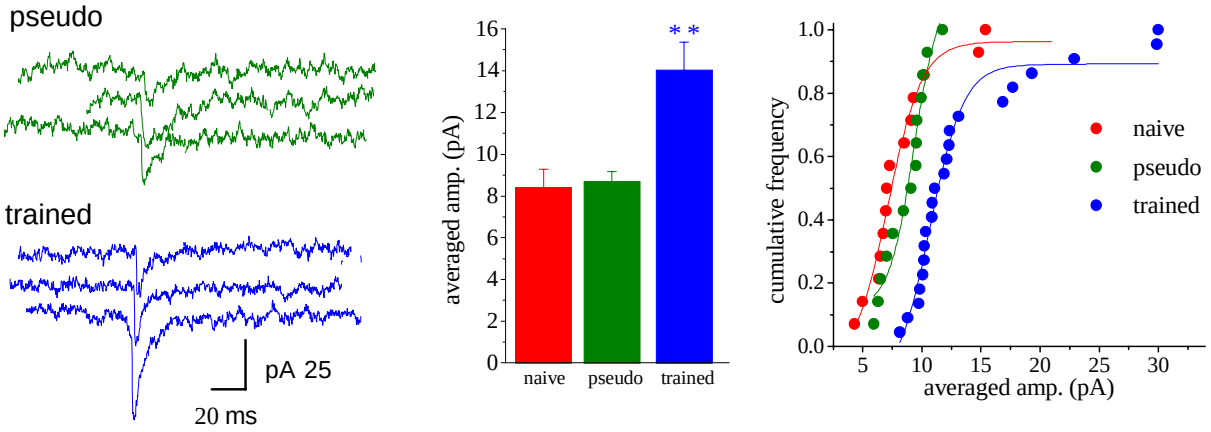

Figure 4

Learning-induced modulation of excitatory synaptic transmission

Modulation of post synaptic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors has been suggested to have a key role in synaptic plasticity and to mediate the early cellular events leading to learning and memory [31]. The increase in synaptic strength that mediates memory formation through Hebbian-type learning is traditionally thought to be synapse-specific, where mostly the synapses that connect a subset of active neurons are enhanced [32]. Taken together with the notion that learning involves both potentiation and depression of synaptic strength [32], the overall increase in excitatory synaptic strength onto any particular cell should be relatively small. Indeed several studies which reason that Hebbian learning underlies the increase in synaptic strength demonstrate a small increase in the total synaptic strength in a cell following learning [33, 34, 35, 36, 37, 38].

However, recently, a growing body of evidence demonstrate large overall increase in synaptic strength (> 50%) following various training paradigms, in different brain structures [39, 40, 41, 42, 43, 44, 45]. Such enhanced synaptic transmission is transient, returning to baseline few days after training termination [39, 41]. Moreover, the synaptic increase was observed in the majority of cells of the relevant region [39, 44]. The functionality of this increase is yet to be described; its magnitude, its presence in the majority of the cells and its transient nature do not agree with the principle of classical Hebbian learning.

Olfactory-discrimination rule learning induces a dramatic increase in the averaged amplitude of spontaneous miniature excitatory currents in piriform cortex pyramidal neurons (Figure 4A, B). As seen for enhanced neuronal excitability, the increase in mEPSCs averaged amplitude was apparent throughout the sampled neuronal population (Figure 4C).

The problem of unbalanced over-excitation

Since excitatory synaptic transmission and neuronal excitation are both profoundly enhanced by learning, the cortex may enter an over-excited state, during which epileptic-like activity propagates along the tissue [46]. Such hyper-excitable activity may prevent any efficient ability to store memories (see for example, [47, 48]). Homeostatic mechanisms that keep the neuronal activity within a certain range have been found in many systems [49]. Strengthening inhibition is a possible homeostatic mechanism for restoring the balance between excitation and inhibition, and hence for preventing

Legend to Figure 3. The post-burst AHP is transiently reduced after rule learning in most neurons from trained rats. A. Post-burst AHP measurements in a piriform cortex pyramidal neuron. Neuron was held at a membrane potential of -60 mV and an AHP was generated by a 100 ms depolarizing current step injection via the recording electrode, with intensity sufficient to generate a train of six action potentials. **B.** Time course of AHP reduction in neurons from trained rats. Amplitudes of AHPs recorded in neurons from trained rats on different days after the beginning of training compared with AHPs in neurons from pseudo-trained recorded at the same day. **C.** Cumulative frequency distribution of AHP amplitudes. Each point represents the AHP in one cell. AHP amplitudes in neurons from trained rats create a curve that smoothly shifted to the left along the x axis, relative to the curve of neurons from pseudo trained rats, indicating that AHP reduction occurs throughout the neuronal population.

Legend to Figure 4. Learning-induced enhancement of excitatory synaptic currents. A. Spontaneous synaptic events recorded in neurons from a pseudo trained and a trained rat at holding potential of -80 mV, four days after rule learning. In each neuron, three traces are superimposed. High amplitude events (> 25 pA) were seen in most neurons taken from trained rats, but very seldom in neurons from controls. In these recording conditions, application of the AMPAR blocker, DNQX (20 μM), abolished all spontaneous events, indicating that only sEPSCs were recorded. **B.** Averaged amplitude of spontaneous EPSCs in neurons from trained rats is markedly higher than in neurons from the two control groups, which do not differ between each other. The averaged amplitude was calculated for each neuron from all spontaneous events. Values (mean±SE) represent the average of all cells in each group (**P<0.01). **C.** Cumulative-frequency distributions of all averages in the three rat groups. Each point represents the averaged sEPSC in one neuron. Note that the averaged EPSC amplitude appears to increase in most neurons in the trained group. Data was taken for 20 trained, 13 pseudo trained and 14 naïve rats. Figure modified from ref 61.

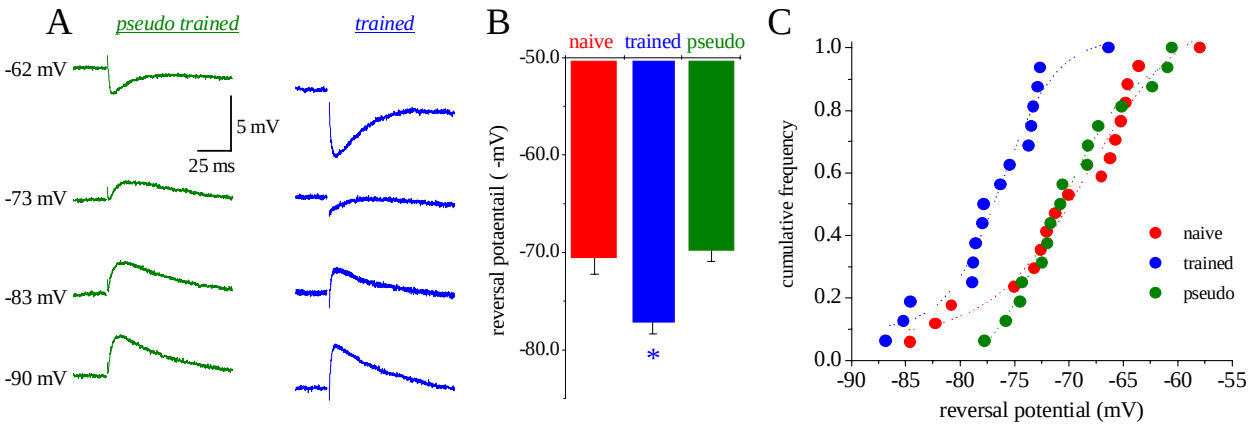

Figure 5. Learning-induced hyper-polarization of the fast IPSP's reversal. A. Typical recording at different membrane potentials in a neuron from a pseudo trained rat (left) and a neuron from a trained rat (right). The reversal potential of the IPSP in the control neuron is at -69 mV and in the trained neuron at -75 mV. Numbers on left of traces note the holding membrane potential. **B.** Averaged values of the IPSP's reversal potential in the three experimental groups (N = naïve, T = trained, P = pseudo trained). This value is significantly lower for the neurons taken from trained rats (*p<0.01). Values represent mean ± SE. **C.** A cumulative frequency graph comparing the reversal potentials of the fast IPSP in neurons from controls versus trained rats. Each point represents the reversal potential in one neuron. Notably, the curve for the trained group is shifted smoothly leftwards relative to the controls.

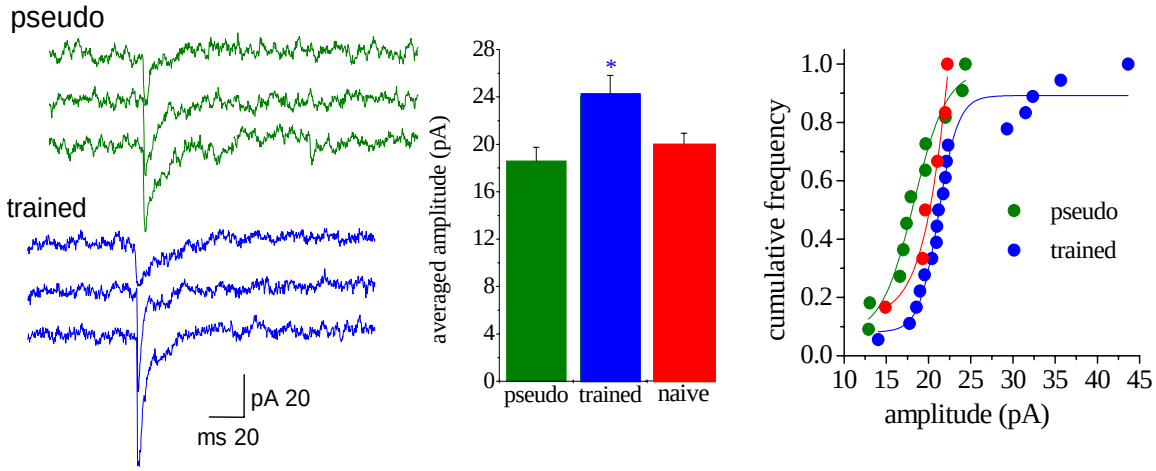

Figure 6. Learning-induced enhancement of $GABA_A$-mediated currents. A. Miniature inhibitory synaptic events in a neuron from a pseudo trained and a neuron from a trained rat at holding potential of -60 mV, recorded in the presence of TTX (1 uM), DNQX (20 uM) and APV (50 uM), four days after rule learning. Note the marked differences in the IPSCs amplitudes between the neurons. In these recording conditions, application of the $GABA_A$ blocker, BMI (10 µM), abolished all miniature events, indicating that only IPSCs were recorded. **B.** Averaged median of miniature events in neurons from trained rats is significantly higher than in neurons from the pseudo-trained groups. The median was determined for each neuron from all spontaneous events. Values (Mean ± SE) represent the average of all cells in each group (*P<0.05). **C.** Cumulative-frequency distributions of event averages of the three groups. Each point represents the average sIPSC in one neuron. The averaged sIPSC appears to increase in most neurons recorded in the trained group. Data was taken for 14 trained, 10 pseudo trained and 6 naïve rats. Figure modified from ref 61.

the epileptic-like activity. Using theoretical analysis of network models, Golomb and colleagues have discovered that if the excitatory-to-excitatory synaptic coupling is increased, a substantial enhancement in inhibition is needed to prevent the appearance of such epileptic discharge [50].

Learning-induced modifications in inhibitory synaptic transmission

Activity-induced enhancement of inhibitory synaptic transmission has been shown in several brain regions of the mammalian brain [51, 52, 53, 54]. Such long-lasting plasticity of GABAergic synaptic transmission is crucially dependent on calcium entry into the post-synaptic neuron (for review, see [55]). Both pre and post-synaptic mechanisms are implicated in the process. For example, activity-induced enhancement in the number of $GABA_A$ receptors was shown in the hippocampus after kindling [56] and enhanced GABA release was shown after BDNF application [57]. In addition, activity-induced shift in the reversal potential of Cl^- currents toward positive levels was shown in CA1 hippocampal neurons [58]. Thus, such long-term modification is suggested to be mediated by modulation of a chloride co-transporter. Indeed, inhibition of the potassium-chloride co-transporter, KCC2, occluded the shift [58]. Learning was also shown to trigger an increase in inhibitory synaptogenesis and the GABA content of inhibitory synapses [59].

Olfactory discrimination rule-learning results with long-lasting enhancement of inhibitory synaptic transmission onto proximal dendrites of these pyramidal neurons. Such enhancement is mediated by a strong hyperpolarizing shift in the reversal potential of fast inhibitory post synaptic potentials ([60], Figure 5) and by enhancement of the amplitudes of spontaneous inhibitory synaptic currents (sIPSCs, see Figure 6A, B). Similar to miniature excitatory synaptic events, the increase in mIPSCs averaged amplitude was apparent throughout the neuronal cell population ([61], Figure 6C).

CONCLUSIONS

Training in a particularly difficult olfactory-discrimination task results with acquisition of the skill to perform superbly in this very complex task. Such skill acquisition, termed ‘rule learning’ or ‘learning set’, is accompanied by profound long-lasting biophysical modification in most elements of pyramidal neurons populations in the relevant brain areas area.

Ample evidence indicates that at the cellular level, learning-induced long-term modifications occur in the three components controlling neurons activation: the excitatory synaptic drive, mainly mediated by glutamate receptors, the intrinsic neuronal excitability, and synaptic inhibition mediated by $GABA_A$ receptors.

Such profound, wide spread, modifications are manifested in transfer of the relevant neuronal networks into ‘learning mode’. This state allows the animal to perform complex learning tasks rapidly and efficiently while maintaining the network stability.

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