Pause and rebound: sensory control of cholinergic signaling in the striatum

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Cholinergic interneurons have emerged as one of the key players controlling network functions in the striatum. Extracellularly recorded cholinergic interneurons acquire characteristic responses to sensory stimuli during reward-related learning, including a pause and subsequent rebound in spiking. However, the precise underlying cellular mechanisms have remained elusive. Here, we review recent advances in our understanding of the regulation of cholinergic interneuron activity. We discuss evidence of mechanisms that have been proposed to underlie sensory responses, including antagonistic actions by dopamine, recurrent inhibition via local interneurons, and an intrinsically generated membrane hyperpolarization in response to excitatory inputs. The review highlights outstanding questions and concludes with a model of the sensory responses and their downstream effects through dynamic acetylcholine receptor activation.

Introduction

When an animal is confronted with a salient sensory event, it is faced with two fundamental questions. The first involves selecting an appropriate response to the sensory stimulus [1]. This problem is best solved by learnt or innate stimulus–response associations. The second question is whether the animal directly contributed to the sensory event in a causative way [1,2]. The ability to learn how to manipulate the environment from previous experience greatly extends the animal's repertoire of goal-directed behaviors. Both stimulus–response and action–outcome associations are probably mediated by related mechanisms of reinforcement learning in the basal ganglia [1–3]. Tonically active neurons (TANs) in the striatum, the major input nucleus of the basal ganglia, have received considerable attention, because they are known to exhibit prominent responses to salient sensory events during behavioral conditioning. These neurons are widely believed to be cholinergic interneurons and have emerged as one of the key players controlling network functions in the striatum in the healthy and diseased brain [4–11]. This review focuses on recent advances in our understanding of how spike firing in cholinergic interneurons is regulated by intrinsic cellular and network dynamics and their potential contributions during different behavioral conditions.

Cellular characteristics of TANs

The cellular population within the striatum is dominated by the principal medium spiny neurons (MSNs). The *in vivo* membrane potential of MSNs is characterized by large amplitude fluctuations between a very hyperpolarized and a more depolarized state during which action potentials are elicited infrequently [12]. Most of the phasically active neurons (PANs) encountered in extracellular studies are believed to correspond to this neuron class, although some fast-spiking interneurons may also contribute [13]. By contrast, cholinergic interneurons are more depolarized with a membrane potential of approximately –60 mV and usually exhibit tonic spike discharge [14–16] due to intrinsic pacemaker mechanisms that persist *in vitro* even in the absence of synaptic inputs [17,18]. Because of this tonic activity pattern, a relatively broad spike waveform, and their sparse distribution, it has been widely accepted that extracellularly recorded TANs correspond to cholinergic interneurons [14,16,19].

The first direct evidence to support this hypothesis was provided recently when TANs recorded juxtacellularly in the anesthetized rat were immunohistochemically identified as cholinergic interneurons (Figure 1a) [13]. The small number of TANs exhibited very diverse activity patterns, ranging from tonic regular spiking to phasic bursting activity. A similarly broad range of spiking patterns of cholinergic interneurons was recently described *in vivo* in a study using an intracellular recording technique (Figure 1c) [20]. *In vitro*

Glossary

Classical conditioning: repetitive pairing of a neutral sensory stimulus (i.e., without any intrinsic meaning; conditioned stimulus) with a positive (e.g., food) or aversive stimulus (e.g., air puff).
Extracellular recording: recording of spike activity of one or several neurons with an electrode (either metal or glass pipette) close to the cell.
Instrumental conditioning: commonly, pairing of a neutral sensory stimulus (i.e., without any intrinsic meaning) with a reward (e.g., food) on the condition that the animal correctly performs a certain motor response.
Intracellular recording: traditionally, recording of the membrane potential of a neuron with the tip of a glass electrode inside the cell (sharp microelectrode). Today, patch-clamp pipettes are often used to record the membrane potential intracellularly in the whole cell configuration.
Juxtacellular filling: if an extracellular glass electrode contains a dye and is close enough to the cell, then it is possible to fill the neuron with the dye. This allows subsequent morphological identification of the recorded neuron.
Phasically active neuron (PAN): extracellularly recorded neurons mainly from the primate striatum that exhibit spike activity in bursts, frequently with long phases of silence in between.
Tonically active neuron (TAN): extracellularly recorded neurons mainly from the primate striatum that exhibit tonic spike activity without long phases of silence.

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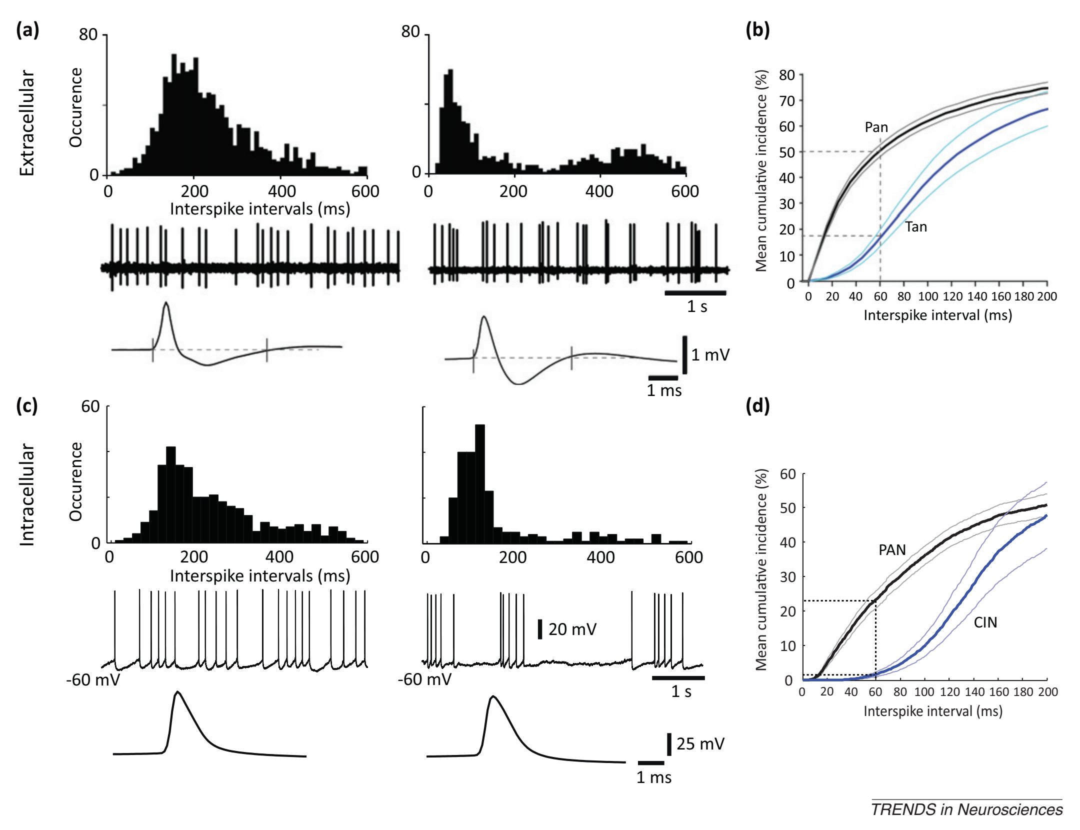

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Figure 1. Electrophysiological properties of cholinergic interneurons *in vivo*. **(a)** Two examples of extracellular recordings from tonically activated neurons (TANs) in a urethane-anesthetized rat. These were filled juxtacellularly and subsequently identified as cholinergic interneurons by immunohistochemical markers. The tonic activity (middle) and the broad spike waveforms (bottom) are indicative of cholinergic interneurons. The distribution of the interspike intervals (top) shows differences in the activity pattern of TANs: one has a classical unimodal distribution, whereas the other shows a bimodal distribution indicative of more rhythmic firing (reproduced, with permission, from [13]). **(b)** The mean cumulative distribution of interspike intervals over a large population of extracellular recordings shows that TANs tend to have far fewer short interspike intervals than phasically active neurons (PANs; contains both morphologically identified medium spiny neurons and fast-spiking interneurons; reproduced from [13]). **(c)** Example intracellular recordings of electrophysiologically identified cholinergic interneurons (CINs) in a urethane-anesthetized rat (data from neurons recorded in [20]). One neuron exhibited regular tonic activity (left), whereas another neuron fired rhythmically (right). The very broad intracellular spike waveform is shown for both neurons (bottom). **(d)** The mean cumulative distribution of interspike intervals over a large population of intracellular recordings (PANs contain both electrophysiologically identified medium spiny neurons and fast-spiking interneurons; data reanalyzed from [15]). Taking into account a bias of extracellular recording towards more active neurons and potential variations in the anesthetic regime between studies, this shows the same trend as the results from the extracellular recording study.

cholinergic interneurons can autonomously maintain diverse activity patterns [17,21–23]. However, more phasic activity patterns of cholinergic interneurons *in vivo* tend to be entrained to the slow-wave activity in afferent networks [20]. This suggests that the interaction of cell-intrinsic pacemaker mechanisms [24] and synaptic drive determine the spike output pattern of cholinergic interneurons.

A common observation of recent *in vivo* studies [13,20] is that putative cholinergic interneurons emit considerably fewer spikes at short intervals than PANs do (Figure 1b,d), although cholinergic interneurons exhibited higher average spiking rates in both studies. The main reason for the absence of rapid spiking is the strong spike afterhyperpolarization (AHP) in cholinergic interneurons [22]. This feature may therefore set cholinergic interneurons apart from other neurons in the striatum. It is likely that neurons classified as TANs largely correspond to cholinergic interneurons in most studies, depending on the exact criteria used. However, for clarity we distinguish between results from extracellular and intracellular recording studies and refer to the recorded neurons as TANs and cholinergic interneurons, respectively, throughout this review.

Behavioral conditions for sensory responses in TANs

Unlike most PANs, TANs recorded in the primate striatum exhibit prominent responses to sensory events during behavioral tasks (Figure 2) [25,26]. In general, these sensory responses consist of three components: initial excitation followed by relative quiescence, often called the pause, that is terminated by increased excitation [19,26,27]. The general view presented in the literature is that most TANs acquire sensory responses only after extensive training involving many pairings of the stimulus with a food or liquid reward [26]. Therefore, it was generally accepted that sensory responses of TANs were mainly signaling the occurrence of those stimuli that had become reliable predictors of reward [26,28]. However, some TANs respond to stimuli even before conditioning [26,29]. Increasing the salience of the stimulus (e.g., by increasing the volume of a sound [26]), increased the responsiveness of these TANs. Furthermore, single TANs acquired responses to a conditioned stimulus within 10 min, rather than over days [26]. In more recent studies, when various visual stimuli were associated with different reward probabilities and presented at random, TANs responded to all stimuli,