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Research report

Phase-dependent activity of neurons in the rostral part of the thalamic reticular nucleus with saccharin intake in a cue-guided lever-manipulation task

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ABSTRACT

Neurons in the rostral part of the thalamic reticular nucleus (rTRN) receive somatosensory and motor information and regulate neural activities of the thalamic nuclei. Previous studies showed that when activity in visual TRN neurons is suppressed prior to the visual stimuli in a visual detection task, the performance of the task improves. However, little is known about such changes in the rTRN preceding certain events. In the present study, we performed unit recordings in the rTRN in alert rats during a cue-guided lever-manipulation task in which saccharin was provided as a reward. Changes in neural activity during saccharin intake were observed in 56% (51 of 91) of the recorded neurons; the firing rates increased in 21 neurons and decreased in 23 neurons. Seven neurons both increased and decreased their firing rates during saccharin intake. Changes in firing rates during the reward-waiting stage between task termination and saccharin intake were also observed in 73% (37 of 51) of the neurons that responded to saccharin intake. Increased activity during saccharin intake did not correlate with increased activity during lever-manipulation or activity during the reward-waiting stage. However, decreased activity during saccharin intake was correlated with activity during the reward-waiting stage. These results suggest that rTRN neurons have phase-dependent changes in their activity and regulate the thalamic activities. Furthermore, the decreased activity of rTRN neurons before reward may contribute to refine somatosensory and motor information processing in the thalamic nuclei depending on the status of mind such as expectation and attention.

1. Introduction

The thalamic reticular nucleus (TRN) consists of GABAergic neurons that regulate sensory thalamic nuclei that process visual (McAlonan et al., 2000, 2008; Halassa et al., 2014; Kimura, 2014; Wimmer et al., 2015), auditory (McAlonan et al., 2000; Yu et al., 2009; Kimura, 2014; Wimmer et al., 2015), somatosensory (Shosaku et al., 1984; Crabtree, 1999; Hartings et al., 2000) or gustatory information (Hayama et al., 1994). TRN neurons also project to motor (Cicirata et al., 1990; Guillery et al., 1998; Pinault and Deschênes, 1998; Lam and Sherman, 2015) and limbic (Gonzalo-Ruiz and Lieberman, 1995; Lozsádi, 1995) thalamic nuclei. Although it is well established that the TRN plays a critical role in regulation of thalamic activity during sleep (Steriade and Llinás, 1988; Cox et al., 1997; Crabtree, 1999; Magnin et al., 2010; Halassa et al., 2014), it is not fully understood when and how the activity of TRN neurons changes in freely moving animals during wakefulness.

The TRN regulates the gain of the thalamus, which relays sensory inputs to the cortex (Crick, 1984; Halassa et al., 2014;

Abbreviations: ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; PB, phosphate buffer; PSTH, peristimulus time histogram; SD, standard deviation; SEM, standard error of the mean; TRN, thalamic reticular nucleus; rTRN, rostral part of the thalamic reticular nucleus.

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Wimmer et al., 2015). In a visual detection task, the activity of the TRN neurons projecting to the visual thalamic nucleus was suppressed before the visual stimuli, and as a result, the task performance was improved (Halassa et al., 2014; Wimmer et al., 2015). Such a mechanism for improving sensory information processing could be applicable to other systems, such as the somatosensory and motor systems.

The rostral part of the TRN (rTRN) includes somatosensory and motor sectors (Shosaku et al., 1984; Cicirata et al., 1990; Lam and Sherman, 2015). The rTRN receives projections from multiple cortical areas including the medial prefrontal cortex (mPFC), the orbitofrontal cortex (OFC), and the anterior cingulate cortex (ACC) (Cornwall et al., 1990; Çavdar et al., 2008). In studies of task-related tastant stimuli as reward for task performance, neural activity is modulated before intake of the reward in the mPFC (Pratt and Mizumori, 2001; Totah et al., 2009; Petykó et al., 2009), the OFC (van Duuren et al., 2007; Pennartz et al., 2011), and the ACC (Totah et al., 2009). These neural modulations preceding stimuli may control the rTRN and/or may be controlled by the rTRN. However, it is still unclear whether the activity of rTRN neurons changes in a period preceding a reward stimulus and, if it does, how the activity during the reward stimulus correlates with the preceding changes in activity.

In the present study, we recorded single-unit activity from rTRN neurons in alert rats during the ingestion of saccharin, which was provided as a reward in a cue-guided lever-manipulation task. We examined whether neural activity in the rTRN changes during saccharin intake, and we addressed the question of whether neural activity during the phase of expectation prior to saccharin delivery was related to neural activity during saccharin intake.

2. Results

2.1. Classification of the phases of neural activity

Putative TRN and thalamo-cortical neurons have narrow and wide spike waveforms, respectively (Lewis et al., 2015). We defined the neurons with spikes with a half-width shorter than 200 μs as TRN neurons (Fig. 1A and B). We recorded 91 rTRN neurons in 17 trained rats during a cue-guided lever-manipulation task to obtain saccharin solution. In this task, a pure-tone cue sound for 1 s was presented while the lever located in the center position. If the rat pushed the lever within 1.5 s after the cue onset, the cue sound stopped, and 1 s after, the rat received 5 mM saccharin solution in the mouth from a spout connected to a syringe pump as a reward (Fig. 1C). The total rate of the cue sound-evoked lever-press was 60%. The level of consciousness affects neural activities in the TRN (Marks and Roffwarg, 1993; Crabtree, 1999; Halassa et al., 2014). Therefore, we didn't analyze the trials in which the rat ignored the sound cue. For each neuron, a peristimulus time histogram (PSTH) with a bin size of 100 ms was obtained by averaging approximately 50 trials in which the rat successfully performed the task. The reward onset was set at 0 s in the PSTHs, which were generated from −4 to 4 s. In this study, baseline was obtained from the pre-reward period (−4 to −3 s), which was used in the analysis (Fig. 1C). Each PSTH was then summed to determine the mean PSTH for the 91 neurons. The mean PSTH showed increases in the firing rate around the onset of the lever manipulation (Fig. 2A). A subsequent decrease in firing rate was observed after saccharin intake. These findings suggest that neural activity in the rTRN varies in response to not only saccharin stimuli but also lever manipulation. To evaluate the changes in activity in individual neurons, we classified the rTRN neurons according to their temporal changes in firing rates.

To accurately identify the phases in which neural activity was modulated, the firing rate of each neuron was transformed into a Z-score (Fig. 2B). The Z-score was calculated from neural activity recorded during the baseline from 4 to 3 s before the reward onset (see the Section 4). Fig. 2C shows the number of neurons with a Z-score >3 or <−3 in each bin. For example, at 1 s before the reward onset, the firing rate increased significantly (Fig. 2A; $P < 0.01$, paired t-test, vs. baseline) and the Z-scores were greater than 3 for 29 neurons (Fig. 2C). In contrast, 0.8 s after the reward onset, the firing rate decreased significantly (Fig. 2A; $P < 0.001$, paired t-test, vs. baseline) and the Z-scores were lower than −3 for 27 neurons (Fig. 2C). As shown in Figs. 1C, 2B, and C, we divided the task into 3 phases (see the Section 4).

Phase I was defined as the lever-manipulation stage. Many neurons increased their activity during this phase. Phase II was the reward-waiting stage. The number of neurons demonstrating an increase in their firing rate in this phase was comparable to those demonstrating a decrease. The stage of saccharin intake was defined as Phase III. In this phase, some neurons showed an immediate transient increase in their firing rate after saccharin delivery. In addition, during the consumption of the saccharin solution, some of the neurons showed increases and/or decreases in activity. In each phase, if the Z-score of at least 2 consecutive bins was greater than 3 or less than −3, we considered it as a significant increase or a decrease in neural activity, respectively.

2.2. Neural subtypes and their profiles

We found that 51 of 91 neurons demonstrated a significant change in activity during Phase III. We divided these 51 neurons into 3 types (Fig. 2D). The first type demonstrated an increase in activity during Phase III (I neurons, n = 21). The second type demonstrated a decrease in activity during Phase III (D neurons, n = 23). The third type demonstrated both increases and decreases in activity during Phase III (B neurons, n = 7). There remained 40 neurons that did not demonstrate a significant change in activity during Phase III (N neurons; Fig. 2D). For the most part, N neurons did not change their activities during Phase I and Phase II; therefore, we did not perform additional analysis on these N neurons (Table 1).

The mean Z-score and typical examples for each type of neuron are shown in Fig. 3. In I neurons, the mean Z-score increased not only during Phase III but also during Phases I–II (Fig. 3A). The activity of 57% and 71% of I neurons significantly increased during Phase I and Phase II, respectively (Table 1). In D neurons, the mean Z-score decreased during Phase II and then drastically decreased after saccharin delivery (Fig. 3B). The activity of 70% of D neurons decreased during Phase II, whereas only one neuron showed an increase in activity during Phase II (Table 1). The temporal profile of B neurons resembled a mixture of I neurons and D neurons. The mean Z-score of B neurons increased during Phase I, and then, the mean Z-score increased and decreased during Phase III (Fig. 3C). Some B neurons showed increased and/or decreased activity during Phase I and/or Phase II (Table 1).

Thus, 68% (19 of 28) of I and B neurons also showed an increase in activity during Phase II. To assess the relationship between the activity during Phase II and the extent of the increase in activity during Phase III, the highest Z-scores during Phase III were plotted against the mean Z-scores during Phase II in I and B neurons. However, there was no correlation between these measures (Fig. 4A; $R^2 = 0.08$). Meanwhile, 57% (17 of 30) of D and B neurons showed a decrease in activity during Phase II. There was a positive correlation between the neural activity during Phase II and the extent of the decrease in activity during Phase III in D and B neurons (Fig. 4B; $R^2 = 0.57$, $P < 0.001$, Pearson's correlation coefficient test). In addition to the increase in activity during Phase II, 64% (18 of 28) of I