Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Implications for the thalamic reticular nucleus in impaired attention and sleep in schizophrenia

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ARTICLE INFO

Article history:
Received 12 May 2016
Received in revised form 12 July 2016
Accepted 15 July 2016
Available online xxxx

Keywords:
Inhibition
Optogenetics
Schizophrenia
Attention
Spindles
Sleep

ABSTRACT

The thalamic reticular nucleus (TRN) is an inhibitory shell positioned between the thalamus and the cortex. It is uniquely situated to modulate the flow of sensory information from the surroundings to the cortex as well as influencing ongoing cortical activity by modulating cortico-thalamo-cortical transmission. Although the thinness, architecture and location of the TRN deep in the brain has previously made this a difficult structure to study, novel optical and genetic tools have allowed for more precise targeting of this area. Recent research has implicated a role for the TRN in attention and sleep. Interestingly, impairments in attention and sleep resulting from TRN perturbation are strikingly similar to the clinical deficits observed in schizophrenia. This review aims to discuss recent evidence for the role of TRN in attention and sleep born from optogenetic work and connect these findings with those clinically observed in schizophrenia.

1. Introduction

Schizophrenia, a primary psychotic disorder, is a severe mental illness that affects a person's cognition, emotions, and general way of relating to others. It is typically hallmarked by hallucinations, delusions, thought disorder, attentional deficits, apathy, and often disturbed sleep. The thalamus represents the gate through which sensory information from the outside world is relayed to the cortex. In addition, higher order thalamic nuclei connect various brain regions, thereby playing an important role in modulating and supporting ongoing cortical processing. Deficits in thalamic function have long been suggested to explain a substantial number of the symptoms seen in patients with schizophrenia (Ferrarelli and Tononi, 2011; Pergola et al., 2015; Pratt and Morris, 2015). Enveloping a large portion of the thalamus is an inhibitory shell made of gamma-amino-butyric-acid- (GABA)-ergic neurons, the thalamic reticular nucleus (TRN) (Ferrarelli and Tononi, 2011). It provides the major inhibitory input to the thalamus and represents a powerful mechanism to modulate thalamic activity, thereby influencing both information flow from the periphery to the cortex as well as ongoing cortical processing. Because the TRN is a thin, shell-like structure located deep in the brain that is being passed by both cortical and thalamic fibers, its direct manipulation has been difficult in the past. Recent studies have overcome these issues using viral approaches allowing for neuronal labeling based on anatomical connectivity in combination with genetic and optical tools. These studies have shed light on various functions of the TRN, including a role for the TRN in sensory gating, attention and sleep. Here, we focus on recent evidence linking thalamic inhibition and its disruption to attentional deficits and disturbed sleep patterns observed in schizophrenia.

2. TRN architecture and connectivity

The structural organization and connectivity within the thalamocortical network places the TRN in a position to modulate information flow between thalamus and cortex. TRN forms a shell-like structure wrapped around the dorsal thalamus and contains at least seven sectors (five sensory, one motor, and one limbic) which are topographically organized (Guillery et al., 1998; Pinault, 2004; Ferrarelli and Tononi, 2011; Pratt and Morris, 2015). Each sector receives afferents from corresponding cortical and thalamic neurons and projects back to the thalamic nuclei by which it is innervated (Ferrarelli and Tononi, 2011). In addition to receiving excitatory projections from thalamocortical and corticothalamic neurons, the TRN also receives monoaminergic and cholinergic projections from the brainstem and GABAergic projections from the basal forebrain (Ferrarelli and Tononi, 2011).

By inhibiting primary sensory thalamic nuclei TRN can directly modulate sensory input from the periphery on the way to the cortex. In

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http://dx.doi.org/10.1016/j.schres.2016.07.011
0920-9964/

general, TRN neurons do not seem to project back to the thalamocortical neurons they receive input from, suggesting an open-loop connection. This type of circuit is postulated to facilitate lateral inhibition, which may allow TRN cells to modulate thalamocortical cells in such a way as to amplify relevant information to cortical areas while reducing distracting information (Pinault, 2011; Pratt and Morris, 2015). In addition, the innervation of higher order thalamic nuclei by the TRN allows influencing cortico-thalamocortical information flow, giving this nucleus a central role within brain circuits controlling higher order processing and cognitive function.

3. TRN and attention

Based on location and connectivity, Francis Crick hypothesized already a role for the TRN in attention in 1984 (Crick, 1984). Lesioning studies conducted in the 1990s demonstrated that ablation of the TRN causes impairment in attention, suggesting a role for the TRN in this essential cognitive function (Bucherelli et al., 1993; Weese et al., 1999). The major limitation to these studies is the lack of spatial/structural specificity given the thin shape of the TRN and its close proximity to the dorsal thalamus. Later pioneering work performed by McAlonan et al. (2008) in monkeys allowed for more specific study of TRN neurons. These studies linked shifts in visual attention with change in activity as well as increase in C-Fos levels in TRN neurons, implicating TRN circuitry involvement in attention. Although more spatially specific, these studies were not able to demonstrate a causal link between TRN circuitry and behavior. Genetic and optogenetic techniques have allowed researchers to overcome both of these limitations by allowing for the selective manipulation of TRN neurons in behaving mice.

Two such studies combined multi-electrode recordings with optogenetics in order to record and manipulate TRN cells during attentional tasks. Optogenetics offers many advantages to studying the TRN - providing good spatial and temporal resolution as well as enabling thalamocortical and corticothalamic axons to stay intact during TRN manipulation. In the first study, Halassa et al. (2014), recorded TRN neurons during a visual detection task and found a reduction in firing rate in visual thalamus-projecting neurons but not in limbic thalamus-projecting cells just before stimulus presentation, suggesting that the sensory thalamus specifically is modulated by the TRN during attentional engagement to enhance sensory processing. Going a step farther, the authors utilized excitatory or inhibitory opsins to bi-directionally manipulate TRN activity. They found that driving or inhibiting the spiking of these neurons led to either decrease or increase in behavioral performance, respectively, further demonstrating the causal role for TRN neurons in attentional performance (Halassa et al., 2014).

To address the role of the TRN in cortex mediated, top-down sensory selection, Wimmer et al. (2015) utilized a similar set of optogenetic techniques while employing a novel two-alternative forced-choice task in which mice selected between conflicting auditory and visual stimuli on a trial-by-trial basis. High- or low-frequency filtered white noise was used to instruct the mice whether it was a visual or auditory trial. Consistent with human studies on task-switching, the authors found that there was a cost to switching attention between modalities as the visual detection threshold was higher in cross-modal compared to single modality trials. This cost remained even when the conflicting stimulus was randomly omitted, suggesting that the cost was the result of a top-down process. The PFC-dependence of the task was demonstrated through optogenetic inactivation experiments. Disruption of PFC activity in the VGAT-ChR2 mouse, where the light-activated ion channelrhodopsin-2 is expressed under vesicular GABA transporter promoter (VGAT), specifically decreased cross-modal performance but had no impact on single modality trials. Importantly, they found that manipulation of the sensory cortex did not cause impaired performance in the cross-modal task, but manipulation of the visual thalamus (lateral geniculate nucleus, LGN) did, indicating that this top-down influence occurred at the level of the thalamus, rather than cortex. To further characterize the locus of this top-down process, the authors used retrograde lenti-viruses to specifically tag visual TRN (visTRN) neurons. They found that the firing of these neurons were reduced when mice were to attend to the visual stimuli and increased when they were to attend to auditory stimuli. Using chloride photometry in the LGN, a proxy for GABAergic inhibition at the population level, the authors were able to demonstrate that visTRN activity controls visual thalamic gain through feedforward inhibition. This study introduced the TRN as the mediator of top-down attentional processes in sensory selection (Wimmer et al., 2015).

Ahrens et al. (2015) also employed a set of genetic and optogenetic tools to study the TRN's role in top-down attentional processes, specifically, guiding and switching attention. This team removed the receptor tyrosine kinase ErbB4 in somatostatin (SOM)-positive cells, resulting in a deletion of ErbB4 largely limited to the TRN. They then examined these mutant mice in a two-alternative forced choice paradigm in which mice had to select among competing sensory inputs, including identifying a target sound among distractor tones (a single modality task) and responding to light cue while ignoring sound (a cross-modality task). By utilizing a combination of these tasks, Ahrens et al. (2015) were able to engage both feature detection as well as attentional switching. In mutant mice, the performance in the single modality task was enhanced, whereas performance in the cross-modality task was impaired. This suggests that loss of ErbB4 in the TRN leads to enhanced feature detection but impaired attentional switching. Utilizing optogenetic approaches to individually excite corticothalamic and thalamocortical projections, the team identified that loss of ErbB4 in SOM-positive TRN neurons causes selective strengthening of the excitatory synapses driven by cortical inputs (Ahrens et al., 2015).

Most recent evidence corroborating the role of the TRN in attention comes from a study utilizing a mouse model of human disease. In humans, PTCHD1 deletion is associated with ADHD, autistic traits and intellectual disability (Chaudhry et al., 2015). In mice, PTCHD1, a sonic hedgehog receptor, expression is restricted to the TRN during development and continues to be TRN-enriched throughout life. Deletion results in diminished TRN excitability and reduced performance on a visual detection task in the presence of distractors. The authors of this study showed that the ADHD symptoms in PTCHD1 KO mice precisely map onto TRN dysfunction. Deleting PTCHD1 selectively from the TRN replicates the attention deficit and hyperactivity found in the full KO, but not other disease-related behavioral phenotypes. In addition, pharmacological rescue of TRN biophysical dysfunction, which was determined by whole cell recordings in slice, also selectively rescued ADHD-related behaviors in the full KO (Wells et al., 2016).

In summary, the use of genetic and optogenetic strategies in these studies allowed for the selective manipulation of TRN neurons and demonstrated a causal effect of TRN neuronal modulation on performance on attentional tasks. Moreover, these studies demonstrate a role for the TRN in top-down controlled selection of specific sensory stimuli and raises the possibility that what could appear as a deficit in top-down attentional performance might in fact result from defective TRN function.

4. Schizophrenia and attention

Attentional impairment has long been recognized in patients with schizophrenia. Interestingly, the early conception of schizophrenia as “dementia praecox,” or a premature dementia, identified cognitive dysfunction, including attentional impairment, as the core feature of schizophrenia. Since that time, many studies have highlighted the impaired attention in patients with schizophrenia when compared to both normal controls as well as controls with other mental illnesses. Furthermore, among cognitive deficits, the supporting evidence for perturbed attention in schizophrenia has been the most robust (Elvevag et al., 2000; Nuechterlein et al., 2004; Shen et al., 2014). There has been some heterogeneity in this research, including the

Please cite this article as: Young, A., Wimmer, R.D., Implications for the thalamic reticular nucleus in impaired attention and sleep in schizophrenia, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.07.011