Medical Hypotheses 84 (2015) 47–52

Contents lists available at ScienceDirect

Medical Hypotheses

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

Elevated striatal dopamine attenuates nigrothalamic inputs and impairs transthalamic cortico-cortical communication in schizophrenia: A hypothesis

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ARTICLE INFO

Article history:
Received 12 July 2014
Accepted 11 November 2014

ABSTRACT

Schizophrenia has been found to involve source-monitoring deficits, whereby perceptions that result from self-initiated motor output become attributed to outside sources. One example of this phenomenon are the so called passivity experiences, such as delusions of control, during which the individual feels that own actions are controlled remotely by someone else. To explain these phenomena, it has been proposed that this illness involves efference copy failure. In other words, brain mechanism that prepare perceptual processes for the sensory consequences of self-initiated actions are impaired leading to their misattribution and to psychosis. In earlier work, it was argued that efference copy failure in schizophrenia is related to thalamic abnormalities. Namely, the thalamus can be thought of as a hub for cortico-cortical interactions, and these transthalamic cortico-cortical interactions were found to play a part in internal motor monitoring. Cortico-cortical communication via the thalamus can be impaired in a number of ways. For example, one way to impair these interactions is by interfering with the ability of the thalamus to display bursts of firing. As the burst firing mode in the thalamus requires a preceding period of prolonged hyperpolarization (100 ms), one way to reduce the burst propensity of thalamic neurons is to interfere with the ability to display prolonged hyperpolarizations. In this paper, we argue that elevated striatal dopaminergic activity in schizophrenia attenuates nigrothalamic GABAergic inputs, and thereby reduces burst propensity of the mediodorsal (MD) thalamic nucleus in schizophrenia, with the ultimate result of reduced transthalamic cortico-cortical communication, relative disconnection between functionally associated cortical areas and to psychosis. Conversely, dopamine D2 receptor blockers (antipsychotics) may help restore nigrothalamic GABAergic inputs, thereby increasing the burst propensity in the thalamus.

Introduction

It has long been known that schizophrenia, and psychosis in particular, likely involve dopaminergic mechanisms [1]. In addition, accumulating evidence has implicated the thalamus in the pathophysiology of this illness [2]. The purpose of this brief theoretical paper is to attempt to integrate these two lines of inquiry. Namely, in earlier reviews [3–9], it was argued that psychosis involves an impairment in transthalamic cortico-cortical interactions. As such interactions are important for internal motor monitoring [10], their impairment could result in a failure of internal motor monitoring mechanisms, which could in turn lead to a disintegration of perceptual and cognitive processes [11], such as is typical of schizophrenia [12].

In the neuroscientific literature, the terms efference copies or corollary discharges have been used to denote internal motor monitoring mechanisms. It has long been argued that efference copy failure is a core feature of schizophrenia [13], with the consequence that sensory inputs that result from self-initiated actions are misattributed to sources other than oneself (i.e., source-monitoring deficits) [14]. Indeed, there is now experimental evidence that schizophrenia involves (1) efference copy failure [15], (2) impaired transthalamic cortico-cortical interactions [16], and (3) that this illness is associated with source monitoring deficits [17–25]. The following section will discuss the importance of the thalamus in cortico-cortical communication and, more specifically, in the transmission of efference copies between cortical areas. Subsequent sections will then address how elevated striatal dopamine can indirectly impair transthalamic cortico-cortical interactions, and thereby lead to efference copy failure and psychosis.

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http://dx.doi.org/10.1016/j.mehy.2014.11.014
0306-9877/

Higher order thalamic relays

Traditionally, the thalamus has been viewed as a relay for inputs from non-cortical sources on their way to the cortex. However, seminal work of Sherman and Guillery suggests that this is the case for only some parts of the thalamus, which they termed first order nuclei (FO) [10] (Fig. 1). One example of a FO nucleus is the lateral geniculate nucleus (LGN), which relays retinal inputs to the primary visual cortex (V1). The term FO nucleus is appropriate in this case, as the relayed information has not been processed by any cortical area prior to reaching V1. This is in contrast to higher order relays (HO), which receive their main inputs from cortical sources and then relay these inputs to other cortical areas. One example of a HO relay is the mediodorsal (MD) nucleus, which is implicated in the pathophysiology of schizophrenia [27]. In general, the HO relays transmit information that has already been processed by at least one cortical area prior to reaching the HO relay.

The distinction between the FO nuclei and the HO relays is not arbitrary but is based on morphological and neurophysiological evidence. Before discussing this evidence, it first has to be pointed out that inputs to the thalamus, regardless of their source, can be subdivided into two categories, the driver and the neuromodulatory inputs. The driver inputs present the main information route, while the neuromodulatory inputs modify how the information is relayed (more on this later). For example, the retinal inputs to the LGN are the driver inputs to this nucleus, while inputs from the parabrachial region are neuromodulatory. There are a number of criteria that distinguish driver and neuromodulatory inputs. First, driver inputs to a thalamic nucleus are less numerous. For example, 7% of inputs to the LGN arrive from the retina, while the parabrachial inputs constitute 30% of all inputs. Additionally, driver inputs have larger terminals that are more proximal to the cell soma, thicker axons, utilize ionotropic glutamate receptors and produce larger excitatory post-synaptic potentials (EPSP's). Importantly, available evidence also suggests that driver inputs, regardless of their source, have branches that also innervate lower motor centers in the central nervous system. To use retinogeniculate inputs as an example, these inputs actually branch and innervate the superior collilulus in the midbrain that controls eye movements.

In contrast, neuromodulatory inputs to the thalamus have smaller and more distal terminals, they utilize a variety of neurotransmitters, as well as metabotropic and ionotropic receptors; they produce smaller post-synaptic potentials. The distinction between drivers and modulators is important, as it informs our understanding of the nature of the information that arrives in the thalamus for relay to the cortex. For example, if we focus on numbers of inputs only and do not consider the origin of the driver inputs to the LGN, we could be misled into thinking that parabrachial inputs to this nucleus are more important for its function than the retinogeniculate inputs, which constitute only 7% of the inputs. Thus, not all inputs to the thalamus are equal and paying attention to the origin of the main or driver inputs is of potential importance in elucidating patterns of information processing in thalamocortical circuits.

The driver inputs to the HO thalamic relays (such as the MD nucleus) arrive from the cortex and are relayed back to the cortex. More specifically, these driver inputs originate from axonal branches of layer V cortical neurons, which also innervate lower motor centers in the brain stem and the spinal cord. Thus, the HO nuclei, functionally speaking, may be concerned with relaying copies of cortical motor instructions to those lower motor centers (i.e., efference copies). Indeed, inactivating the MD nucleus was found to block corollary discharge signals in primates [28]. In contrast to transthalamic cortico-cortical links via the HO nuclei, direct cortico-cortical links reside entirely in the cortex [10].

The mediodorsal nucleus and schizophrenia

In earlier reviews, we have argued that the reported reduced cell numbers and volumes of the MD and the pulvinar nuclei in schizophrenia [2] are consistent with proposals that this illness involves efference copy failure, as they both are major HO nuclei. In the rest of this paper, the focus will be on the MD nucleus for two reasons: (1) It is a major recipient of nigrothalamic inputs and (2) it is interconnected with the prefrontal cortex (PFC), the hypofunction of which has long been implicated in schizophrenia [29]. It should be noted, however, that the pulvinar nucleus also sends some projections to the PFC [29]. It is possible that the hypofunction of the PFC in schizophrenia could be related to abnormalities in the MD nucleus, which is its main subcortical partner.

The MD thalamic nucleus can be subdivided into two portions, based on cytoarchitectonic differences [29]. The medial component is composed of larger cells and is known as magnocellular (MDmc) and a lateral component composed of smaller cells (parvocellular or MDpc). The MDmc component tends to project to the medial and the orbitofrontal PFC, while the MDpc projects to the lateral PFC. Another lateral portion of the nucleus, the pars paralamellaris, that is located between the MDpc and the internal lamina, tends to project to the frontal eye fields (FEF). Despite these differences in connectivity, each component of the MD nucleus projects to more than one PFC region. The MD nucleus, on the other hand, is the main subcortical recipient of PFC inputs.

Schizophrenia involves a marked cell and volume loss in the MD nucleus (40% and 25% loss, respectively) [30–32]. These abnormalities did not appear to be attributable to antipsychotic medications [31]. Moreover, the neuronal loss was reported to be restricted to the MDpc and the pars paralamerralis portions [33]. Thus, one way to think about the MD nucleus is as a partner to the PFC, that serves as a conduit that informs wider cortical regions about the ongoing efferent motor instructions issued to lower motor centers [34]. Its pathology in schizophrenia may, therefore, result in impaired internal motor monitoring and in a reduced ability to recognize oneself as an agent, which could in turn contribute to the so called passivity experiences in this illness, such as the delusions of control.

The reasons for the cell loss in the thalamus in schizophrenia are currently unknown. However, Stevens reported that schizophrenia involves gliosis in the thalamus [35], which is suggestive of a central nervous system insult. As of yet, this finding has not been replicated, but this author is not aware of any attempts to do so. Additionally, gliosis is somewhat difficult to determine, and this issue may simply require further studies. One possibility for how such an insult to the thalamus could occur, in some individuals with this illness, is cannabis use, which has been reported to have thalamotoxic effects [36]. This longitudinal neuroimaging study found that cannabis use in adolescents at familial risk for schizophrenia is associated with increased risk of developing this illness, as well as with volume loss in the thalamus.

Thus, volume loss in the thalamus, and more specifically its HO nuclei, may be related to deficits in cortico-thalamo-cortical circuitry in some individuals with schizophrenia. Another contributing factor to deficits in transthalamic cortico-cortical communication in psychosis may be a relative failure of neuromodulatory mechanisms in the thalamus to support such interactions. In the following sections, we will turn to a potential mechanism whereby elevated striatal dopamine in schizophrenia indirectly impairs the function of the MD nucleus. However, it is first necessary to discuss two possible thalamocortical relay modes, the burst and the tonic firing modes.