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Case Report

NEW INSIGHTS INTO THE MECHANISM OF RAPHE NUCLEUS CONTROL OF COGNITION AND BEHAVIOUR: INTERACTION WITH DENDRITIC AND T CELLS

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ABSTRACT

The raphe nucleus in the brain i.e dorsal and median raphe nucleus is the main source of serotonin (5-HT), an important brain chemical in regulating cognition and behavior. The raphe nucleus is well connected neuronally to medial prefrontal cortex, limbic system and also hippocampus. Signal integration in pyramidal neurons is exerted at various cellular levels, with a key role played by the large apical dendrites. These are highly enriched in serotonergic receptors. There is now evidence showing a direct pathway from the retina to the raphe nucleus suggesting that optic stimulation may directly influence dorsal raphe nucleus neurons (DRN). 5-HT receptors located on optic afferent terminals can exert pre-synaptic inhibition of retinocollicular input and direct electrical stimulation of raphe nucleus. Serotonin in the DRN exhibits a diurnal rhythm that is influenced by sleep waking cycle and light dark cycle. On the other hand, Dendritic cells (DC) are capable of activating T cells. DCs take up and sequester 5-HT in lysosomal vesicles for subsequent release. Because DCs are specialized to stimulate naive T cells and 5-HT is postulated to be taken up by T cells, 5-HT released from DCs may modulate T-cell function. It appears that sequestration of 5-HT from neurons to DC and T cells and vice versa following optical stimulation of raphe nucleus leads to a regulatory effect on cognition and behaviour.

Key Words: *Cognition, Raphe Nucleus, Pre-Frontal Cortex, Serotonin, Dendritic Cells, T Cells*

INTRODUCTION

The raphe nuclei have a vast impact upon the central nervous system (Adell *et al.*, 2002). Many of the neurons in the nuclei are serotonergic; i.e., contain 5-HT, a type of monoamine neurotransmitter. The raphe nuclei are distributed near the midline of the brainstem along its entire rostro-caudal extension. The serotonergic neurons are their main neuronal components, although a proportion of them lie in subdivisions of the lateral reticular formation. They develop from mesopontine and medullary primordia, and the resulting grouping into rostral and caudal clusters is maintained into adulthood, and is reflected in the connectivity. The dorsal raphe nucleus (DRN) of the mesencephalon is a complex multi-functional and multi-transmitter nucleus involved in a wide range of behavioral and physiological processes. Numerous studies demonstrate that the DRN receives a wide range of inputs including afferents from the locus coeruleus, the lateral habenula, several midbrain areas including the substantia nigra, and the peri-aqueductal gray, as well as fibers from the hypothalamus and the medial prefrontal cortex. The retina sends axons to the DRN which is a retino-raphe projection. Previous studies showed that the DRN received a direct retinal input, which consisted of a small number of retinal ganglion cells (RGCs), some of which exhibited alpha-like morphology (Foote *et al.,* 1978 and Shen and Samba, 1994). Fite and colleagues continued this line of work and reported a substantial number of DRN-projecting RGCs, with both small and large soma sizes (Fite *et al.,* 1999) and suggested that these cells arose from the non-image forming component of the retina (Fite *et al.,* 2003). Intrinsically photosensitive retinal ganglion cells (ipRGCs) are considered the primary retinal component mediating non-image forming functions and these cells project to various visual and non-visual nuclei including lateral geniculate nucleus (LGN) (Provencio *et al.,* 2002 and Hattar *et al.,* 2002) suprachiasmatic nucleus (SCN), intergeniculate leaflet

(IGL) of the LGN complex, and olivary pretectal nucleus (Morin *et al.,* 2003; Sollars *et al.,* 2003; Dacey *et al.,* 2005 and Baver *et al.,* 2008). In this review we evaluate the influence of retina on raphe nuclear levels of 5-HT and its sequestration into DC and T cells.

General Anatomical and Functional Characteristics of 5ht System

The 5-HT-producing neurons are mainly located in the brainstem raphe nuclei that have been shown to give rise to two major groups of neurons: (1) the superior group at the interface between the midbrain and the pons; and (2) the inferior group located more caudally in the pons (Azmitia *et al.,* 1995). They form the largest and complex neuro-chemical efferent system in the brain. The superior group of 5-HT neurons comprising the dorsal and median raphe nuclei is the source of projections to various sites in the forebrain as shown in Figure1.

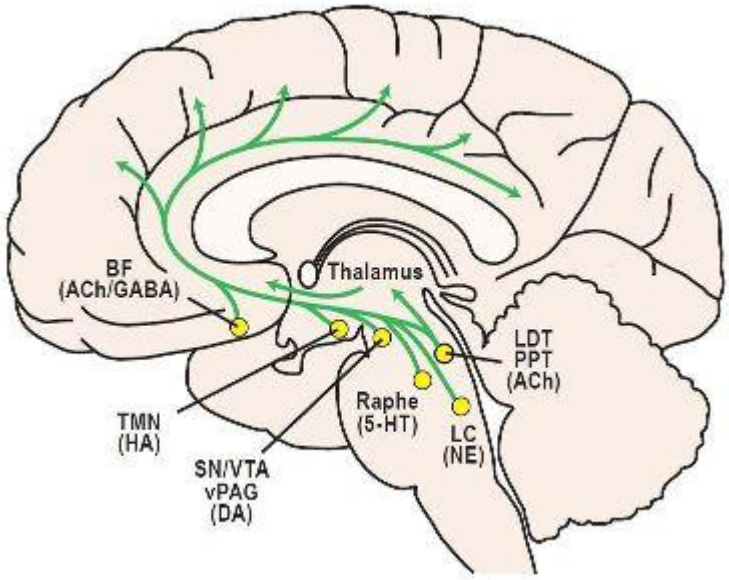

Figure 1: Neuronal pathways of raphe nucleus in the brain

Rich 5-HT innervations of telencephalic limbic regions such as the prefrontal and cingulate cortices, the amygdala, hippocampus, and ventral striatum, and diencephalic structures, especially the hypothalamus and thalamus, are found (Azmitia *et al.,* 1995 and Bentivoglio *et al.,* 1993). The dorsal and median raphe nuclei differentially innervate the forebrain regions. For instance, the dorsal raphe nucleus provides projections primarily to the amygdala and ventral striatum, whereas the median raphe nucleus preferentially innervates the prefrontal and cingulate cortices and the hippocampus. The least levels of 5-HT fibers are seen in the motor regions of the frontal lobe (Murphy *et al.,* 1998). The inferior group of 5HT-containing neurons sends abundant descending spinal projections.Therefore, determining the morphological and physiological properties of DRN-projecting RGCs will provide much needed information about the type of retinal information processing performed by the DRN. The prefrontal cortex is involved in an array of higher brain functions that are altered in psychiatric disorders. Serotonergic neurons of the midbrain raphe nuclei innervate the prefrontal cortex and are the cellular target for drugs used to treat mood disorders such as the selective serotonin (5-HT) reuptake inhibitors (Abi-Saab *et al.,* 1999). Anatomical evidence supports the existence of projections from the medial prefrontal cortex (mPFC) to the dorsal raphe nucleus (DR). Pyramidal neurons of the mPFC co-express postsynaptic 5-HT (1A) (inhibitory) and 5-HT (2A) (excitatory) receptors. Consistent with the above observations, the selective activation of both receptors in mPFC reduced and increased, respectively, the firing activity of DR 5-HT neurons and the 5-HT release in mPFC. Overall, these data indicate that the activity of the 5-HT

system is strongly controlled by the mPFC. Moreover, the activation of postsynaptic 5-HT1A receptors in the mPFC reduced the local release of 5-HT (Casanovas *et al.*, 1999) and the firing rate of dorsal raphe 5-HT neurons (Birkett and Fite, 2005). These data suggest that pyramidal neurons containing 5-HT 1A receptors may play a role in the distal control of serotonergic activity.The 5-HT system has been widely demonstrated to be involved in the pathogenesis of diverse mental illnesses such as obsessive compulsive disorder (OCD). Several lines of evidence suggest that the dysfunction of 5-HT neurotransmission, and especially an altered sensitivity of the 5-HT receptor subtype, may constitute a crucial factor in the patho-physiology of OCD.

Immune System and Central Nervous System

Immune cell function in the CNS has now been shown to extend beyond pathological conditions. Indeed, recent data have suggested key roles for immune cells in healthy brain functions, including psychological stress responses, spatial learning and memory, and adult neurogenesis (Kipnis *et al.*, 2004; Brynskikh *et al.*, 2008; Ziv *et al.*, 2006 and Goehler *et al.*, 1999). In reality there is abundant communication between the immune system and the CNS. For example, intraperitoneal injection of pro-inflammatory cytokines was shown to generate CNS-mediated sickness behaviour, which could be blocked by vagus nerve transaction (Akwa *et al.*, 1998). The beneficial effect of T cells specific for CNS-restricted self antigens has been observed in models of optic nerve injury, spinal cord contusion and stroke, as well as in other models of acute and chronic neurodegenerative conditions. T cells have been proposed to mediate their neuroprotective effect via the production of neurotrophins, the modulation of glutamate release by astrocytes and microglia, the regulation of innate immunity at the site of injury and other, as yet unexplored, mechanisms. These data suggest that there is a link between the neuroprotective function of T cells and their recognition of self antigens. The possible contribution of astrocytes to immune responses within the brain has been described in several settings, including those involving the targeted overexpression of cytokines such as TNF, IFN-α, TGF-β, IL-6, and IL-12 by astrocytes, which leads to chronic inflammation and progressive neurodegeneration (Pagenstecher *et al* 2000, Wyss-Coray *et al* 1997, Krishnamoorthy *et al.*, 2007). More recent studies analyzing mice in which the ability of astrocytes to participate in immune function is compromised through the specific loss of a cytokine receptor such as gp130 or reduced NF-κB signaling, have shown that this alters the course of immune responses in the CNS (Drogemuller *et al.*, 2008). Thus, in a mouse model of spinal cord injury, astrocyte-specific inhibition of NF-κB (which is necessary for the activation of many cytokine genes) resulted in a reduction in the number of reactive astrocytes in the CNS, in lower levels of chemokines, and in reduced infiltration of T cells and macrophages (Sofroniew, 2005). Consequently, this led to improved spinal cord healing. Future challenges include determining how individual cytokines, adhesion molecules, and chemokines produced by astrocytes influence the development of inflammation and the behavior of infiltrating immune cell populations.

Sequestration of 5-Ht from the Raphe Nucleus into Immune Cells and Vice Versa and Distribution into Discrete Brain Sites: A Novel Hypothesis

Several types of immune cells including B and T cells, granulocytes, macrophages, mast cells and dendritic cells are located within the meningeal structures of the brain. Although functional roles of these DRN-projecting ganglion cells remains unclear, there is evidence that DRN neurons respond to changes in the light and dark cycle (Nautiyal *et al.*, 2011 and Wolf *et al.*, 2009) and they are sensitive to phasic flashing light stimulation. There is a direct anatomical connection between the DRN and SCN (Filippova *et al.*, 2004 and Heym *et al.*, 1982). Furthermore, in addition to the conventional retino-hypothalamic tract (RHT) that provides luminance information necessary for entrainment, brief millisecond photo stimulation has been shown to be capable of inducing circadian phase shifts (Van Den Pol *et al.*, 1998 and Morin, 1999). All the members of the 5HT1 receptor subtype belong to the family of G protein-coupled receptors. They generally reduce adenylate cyclase activity, leading to decreased cyclic adenosine monophosphate (cAMP) production. The 5TH1A receptor represents a somato-dendritic autoreceptor on

the cell body of 5HT neurons in the brainstem raphe nuclei. Another subtype, the 5HT1B receptor and its human homolog, 5HT1D has been found to function as an autoreceptor on axon terminals (Arvanitogiannis and Amir, 1999). When activated, these two receptors attenuate the intrinsic firing of the raphe cells, thereby inhibiting 5HT release. The 5HT1A receptors have also been characterized at postsynaptic sites (Backstrom *et al.*, 1995 and Marek and Aghajanian, 1999). A significant amount of 5HT1B receptors are present on postsynaptic structures, although their function is still unknown (Sander-Bush and Mayer, 2001). Therefore, there could be a second pathway that conveys fast luminance changing signals to SCN. Dendritic cells (DC) are capable of activating T cells. DCs take up and can sequester 5-HT in lysosomal vesicles for subsequent release. Because DCs are specialized to stimulate naive T cells and 5-HT is postulated to be taken up by T cells, 5-HT released from DCs may modulate T-cell function (Eberl *et al.*, 2004). It appears that sequestration of 5-HT from neurons to DC and T cells following optical stimulation of raphe nucleus leads to a regulatory effect on memory and learning (Hornung, 2003 and Tyagi, 2012). The effect of T cells on the CNS might also be mediated via soluble cytokines that are released into the circulation. This raises the issue of the variability of blood–brain barrier permeability and how this influences the possibility of a peripheral T cell effect (Bird, 2005).

CONCLUSION

This study clearly suggests a novel mechanism for 5-HT sequestration and distribution in the brain after photo-stimulation. There is enough evidence showing a direct pathway from the retina to the raphe nucleus suggesting that optical stimulation may directly influence dorsal raphe nucleus neurons (DRN). 5-HT receptors located on optic afferent terminals can exert pre-synaptic inhibition of retinocollicular input and direct electrical stimulation of raphe nucleus. It is suggested that DCs take up and sequester 5-HT in lysosomal vesicles for subsequent release. Because DCs are specialized to stimulate naive T cells and 5-HT is postulated to be taken up by T cells, 5-HT released from DCs may modulate T-cell function. It appears that sequestration of 5-HT from neurons to DC and T cells and vice versa following optical stimulation of raphe nucleus leads to a regulatory effect on cognition and behavior.

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