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Review

The neurobiology of thalamic amnesia: Contributions of medial thalamus and prefrontal cortex to delayed conditional discrimination

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ABSTRACT

Although medial thalamus is well established as a site of pathology associated with global amnesia, there is uncertainty about which structures are critical and how they affect memory function. Evidence from human and animal research suggests that damage to the mammillothalamic tract and the anterior, mediodorsal (MD), midline (M), and intralaminar (IL) nuclei contribute to different signs of thalamic amnesia. Here we focus on MD and the adjacent M and IL nuclei, structures identified in animal studies as critical nodes in prefrontal cortex (PFC)-related pathways that are necessary for delayed conditional discrimination. Recordings of PFC neurons in rats performing a dynamic delayed non-matching-to position (DNMTP) task revealed discrete populations encoding information related to planning, execution, and outcome of DNMTP-related actions and delay-related activity signaling previous reinforcement. Parallel studies recording the activity of MD and IL neurons and examining the effects of unilateral thalamic inactivation on the responses of PFC neurons demonstrated a close coupling of central thalamic and PFC neurons responding to diverse aspects of DNMTP and provide evidence that thalamus interacts with PFC neurons to give rise to complex goal-directed behavior exemplified by the DNMTP task.

Contents

1. Introduction

Focal lesions in medial thalamus are associated with global amnesia, affecting the ability to remember declarative information in multiple sensory modalities both before and after disease onset while sparing other cognitive functions measured by standard intelligence tests. Thalamic amnesia has been observed with tumors (McEntee et al., 1976; Williams and Pennybacker, 1954), strokes (van der Werf et al., 2003; von Cramon et al., 1985), trauma (Squire et al., 1989), and Wernicke–Korsakoff syndrome (WKS), a disease most commonly associated with thiamine deficiency in chronic alcoholics (Malamud and Skillicorn, 1956; Victor et al., 1989).

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The neurological basis of thalamic amnesia is uncertain. In a large cohort study of WKS Victor et al. (1989) observed a consistent correlation between amnesia and lesions damaging the medial mediodorsal nucleus (MD) and adjacent medial thalamic nuclei. Although all these cases also had mammillary body lesions, Victor et al. argued that MD was the critical site of pathology based on five other cases who recovered from the acute phase of Wernicke's disease with substantial mammillary body pathology but without memory impairment and without apparent medial thalamic damage. Contrary evidence has come from several well-studied amnesic cases of WKS with medial thalamic pathology largely sparing MD and with substantial damage to the mammillary bodies, mammillothalamic tracts, and anterior nuclei (Gold and Squire, 2006; Mair et al., 1979; Mayes et al., 1988). Studies of thalamic amnesia resulting from stroke or trauma has also provided conflicting evidence with some cases where the primary pathology appears to involve MD and adjacent medial thalamic nuclei (Gold and Squire, 2006; von Cramon et al., 1985; Squire et al., 1989; Tanji et al., 2003) and others where the primary pathology is ascribed to the mammillothalamic tracts or anterior nuclei or damage to both medial and anterior thalamic systems (Aggleton and Brown, 1999; Carlesimo et al., 2011; Krill and Harper, 2012; Pergola and Suchan, 2013; van der Werf et al., 2003).

Here we focus on the potential contributions of MD and adjacent M and IL thalamic nuclei. Clinical studies have associated infarcts damaging these nuclei with impairment of "executive" aspects of memory (Carlesimo et al., 2011; van der Werf et al., 2003). Lesion studies in animal models have confirmed that MD plays a role in memory and decision making (Mitchell and Chakroborty, 2013) and have provided evidence that combined damage to MD, as well as M and IL, can produce global impairment of delayed conditional discrimination consistent with human WKS (Sections 2–4 below). MD, M and IL are higher order thalamic nuclei that receive Class 1/driver and Class 2/modulator inputs from PFC, forming cortico-thalamocortical pathways thought to regulate transmission of information in neural networks involving PFC, parietal, and medial temporal cortices (Saalmann, 2014; Sherman and Guillery, 2002, 2011; Steriade et al., 1997). Thus lesions damaging these nuclei should affect the timing of activity in distributed neural networks thought to play a critical role in memory (Johnson and Knight, 2015; Staudigl et al., 2012; Watrous et al., 2015). Recent electrophysiological studies in our lab have confirmed an important role of central thalamus and PFC in delayed conditional discrimination and provided evidence that the "executive functions" of central thalamus and PFC reflect a fundamental concern with planning, actions, and action-outcomes that underlie complex intentional behavior (Section 5).

2. The post thiamine deficiency (PTD) model of the Wernicke–Korsakoff syndrome (WKS)

The PTD model first demonstrated a consistent correlation between lesions centered on the internal medullary lamina, involving MD and adjacent M and IL nuclei, and a pattern of behavioral impairment consistent with WKS: delayed conditional discrimination impairment in multiple sensory modalities coupled with a spared capacity for rule-based responding in serial reversal learning (Mair, 1994). Clinical studies have attributed WKS to thiamine (vitamin B1) deficiency most frequently in chronic alcoholic persons and associated this syndrome with bilateral lesions along the walls and floor of the third ventricle, periaqueductal areas of the midbrain, and the floor of the fourth ventricle (Malamud and Skillicorn, 1956; Victor et al., 1989), as well as signs of widespread cortical impairment in imaging studies (Pitel et al., 2012; Reed et al., 2003; Sullivan and Pfefferbaum, 2009).

Mair et al. (1985, 1988) developed the PTD model to examine chronic effects that outlast a subacute bout of thiamine deficiency, using existing methods to deplete thiamine rapidly by dietary restriction and daily pyrithiamine injections for about 2 weeks until rats reached a critical stage of impairment when thiamine deficiency was reversed by injection of a large dose of thiamine. This treatment produces a characteristic thalamic lesion centered on the internal medullary lamina, tissue loss in the mammillary bodies, signs of diffuse degeneration of thalamocortical projections, and localized loss of monoamine and amino acid neurotransmitters: pathological effects consistent with human WKS (Fig. 1; Langlais et al., 1987, 1988; Mair et al., 1985, 1988, 1989, 1991a,b). Subsequent studies provided evidence that PTD-induced lesions are caused by an excitotoxic response to elevated levels of extracellular glutamate associated with down regulation of astrocytic glutamate transporters that can be prevented by the noncompetitive NMDA antagonist dizocilpine (Hazell et al., 2001; Langlais and Mair, 1990; Langlais and Zhang, 1993; Robinson and Mair, 1992; Zhang et al., 1995). This apparent excitotoxic reaction occurs in the context of multiple metabolic and vascular consequences of thiamine deficiency related to oxidative stress, excitotoxicity, and cerebral inflammation (Hazell and Butterworth, 2009).

Behavioral analyses using directly comparable tasks have revealed a pattern of impairment in the PTD model consistent with human WKS (Fig. 2) that persists chronically for many months after restitution of nutritional status (Mair et al., 1988). Comparative neuropsychological studies have shown that WKS affects delayed conditional discriminations of sensory stimuli in multiple sensory modalities, including delayed matching (DM) or nonmatching (DNM) tasks in which subjects choose between two response alternatives based on stimulus information presented in a preceding sample trial (Aggleton et al., 1988; Oscar-Berman et al., 1992; Squire et al., 1988). WKS patients also make more errors to criteria learning two choice discrimination and serial reversal learning tasks, although they retain the ability to perform discriminations at criteria once learned and exhibit positive transfer across a series of reversal problems (Oscar-Berman and Zola-Morgan, 1980). PTD rats are likewise impaired in multiple sensory modalities performing two choice DM and DNM tasks (Knoth and Mair, 1991; Mair et al., 1985, 1988, 1991a; Mumby et al., 1995, 1999; Robinson and Mair, 1992) and in errors to criterion in discrimination and serial reversal learning (Mair et al., 1991b). Like WKS patients, PTD rats exhibit a spared capacity for rule-based responding shown by the abilities to perform discriminations at criterion once they have been learned and positive transfer across a series of reversal discrimination problems (Fig. 2). It should be noted that while these tasks allow for direct comparison of animal and human performance for functions spared and impaired by amnesia, they by no means represent the full range of cognitive functions affected by WKS (Butters and Cermak, 1980; Fama et al., 2012; Oscar-Berman, 2012; Talland, 1965).

3. Experimental studies of the PTD model

The PTD rat has three main claims to validity as a model of WKS: etiology associated with thiamine deficiency, symmetrical lesions involving mammillary bodies and medial thalamus and signs of broad thalamo-cortical degeneration (Fig. 1), and similar patterns of chronic behavioral impairment (Fig. 2). Both PTD and WKS have also been associated with lesions involving multiple systems in the brain including signs of diffuse cortical pathology that limit their utility for elucidating the contributions of specific nuclei or pathways to signs of memory impairment.

To determine the critical sites of pathology in the PTD model, we compared the effects of lesions selectively targeting different systems affected by PTD treatment. We found that medial thalamic lesions involving both MD and rostral IL, produced by either electrolytic radio frequency current or microinjection of excitotoxic

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