Neuroscience and Biobehavioral Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Anterior thalamic nuclei lesions and recovery of function: Relevance to cognitive thalamus

John C. Dalrymple-Alford[a,b,*], Bruce Harland[a], Elena A. Loukavenko[a], Brook Perry[a], Stephanie Mercer[a], David A. Collings[c], Katharina Ulrich[d], Wickliffe C. Abraham[d], Neil McNaughton[d], Mathieu Wolff[e,f]

[a] New Zealand Brain Research Institute, and Department of Psychology, University of Canterbury, Christchurch 8140, New Zealand
[b] Department of Medicine, University of Otago, Christchurch, New Zealand
[c] School of Biological Sciences, University of Canterbury, Christchurch, New Zealand
[d] Department of Psychology and Brain Health Research Centre, University of Otago, Dunedin, New Zealand
[e] University of Bordeaux, INCIA, UMR 5287, F-33400 Talence, France
[f] CNRS, INCIA, UMR 5287, F-33400 Talence, France

ARTICLE INFO

Article history:
Received 13 July 2014
Received in revised form 2 November 2014
Accepted 4 December 2014
Available online xxx

Keywords:
Thalamic amnesia
Enrichment
Spines
Retrosplenial
CA1
Cerebrolysin

ABSTRACT

Injury to the anterior thalamic nuclei (ATN) and their neural connections is the most consistent neuropathology associated with diencephalic amnesia. ATN lesions in rats produce memory impairments that support a key role for this region within an extended hippocampal system of complex overlapping neural connections. Environmental enrichment is a therapeutic tool that produces substantial, although incomplete, recovery of memory function after ATN lesions, even after the lesion-induced deficit has become established. Similarly, the neurotrophic agent cerebrolysin, also counters the negative effects of ATN lesions. ATN lesions substantially reduce c-Fos expression and spine density in the retrosplenial cortex, and reduce spine density on CA1 neurons; only the latter is reversed by enrichment. We discuss the implications of this evidence for the cognitive thalamus, with a proposal that there are genuine interactions among different but allied thalamo-cortical systems that go beyond a simple summation of their separate effects.

Contents

* Corresponding author at: University of Canterbury, Psychology, 20 Kirkwood Avenue, Christchurch 8041, New Zealand. Tel.: +64 3 364 2998; fax: +64 03 364 2181.
E-mail addresses: jc.dalrymple.alford@gmail.com, john.dalrymple-alford@canterbury.ac.nz (J.C. Dalrymple-Alford).

http://dx.doi.org/10.1016/j.neubiorev.2014.12.007
0149-7634/

1. Introduction

Diencephalic amnesia is associated with injury to thalamic nuclei and associated fibre tracts (Markowitsch, 1988; Kopelman, 2014). Recognised by clinical studies long before attention became focused on the hippocampal formation and medial temporal lobe, this subcortical pathology is increasingly viewed as an important field of study if we are to achieve a full understanding of the neuroanatomical basis of memory, and episodic memory in particular (Aggleton, 2014; Carlesimo et al., 2014; Child and Benarroch, 2013; Kopelman et al., 2009). Several thalamic structures within the diencephalon have been implicated, most commonly the mediodorsal nucleus (MD), the midline and intralaminar nuclei (ILN), the anterior thalamic nuclei (ATN), and the fibre pathways associated with these nuclei (Aggleton et al., 2011; Dillingham et al., 2014; Mitchell and Chakraborty, 2013; Pergola and Suchan, 2013; Savage et al., 2012; Vann, 2013). It is likely that human cases of amnesia involve damage to multiple thalamic sites and fibre tracts, some of which may affect many cognitive processes in addition to their influence on memory (Carlesimo et al., 2014; Carrera and Bogousslavsky, 2006; Cipolotti et al., 2008; Mennemeier et al., 1992; Nishio et al., 2014). Nonetheless, the bulk of human evidence for impaired recollection and episodic memory dysfunction (the hallmark of anterograde amnesia) most strongly implicates the ATN, the mammillary bodies (MB), and the mammillothalamic tract, a unique tract among limbic system neurocircuits because it provides a unidirectional link from the MB to ATN (Aggleton et al., 2011; Carlesimo et al., 2011; Harding et al., 2000; Van der Werf et al., 2003; Vann et al., 2009).

The variability of unintended brain injury to closely adjacent nuclei and tracts in people with diencephalic amnesia has naturally led to a variety of animal lesion models. These animal models aim to test a circumspect injury and thus identify the region most likely to cause human memory loss. As with the analysis of human cases, this evidence supports an influence on memory of injury to many thalamic nuclei. When highly localised lesions have been made to different limbic thalamic structures, the animal studies generally suggest selectivity for, or differences in, the type of memory that is affected (Alcaraz et al., 2014; Bailey and Mair, 2005; Burk and Mair, 1998; Burk and Mair, 1999; Chudasama et al., 2001; Corbit et al., 2003; Mair et al., 2003; Mitchell and Dalrymple-Alford, 2005; Mitchell and Dalrymple-Alford, 2006; Wolff et al., 2008). For example, Moreau et al. (2013) trained rats with either neurotoxic ILN lesions or ATN lesions in two discrimination learning tasks, using the water maze protocols devised by Packard and McGaugh (1992) in which one of two visual cues was present with one arbitrary cue attached to a submerged escape platform. Irrespective of the order of testing, Moreau et al. (2013) showed that only rats with ATN lesions experienced impaired acquisition of the spatial task, in which the fixed location of a hidden platform was guided by a redundant visual cue, whereas neither lesion impaired acquisition of the specific correct visual cue when spatial information was redundant (Fig. 1). Others have shown that both MD and ILN lesions impaired performance of a delayed matching task trained with retractable levers, producing delay-dependent (MD) and delay-independent (ILN) deficits, respectively (Bailey and Mair, 2005). By contrast, localised MD or ILN lesions did not affect a varying choice radial maze delayed non-matching task, which instead was impaired by ATN and hippocampal system lesions (Bailey and Mair, 2005; Mair et al., 2003).

These and other observations align with a growing body of literature that supports Aggleton and Brown's (1999) initial focus on the ATN as a key site for injury or disconnection that disrupts a functionally inter-dependent extended hippocampal system. Specifically, ATN injury often produces spatial and temporal memory deficits that overlap with those found after explicit hippocampal system injury (Aggleton, 2008; Aggleton et al., 2011; Aggelton and Nelson, 2014; Dumont and Aggleton, 2013; Wolff et al., 2006). Likewise, disconnection and electrophysiological studies show that interactions between the ATN, retrosplenial cortex and hippocampal formation support learning and retrieval of events linked with spatial and context-dependent information (Gabriel, 1993; Henry et al., 2004; Smith et al., 2004; Warburton et al., 2001).

2. The anterior thalamic nuclei (ATN)

This idea of an extended hippocampal system with the ATN as a nodal point in the exchange of both cortical and subcortical information relevant to episodic memory receives considerable support from anatomical descriptions of the neural connections of the ATN (Aggleton et al., 2010; Dillingham et al., 2014; Jankowski et al., 2013; Wright et al., 2013). The three subnuclei of the ATN have a substantial number of reciprocal connections with the subicular cortex of the hippocampus and with the prefrontal cortex. They also exert an influence through reciprocal connections with the different regions of the retrosplenial cortex, thereby making major contributions to serial connections across the extended circuit. An excellent summary of these and other ATN connections was provided by Jankowski et al. (2013) see also, Dillingham et al. (2014). Rather than a purely passive role, however, the ATN may provide a strategic influence on the hippocampal system, perhaps on the basis of the unique modulation made on the ATN by its connections with the MB and brainstem tegmental nuclei (Vann, 2013; see Fig. 2). In addition, the apparent segregation of information transfer to the ATN, both directly from the hippocampal formation and from the MB, as well as from the prefrontal cortex, suggests the potential for subcircuit specificity (Jankowski et al., 2013; Wright et al., 2013).

These descriptions imply that the ATN are a pivotal – and perhaps critical – node in the extended hippocampal system. Thus both lesion and neuroanatomical evidence is consistent with the fact that dysfunction of the ATN has multiple ramifications on the network of brain structures associated with episodic memory. Conversely, the multitude of overlapping pathways and connections across the extended hippocampal system may also permit a degree of functional redundancy across ATN neurocircuitry, and perhaps the extended system as a whole. Indeed, evidence that other structures are failing as a consequence of distal injury to the ATN, MTT and even the ventral tegmental nucleus of Gudden (Dumont et al., 2012; Dupire et al., 2013; Garden et al., 2009; Jenkins et al., 2004; Mendez-Lopez et al., 2013; Poirier and Aggleton, 2009; Reed et al., 2003; Vann, 2013; Vann and Albasser, 2009), raises an interesting question that is relevant to memory impairment associated with lesions to components of the extended hippocampal system and its related neurocircuitry. Can we reverse some of the seemingly permanent memory deficits produced by ATN lesions (and other system lesions)? That is, after ATN injury, can other cortical and subcortical structures retain neuroplasticity and so have the capacity to respond to suitable treatments?

3. Recovery of function after ATN lesions

The prospect of some recovery or sparing of function after thalamic injury may explain some of the variability in memory deficits evident after thalamic injury in humans (Carlesimo et al., 2014; Carrera and Bogousslavsky, 2006; Pergola and Suchan, 2013; Van der Werf et al., 2003). Even in the context of the Korsakoff syndrome, in which permanently impaired memory is regarded as the defining symptom, and loss of ATN neurons the most prominent feature (Harding et al., 2000), only 25% of patients show no

Please cite this article in press as: Dalrymple-Alford, J.C., et al., Anterior thalamic nuclei lesions and recovery of function: Relevance to cognitive thalamus. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2014.12.007