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New learning and memory related pathways among the hippocampus, the amygdala and the ventromedial region of the striatum in rats

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ABSTRACT

Background: The hippocampus, central amygdaloid nucleus and the ventromedial region (marginal division) of the striatum have been reported to be involved in the mechanism of learning and memory. This study aimed elucidating anatomical and functional connections among these brain areas during learning and memory.
Results: In the first part of this study, the c-Fos protein was used to explore functional connections among these structures. Chemical stimulation of either hippocampus or central amygdaloid nucleus results in dense expression of c-Fos protein in nuclei of neurons in the marginal division of the striatum, indicating that the hippocampus and the central amygdaloid nucleus might be functionally connected with the marginal division. In the second part of the study, the cholera toxin subunit B-horseradish peroxidase was injected into the central amygdaloid nucleus to observe anatomical connections among them. The retrogradely transported conjugated horseradish peroxidase was observed in neurons of both the marginal division and dorsal part of the hippocampus following the injection. Hence, neural fibers from both the marginal division and the hippocampus directly projected to the central amygdaloid nucleus.
Conclusion: The results implicated potential new functional and structural pathways through these brain areas during the process of learning and memory. The pathways ran from ventromedial portion (the marginal division) of the striatum to the central amygdaloid nucleus and then to the hippocampus before going back to the marginal division of the striatum. Two smaller circuits were between the marginal division and the central amygdaloid nucleus, and between the central amygdaloid nucleus and the hippocampus. These connections have added new dimensions of neural networks of learning and memory, and might be involved in the pathogenesis of dementia and Alzheimer disease.

1. Background

The learning and memory related brain regions include mainly the hippocampus, amygdala, prefrontal cortex, striatum and basal forebrain etc. (Han and Wu, 1997; Genoux et al., 2002; Packard and Knowlton, 2002). Evidences indicated that the hippocampus plays important roles in learning and memory (Han and Wu, 1997; Levitan and Kaczmarek, 1997). The dorsal and ventral hippocampus had different functions on a learning and memory task mediated by the dorso-lateral striatum (McDonald et al., 2006).

Abbreviations: AD, Alzheimer's disease; CTB-HRP, cholera toxin subunit B-horseradish peroxidase; CeA, central amygdaloid nucleus; MrD, the marginal division of the striatum; TMB, 3,3′,5,5′Tetramethylbenzidine.

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Bilateral damages to the hippocampus caused severe deficits in recent memory but did not affect long term memory. Memory was reported gradually becoming independent of the hippocampus as time passes after learning because memory gradually embedded in distributed brain network (Takehara et al., 2003).

The amygdale body is a large subcortical structure located in the rostromedial part of the temporal lobe and in front of the hippocampus. It is a heterogeneuos structure and made of basolateral, cortical and centromedial nuclear group. The central amygdaloid nucleus is a main body of the amygdale and was reported did not project to the striatum (Heimer, 1994), so we investigated the connections of the central amygdaloid nucleus (CeA) with the striatum and hippocampus in this study. The amygdala was shown to be involved in emotion, escape, learning and memory (Gallagher and Schoenbaum, 1999). Memory has been proved embedded in the brain networks (Takehara et al., 2003). When emotion and memories were processed simultaneously, the amygdala can modulate both the encoding and the storage of hippocampus-dependent memories (Phelps, 2004). The amygdala–hippocampal circuit contributes to the anticipation of aversive events (Hahn et al., 2010). The amygdala projected to widespread striatal domains and prefrontal cortex, and influenced complex behaviors (Roberts et al., 1992; Everitt et al., 1999; Everitt and Robbins, 2000; Fudge et al., 2002; Cho et al., 2013).

The striatum belongs to an extensive network with relation to the predictive value for optimizing behavior (Shohamy, 2011). A newly discovered subdivision consisted of fusiform neurons in the ventromedial margin of the striatum in the brains of the rat, cat, monkey and human was discovered and termed “the marginal division (MrD) of the striatum”. A variety of neuropeptides and receptors were found intensely expressing in the fusiform neurons of the MrD (Shu et al., 1988a, 1990) (Fig. 1).

The 5′-nucleotidase activity was densely expressed in the developing rodent MrD (Schoen and Graybiel, 1993). The pedunculopontine nucleus gave rise to massive afferent terminals in the MrD of the squirrel monkey (Lavoie and Parent, 1994). The MrD connected to the interstitial nucleus of the posterior limb of the anterior commissure (Shammah-Lagnado et al., 1999). The α_2-adrenergic receptors were more highly expressed in the MrD than the rest of the rat striatum (Talley, 1996). The MrD was suggested to be one of the five components of the ventral striatum (Heimer et al., 1995). The MrD was verified to play important role in learning and memory by Y-maze test, long-term potentiation and patch clamp in rats (Shu et al., 1999, 2003; Zeng et al., 1999). Learning and memory deficits were caused by a lesion in the marginal of the left putamen in the human brain (Shu et al., 2009). Cooperation between the hippocampus and the striatum was reported during episodic encoding (Sadeh et al., 2011).

Neural pathways among these memory related brain areas were explored by the combination of immunohistochemical localization of the c-Fos protein and cholera toxin subunit B-horseradish peroxidase (CTB-HRP) tract tracing methods in this study to reveal neural circuits uniting the hippocampus, the central amygdaloid nucleus (CeA), and especially the newly discovered MrD of the striatum to jointly contribute to learning and memory function of the brain.

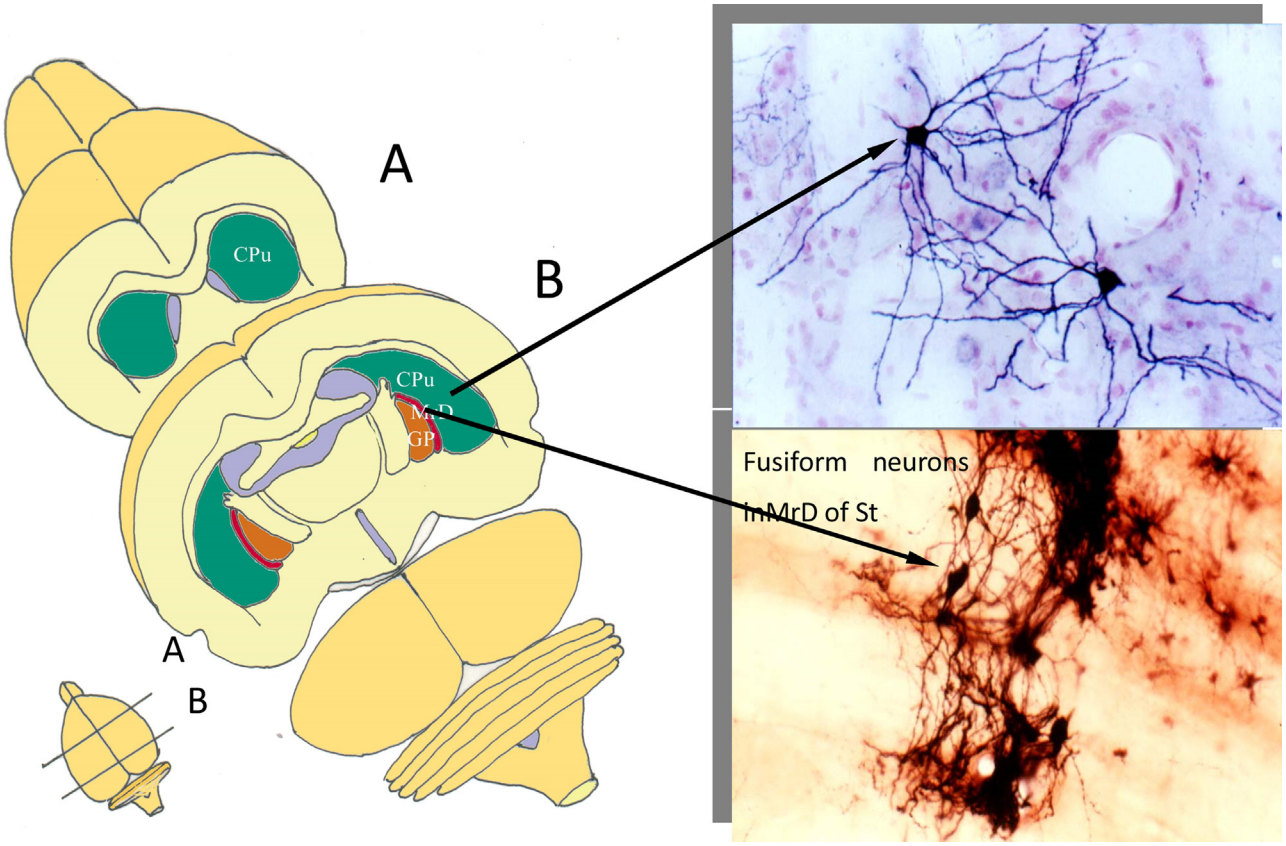

Fig. 1. The figure shows the location and cytoarchitectural characteristics of the MrD in the rat brain. The schemes on the left side represent frontal section pictures of the rat brain (shown in the lower left corner). The MrD is at the caudomedial edge of the CPu and rostrolateral to the globus pallidus. The PHA-L-labeled neuronal bodies in the caudoputamen are mostly of a round or triangular shape (shown in the upper right square). The MrD consists of a band of fusiform neurons labeled with PHA-L, which distinguishes the MrD from the rest of the caudoputamen and globus pallidus (shown in the lower right square). CPu, caudoputamen; GP, globus pallidus; St, striatum.