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MEDIAL PREFRONTAL CORTEX NEURONAL CIRCUITS IN FEAR BEHAVIOR

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Abstract—The medial prefrontal cortex (mPFC) has emerged as a key structure involved in the modulation of fear behavior over the past few decades. Anatomical, functional and electrophysiological studies have begun to shed light on the precise mechanisms by which different prefrontal regions regulate the expression and inhibition of fear behavior. These studies have established a canonical view of mPFC functions during fear behavior with dorsal regions selectively involved in the expression of fear behavior and ventral regions linked to the inhibition of fear behavior. Although numerous reports support this view, recent data have refined this model and suggested that dorsal prefrontal regions might also play an important role in the encoding of fear behavior itself. The recent development of sophisticated approaches such as large scale neuronal recordings, simultaneous multisite recordings of spiking activity and local field potentials (LFPs) along with optogenetic approaches will facilitate the testing of these new hypotheses in the near future. Here we provide an extensive review of the literature on the role of mPFC in fear behavior and propose further directions to dissect the contribution of specific prefrontal neuronal elements and circuits in the regulation of fear behavior. © 2013 Published by Elsevier Ltd. on behalf of IBRO.

Key words: medial prefrontal cortex, fear conditioning, fear extinction, neuronal circuits.

Contents

INTRODUCTION

The medial prefrontal cortex (mPFC) is known to be involved in the regulation of a broad range of behaviors including emotional behaviors (Fuster, 2008), and dysfunction of the mPFC has been related to psychiatric conditions such as post-traumatic stress disorders (PTSD) (Shin and Liberzon, 2010; Pitman et al., 2012). Because of the potential clinical implications of these findings, numerous animal studies have been conducted over the past decades in order to reveal the precise role of mPFC in the modulation of fear behavior. In the laboratory, learned fear behavior is often established using two simple forms of Pavlovian conditioning known as auditory fear conditioning and contextual fear conditioning (cued *versus* contextual fear conditioning). Auditory fear conditioning is a rapid and robust learning paradigm during which an animal learns to associate a previously neutral tone (conditioned stimulus, or CS) with a coincident aversive stimulus such as a mild footshock (unconditioned stimulus, or US). Contextual fear conditioning results from the association between the context and the US. Re-exposure to the tone or the conditioned context elicits an immobilization reaction called ‘‘freezing’’, a behavioral measure of the learned

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Abbreviations: AC, anterior cingulate cortex; BA, basal amygdala; BLA, basolateral amygdala; CB, calbindin; Ce, central nucleus of the amygdala; CeM, central amygdala; CR, calretinin; CS, conditioned stimulus; dACC, dorsal anterior cingulate cortex; ERK, extracellular-regulated kinase; IB, low-threshold spiking or intrinsic bursting; IL, infralimbic; LA, lateral amygdala; LFP, local field potential; LTP, long-term potentiation; LTD, long-term depression; mITC, medial intercalated amygdala neurons; mPFC, medial prefrontal cortex; MD, medio-dorsal thalamus; NIB, non-inactivating bursting; PL, prelimbic; PV, parvalbumin; PrCm, medial precentral cortex; RS, regular spiking ; SOM, somatostatin; US, unconditioned stimulus; vlPAG, ventro-lateral periaquaeductal gray.

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association. Inhibition of conditioned fear can be obtained if the animals are re-exposed to the tone or the conditioned context in the absence of the footshock, a new learning phenomenon called ''fear extinction''. In this review, we provide a detailed description of our current knowledge of mPFC functions related to conditioned fear behavior in rodents with a particular emphasis on the contribution of distinct mPFC regions, neuronal elements, and neuronal circuits. In the first section, we discuss the principal mPFC regions involved in the regulation of cued and contextual fear conditioning that have been identified based on lesion, pharmacological inactivation and activation, or histochemical studies. In the second section, we review the prefrontal neuronal and cellular mechanisms involved in the regulation of fear behavior. This includes a description of the main molecular mechanisms in the prefrontal cortex found to mediate conditioned fear behavior. Section two also contains a discussion of *in vivo* electrophysiological studies performed in behaving animals aimed at understanding how information in prefrontal neuronal circuits is generated, stored and transferred, both locally and in concert with other brain areas. Finally, in the last section we describe the fine anatomy and function of identified prefrontal neuronal elements in the context of conditioned fear behavior and how recently developed optogenetic strategies will be instrumental in proving a causal relationship between specific neuronal circuits and fear behavior.

STRUCTURAL ORGANIZATION AND FUNCTIONAL ROLE OF THE MPFC IN FEAR BEHAVIOR

Gross anatomy of the rodent mPFC

In rodents, the mPFC can be separated based on cytoarchitectonic and hodologic criteria in four distinct areas which, from dorsal to ventral, are the medial precentral cortex (PrCm) or medial agranular cortex (AGm), the anterior cingulate cortex (AC, dorsal and ventral parts), the prelimbic (PL) and the infralimbic (IL) cortices (Leonard, 1969; Krettek and Price, 1977; Guldin et al., 1981; Van Eden and Uylings, 1985; Ray and Price, 1992; Ongur and Price, 2000). In particular, the mPFC receives a strong input from the medio-dorsal thalamus (MD), with the medial segment of the MD projecting to the PL and IL, the lateral segment to both the PL and dorsal AC and the paralamellar segment contacting mainly the PrCm (Uylings and van Eden, 1990). These thalamic projections are mostly ipsilateral and terminate in cellular layers I and III (Krettek and Price, 1977; Groenewegen, 1988; Minciacchi and Granato, 1989; Kuroda et al., 1993). Besides these thalamic afferents, the mPFC receives inputs from numerous sub-cortical neuronal structures including the ventral tegmental area (Thierry et al., 1973), the basal ganglia (Groenewegen et al., 1997), the amygdala (Krettek and Price, 1977; McDonald, 1987, 1991; Shinonaga et al., 1994) and the hippocampus (Swanson, 1981; Jay et al., 1989). Notably, hippocampal glutamatergic inputs from the ventral CA1 and the subiculum terminate in mPFC cellular layers I and III and projections from the basolateral amygdala (BLA) preferentially contact PL and IL regions (Swanson, 1981; McDonald, 1987, 1991; Jay et al., 1989; Gigg et al., 1994). The mPFC also receives cortical projections originating from the paralimbic cortex (enthorinal and perirhinal cortices) that target the PL and IL, and from somatosensory and motor cortices that terminate in the dorsal prefrontal regions. The mPFC contains reciprocal projections to the MD, hippocampus, BLA, and basal ganglia where it participates in several cortico-striato-pallido-thalamo-cortical loops (Krettek and Price, 1977; Alexander et al., 1986, 1990; Terreberry and Neafsey, 1987; Groenewegen, 1988; Sesack et al., 1989; Alexander and Crutcher, 1990; Groenewegen et al., 1990; Takagishi and Chiba, 1991; Berendse et al., 1992; Alexander, 1994; McDonald et al., 1996; McDonald, 1998; Floyd et al., 2000, 2001; Vertes, 2004). The mPFC also projects directly to the ventro-lateral periaquaeductal gray (vlPAG), a neuronal structure involved in the genesis of freezing responses and conditioned fear behavior (Vianna et al., 2001; Gabbott et al., 2005). Finally the mPFC contains important intrinsic ipsilateral connectivity. Namely, the PL region projects to AC, the IL projects to both the PL and the dorsal part of AC. The mPFC also contains an overall homotopic contralateral connectivity (Beckstead, 1979; Audinat et al., 1988; Sesack et al., 1989).

Lesion and pharmacological inactivation/activation studies

The role of the frontal cortex in the modulation of fear behavior has long been discussed. An early evidence of mPFC involvement in learned fear can be traced back more than 50 years ago with experimental data showing that post-conditioning frontal lobotomy eliminates conditioned fear responses in rats and monkeys (Streb and Smith, 1955; Waterhouse, 1957; Maher and McIntire, 1960). More recently, lesions and inactivation have been used to evaluate the role of mPFC in the acquisition and extinction of cued and contextual fear conditioning in rodents. Because of conflicting results gathered using these techniques and for the sake of clarity, the main findings are first described in the text below and further summarized in Table 1. Q4

Pre- and post-training lesions of the dorsal mPFC, including AC and dorsal PL, enhanced cued and contextual fear conditioning (Morgan and LeDoux, 1995; Vouimba et al., 2000, but see Bissiere et al., 2008) and blocked cued and contextual fear extinction (Morgan and LeDoux, 1995). In addition, pre-training electrolytic or pharmacological lesions of the ventral mPFC, including the ventral PL and IL, had no effect on cued and contextual fear conditioning but selectively blocked extinction of cued fear conditioning (Morgan et al., 1993; Morrow et al., 1999b, but see Lacroix et al., 2000, and Fernandez Espejo, 2003). Post-conditioning lesions of the ventral mPFC including the ventral PL and IL produced somewhat inconsistent results as some studies reported blockade of cued fear expression or

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