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Priming locus coeruleus noradrenergic modulation of medial perforant path-dentate gyrus synaptic plasticity

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ABSTRACT

Priming phenomenon, in which an earlier exposure to a stimulus or condition alters synaptic plasticity in response to a subsequent stimulus or condition, known as a challenge, is an example of metaplasticity. In this review, we make the case that the locus coeruleus noradrenergic system-medial perforant path-dentate gyrus pathway is a neural ensemble amenable to studying priming-challenge effects on synaptic plasticity. Accumulating evidence points to a tyrosine hydroxylase-dependent priming effect achieved by pharmacological (nicotine and antipsychotics) or physiological (septal theta driving) manipulations of the locus coeruleus noradrenergic system that can facilitate noradrenaline-induced synaptic plasticity in the dentate gyrus of the hippocampus. The evidence suggests the hypothesis that behavioural experiences inducing tyrosine hydroxylase expression in the locus coeruleus may be sufficient to prime this form of metaplasticity. We propose exploring this phenomenon of priming and challenge physiologically, to determine whether behavioural experiences are sufficient to prime the locus coeruleus, enabling subsequent pharmacological or behavioural challenge conditions that increase locus coeruleus firing to release sufficient noradrenaline to induce long-lasting potentiation in the dentate gyrus. Such an approach may contribute to unravelling mechanisms underlying this form of metaplasticity and its importance in stress-related mnemonic processes.

1. Introduction

Prior experience can modulate subsequent capacity to learn. In particular, exposure to stress or conditions evoking anxiety can alter subsequent behavioural plasticity. Metaplasticity describes plasticity in the ability to induce subsequent synaptic plasticity (Abraham & Bear, 1996; Abraham & Tate, 1997). Priming phenomena in which an earlier exposure to a stimulus or condition alters subsequent induction of synaptic plasticity in response to a challenge stimulus or condition can be viewed as a form of metaplasticity. Stress-induced metaplasticity may have important implications for understanding behaviour (Schmidt, Abraham, Maroun, Stork, & Richter-Levin, 2013). In the current review, we explore priming of locus coeruleus noradrenergic - modulation of medial perforant path-dentate gyrus synaptic plasticity weeks later as an example of metaplasticity. This phenomenon was first reported for nicotine priming and challenge but likely reflects mechanisms that can be induced by any stimulus inducing locus coeruleus tyrosine hydroxylase expression combined with any challenge activating locus coeruleus firing. As such non-reward frustration, anxiety or stress may induce this form of metaplasticity.

The locus coeruleus, comprised of only approximately 1500 densely packed projection neurons bilaterally in the rodent brain, is the sole source of noradrenergic innervation of the mammalian forebrain, including the hippocampus and prefrontal cortex. The neurons of the locus coeruleus express tyrosine hydroxylase. Tyrosine hydroxylase is the rate-limiting enzyme in synthesis of catecholamines, including noradrenaline and dopamine. The roles of the locus coeruleus and its noradrenergic projections in attention, arousal, working memory and other aspects of cognition have been extensively investigated (for reviews see Ramos & Arnsten, 2007; Sara, 2009; Sara & Bouret, 2012). The noradrenergic system has been proposed as a target for treatment of cognitive dysfunction, for example in schizophrenia, attention deficit hyperactivity disor-

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der and Alzheimer's disease (for review see Arnsten, 2004; Arnsten & Jin, 2012; Chalermpalanupap et al., 2013; Harvey, 2009). The locus coeruleus expresses corticotrophin releasing factor (CRF) receptors and is strongly activated by stress (Page & Valentino, 1994; Valentino, Foote, & Aston-Jones, 1983). CRF-mediated activation of locus coeruleus may facilitate shifting of attention between diverse stimuli (Snyder, Wang, Han, McFadden, & Valentino, 2012). Moderate levels of noradrenaline release may enhance working memory and prefrontal cortical function via high affinity alpha-2 adrenoceptors but high levels of noradrenaline release during stress impair prefrontal cortical function via low affinity alpha-1 adrenoceptors and perhaps also beta-1 adrenoceptors (Birnbaum, Gobeske, Auerbach, Taylor, & Arnsten, 1999; Ramos & Arnsten, 2007; Wang et al., 2007). Impairment of prefrontal cortex structure and function by stress signalling pathways may contribute to mental illness (for review see Arnsten, 2009). Medial perforant path-dentate gyrus monosynaptic pathway is a reliable model to study mechanisms of mnemonic processing. Specifically, the medial perforant path plays a role in spatial information processing along with the dorsal hippocampus (Hargreaves, Rao, Lee, & Knierim, 2005; Hunsaker, Mooy, Swift, & Kesner, 2007; Naber, Witter, & Lopez da Silva, 1999). Lesioning of the medial perforant path impaired water maze learning (Ferbinteanu, Holsinger, & McDonald, 1999) and caused a path integration deficit (Van Cauter et al., 2013). N-methyl-D-aspartate (NMDA) receptors in the pathway are predicted to control the direction of plasticity change (Luscher & Malenka, 2012).

Nicotine delivered by tobacco smoking has long been associated with transient improvements in attention and cognitive function but has many adverse effects. Nicotine is the principal neuroactive alkaloid in tobacco and appears to be largely responsible for addiction to smoking (Jaffe & Kanzler, 1979; Pich et al., 1997; Pontieri, Tanda, Orzi, & Di Chiara, 1996; Stolerman & Jarvis, 1995). During abstinence from smoking, heavy smokers are reported to experience cognitive impairment (Abrous et al., 2002). Despite recognition of the liability for abuse and the harmful effects of nicotine, there continues to be interest in the potential for beneficial cognitive enhancing effects (Changeux et al., 1998; Everitt & Robbins, 1997; Levin, 2013; Robbins, McAlonan, Muir, & Everitt, 1997). Nicotine exposure induces persistent neuroplasticity by various mechanisms, including changes in the expression and sensitivity of nicotinic acetylcholine receptors in the midbrain dopaminergic neurons projecting to the dorsal striatum, ventral striatum and nucleus accumbens and prefrontal cortex (for review see Korpi et al., 2015). In addition, nicotine administration produces an intriguing priming effect on locus coeruleus neurotransmission that amplifies responses to subsequent nicotine challenge and enables induction of noradrenaline-dependent synaptic plasticity in the dentate gyrus of the hippocampus.

2. Nicotine priming up-regulates tyrosine hydroxylase expression and noradrenaline release

Acute, systemic administration of nicotine (0.4 mg/kg or 0.8 mg/kg) increased 2-amino-3-(3,4-dihydroxyphenyl)propanoic acid (DOPA) accumulation (a marker of catecholamine synthesis) in the rat nucleus accumbens, hypothalamus and hippocampus but not in several other regions including the frontal cortex (Mitchell, Brazell, Joseph, Alavijeh, & Gray, 1989). The increase in noradrenaline synthesis in response to nicotine appears to be specific to the locus coeruleus projections via the dorsal noradrenergic bundle (Mitchell, Brazell, Schugens, & Gray, 1990). Chronic, systemic nicotine administration (0.8 mg/kg/day) for 28 days further increased DOPA accumulation in the hippocampus in response to a subsequent challenge systemic administration of nicotine (0.4 mg/kg) (Mitchell et al., 1989). Thus chronic nicotine treatment enhanced the subsequent catecholaminergic responses to nicotine treatment in the hippocampus. Chronic nicotine treatment (0.8 mg/kg/day) for 28 days increased tyrosine hydroxylase expression in the hippocampus (Joseph et al., 1990). Subsequently, it was shown that a single, systemic dose of nicotine (0.8 mg/kg) increased tyrosine hydroxylase mRNA 2–6 days later in the noradrenergic locus coeruleus but not in the dopaminergic substantia nigra and ventral tegmental area (Mitchell, Smith, Joseph, & Gray, 1993). By 28 days after nicotine injection, an increase in noradrenaline release in response to systemic administration of a nicotine challenge (0.4 mg/kg) was detected. However, the nicotine priming did not increase the hippocampal release of noradrenaline in response to direct intrahippocampal administration of a nicotine challenge (250 μM) (Mitchell et al., 1993). This suggests that priming might augment nicotinic stimulation of locus coeruleus activity-driven norardrenaline release to a greater extent than it augments presynaptic nicotinic receptor-triggered release at noradrenergic terminals within the hippocampus. Why this is the case if the effect is dependent on tyrosine hydroxylase transport to the noradrenergic terminals, requires further investigation.

Together, these data suggest that nicotine increases tyrosine hydroxylase expression in the locus coeruleus and that there is subsequently a time-dependent anterograde transport of the tyrosine hydroxylase to the terminals of the locus coeruleus projections. The tyrosine hydroxylase reaches the hippocampus at least by 28 days and is accompanied by increased synthesis and release of noradrenaline in the hippocampus. Further studies are required to determine the time course of transport of tyrosine hydroxylase in greater detail. The effect on tyrosine hydroxylase expression and noradrenaline release in cortical regions, including the prefrontal cortex implicated in dysfunctions in selective attention and cognition in schizophrenia, has not been investigated but it might be hypothesised that tyrosine hydroxylase is also transported to the locus coeruleus terminals projecting to the cortex. Due to the longer distance to the prefrontal cortex, the tyrosine hydroxylase and the accompanying increase in capacity to release noradrenaline might be expected to arrive later than in the hippocampus. The role of nicotine-induced changes in locus coeruleus innervation of prefrontal cortex is an interesting avenue of research.

3. Role of locus coeruleus noradrenergic projections in cognitive function

The locus coeruleus, and in particular the dorsal noradrenergic bundle to which the nicotine-induced increase in noradrenaline synthesis appears to be more specific (Mitchell et al., 1990), has been associated with attention. Early work proposed an attentional theory of dorsal noradrenergic bundle function (Mason & Iversen, 1977, 1978a, 1978b, 1979). Similarities between the effects of dorsal noradrenergic bundle lesions and hippocampal lesions on filtering out irrelevant and redundant information suggested that the role of the dorsal noradrenergic bundle on selective attention may, in part, be mediated by modulation of hippocampal function (Tsaltas, Preston, & Gray, 1983) and that the behavioural inhibitory functions of the dorsal noradrenergic bundle may involve projections to the septohippocampal system (Salmon, Tsaltas, & Gray, 1988). A role in behavioural response inhibition continues to be supported by more recent findings (for review see Bari & Robbins, 2013) that electrophysiological activity of locus coeruleus neurons is strongly modulated by drugs, such as methylphenidate and atomoxetine (Bari & Aston-Jones, 2013; Devilbiss & Berridge, 2006), known to improve response inhibition and suggested to improve communication within and between brain regions