Abstract Neuromodulation of frontal-executive function is reviewed in the context of experiments on rats, monkeys and human subjects. The different functions of the chemically identified systems of the reticular core are analysed from the perspective of their possible different interactions with the prefrontal cortex. The role of dopamine in spatial working memory is reviewed, taking account of its deleterious as well as facilitatory effects. Baseline-dependent effects of dopaminergic manipulation are described in rats on an attentional task, including evidence of enhanced function following infusions of D1 receptor agonists into the prefrontal cortex. The precise nature of the cognitive task under study is shown to be a powerful determinant of the effects of mesofrontal dopamine depletion in monkeys. Parallels are identified in human subjects receiving drugs such as the indirect catecholamine agonists L-dopa, methylphenidate and the dopamine D2 receptor blocker sulpiride. The effects of these drugs on different types of cognitive function sensitive to frontal lobe dysfunction are contrasted with those of a manipulation of 5-HT function, dietary tryptophan depletion. Hypotheses are advanced that accord the ascending systems a greater deal of specificity in modulating prefrontal cortical function than has hitherto been entertained, and clinical and theoretical implications of this hypothesis are discussed.

Key words Prefrontal cortex · Orbitofrontal cortex · Dorsolateral prefrontal cortex · Dopamine · Serotonin · Noradrenaline · Acetylcholine · Methylphenidate · Executive function · Working memory · Planning · Set shifting

Introduction

Mapping the functions of the prefrontal cortex (PFC) onto the richness and heterogeneity of its constituent anatomical regions poses a major conceptual problem. The prefrontal cortex is often said to have ‘executive functions’, which can be defined as that set of cognitive control processes that serve to optimize performance in complex tasks engaging the dedicated processing modules (for example, within the posterior cerebral cortex). The anatomical relationships of the prefrontal cortex are characterized by its contribution of inputs to several levels of the neuraxis, which presumably enable this region to participate in many aspects of control. These prefrontal outputs include backprojections to the posterior cortex and projections to the striatal feedback loop circuitry, the hypothalamus and the brain stem (Goldman-Rakic 1987; Pandya and Yeterian 1995). However, of especial relevance to the present chapter, the prefrontal cortex also targets the main sources of the forebrain monoaminergic and cholinergic neurotransmitter systems – including dopamine-containing cells of the ventral tegmental area, noradrenergic neurons of the locus coeruleus, serotonergic neurons of the raphé nuclei, and the cholinergic basal forebrain (Goldman-Rakic 1987). Presumably, therefore, through their diffuse ascending inputs, these projections enable the prefrontal cortex to exert profound control over global influences such as arousal, stress, reinforcing feedback and mood, on processing within all of the main telencephalic structures, including the limbic system, thalamus and striatum, as well as the cortical mantle itself. Specific functions such as error signals in reinforcement learning (Schultz et al. 1997), and selective attention and vigilance (Aston-Jones et al. 1991), have also been proposed. The theoretical challenge therefore is to understand the nature of these global and specific influences and their functional significance.
Dissociable effects of manipulations of the chemically defined systems of the reticular core and their possible relationship to frontal cortex function in the rat

Clues about the functions of the monoaminergic and cholinergic pathways have accrued from a number of studies using electrophysiological and neurochemical as well as pharmacological and behavioural methodologies (see Robbins and Everitt 1995). Our own approach has been to compare the effects of relatively specific neurotoxins to effect changes in each of these systems on performance in common behavioural paradigms. One example is our version of the five-choice reaction time task used to assess attentional performance in rats. We have manipulated different parameters of this task in order to define distinct profiles of deficit following neurochemical lesions. Thus, for example, 6-hydroxydopamine (6-OHDA) lesions of the dorsal noradrenergic pathway, emanating from the locus coeruleus, produce impairments in the accuracy of stimulus detection, but only under certain conditions, in which the stimuli are presented unpredictably in time, or bursts of loud white noise are interpolated to disrupt performance (Carli et al. 1983). Excitotoxic (Muir et al. 1994) or immunotoxic (McGaughy et al. 1999) lesions of the cholinergic nucleus basalis produce deficits in the accuracy of stimulus detection even under baseline conditions (see Everitt and Robbins 1997). By contrast, profound depletion of mesolimbic dopamine (Cole and Robbins 1989) and forebrain serotonin (Harrison et al. 1997) mainly serve to affect the general vigour (speed and probability) of responding without affecting accuracy, and mesostriatal dopamine loss again only leads to significant deficits in accuracy under certain conditions (Baunez and Robbins 1999). Whilst it requires evidence from other, independent procedures to begin to make firm conclusions about the psychological nature of these deficits, the fact that they are distinct is consistent with the notions that these neurochemical systems are all implicated in the efficient performance of this task, and that they modulate performance in different ways. The functions of the chemical ascending systems are often referred to as *neuromodulatory*: the term ‘neuromodulation’ here is taken to mean the enhancement, reduction, prolongation or curtailment of information processing by activity within these systems, often with only their minor participation in the computations of the neural networks they innervate. The ascending systems appear to effect different forms of neuromodulation, which interact in complex ways. This is consistent with previous theorizing that unitary theories of arousal have become outmoded (e.g. Robbins 1984), and must be replaced by more detailed specifications of the roles of these systems.

To what extent the effects of the rather gross manipulations of subcortical neurotransmitter function actually depend on the altered neuromodulation of processes occurring in the prefrontal cortex remains unclear. It is, however, the case that the effects of the basal forebrain cholinergic lesions do somewhat resemble those following excitotoxic lesions of the prefrontal cortex, and also that the effects of forebrain 5-HT depletion to increase premature or ‘impulsive’ responding are matched by similar excitotoxic lesions of the anterior cingulate cortex (Muir et al. 1996). Finally, the effects of catecholamine depletion in the prefrontal cortex on the five-choice task are largely manifest as impaired accuracy under conditions of temporal unpredictability – resembling therefore the effects of depletion of catecholamines from the cerebral cortex (Robbins et al. 1998a). Thus, some of the effects of neurochemical lesions of the ascending monoaminergic and cholinergic systems might serve to alter the neuromodulation of functions of the prefrontal cortex. What is less clear is how prefrontal cortical manipulations regulate these systems, although there is evidence for example that they influence each of the ascending dopamine (Roberts et al. 1994; Wilkinson et al. 1997; Dalley et al. 1999: see Moore et al. 1999 for a review), noradrenaline (Arnsten and Goldman-Rakic 1984; Jodo et al. 1998) and serotonin (Hajos et al. 1998) systems.

The role of prefrontal dopamine in working memory and other cognitive functions in rats and monkeys

There is also considerable evidence that manipulations of prefrontal dopamine systems have seemingly specific effects on working memory processes. This evidence begins with the work of Brozoski et al. (1979), who showed convincingly that 6-OHDA lesions of the prefrontal cortex of macaques impaired their accuracy of performance on a delayed response type test. These deficits could be remedied by dopaminergic agents, indicating that they were mediated largely by dopamine. The evidence was extended and refined further by later demonstrations that iontophoretic applications of dopamine (DA) D1 receptor antagonists to the principal sulcus of the PFC produced similarly specific impairments in performance in delayed saccade tasks. However, since these seminal observations, further behavioural and electrophysiological evidence has shown that the relationship between working memory function and dopaminergic mechanisms of the PFC is far from simple. Thus, for example, Williams and Goldman-Rakic (1995) have shown that low doses of DA receptor antagonists sharpen the firing patterns of prefrontal cortical ‘memory’ cells, predicting that this might lead to behavioural improvements rather than deficits. A number of studies in the rat have suggested that high levels of prefrontal cortical DA activity are associated with poorer delayed alternation performance in the rat (Sahakian et al. 1985; Murphy et al. 1996; Zahrt et al. 1997). These results suggest that the relationship between mesofrontal DA function and efficiency of working memory might be characterized by an inverted U-shaped function, with extreme low and high levels of DA activity being associated with impaired performance (Robbins 1985; Arnsten 1998; Zahrt et al. 1997). This relationship begs the question of what the