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The medial prefrontal cortex as a part of the brain reward system

Review Article

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Summary. This review will briefly summarize experimental evidence for an involvement of the medial prefrontal cortex (mPFC) in reward-related mechanisms in the rat brain. The mPFC is part of the mesocorticolimbic dopaminergic system. It receives prominent dopaminergic input from the ventral tegmental area (VTA) and, via the mediodorsal thalamus, inputs from other subcortical basal ganglia structures. In turn it projects back to the VTA and the nucleus accumbens septi (NAS), which are generally considered as main components of the brain reward system.

Evidence for the involvement of the mPFC in reward-related mechanisms comes mainly from three types of studies, conditioned place preference (CPP), intracranial self-stimulation (ICSS), and self-administration. Work will be summarized that has shown that certain drugs injected into the mPFC can produce CPP or that lesions of the mPFC can disrupt the development of CPP, that ICSS is obtained with the stimulating electrode placed in the mPFC, and that certain drugs are self-administered into the mPFC or that lesions of the mPFC disrupt the peripheral self-administration of certain drugs.

However, it has also been shown that the role of the mPFC in reward is not uniform. For example, the mPFC appears to be particularly important for the rewarding actions of cocaine, while it appears not to be important for the rewarding actions of amphetamine. Also, different subareas of the mPFC appear to be differentially involved in the rewarding actions of different drugs.

Taken together, the available evidence shows that some drugs can produce reward directly within the mPFC, and that some drugs, even though not having direct rewarding effects within the mPFC, depend on the function of the mPFC for the mediation of their rewarding effects.

Keywords: Amino acids – Medial prefrontal cortex – Reward – Conditioned place preference (CPP) – Intracranial self-stimulation (ICSS) – Self-administration

Introduction

The anatomical and functional relationship of the mPFC with the VTA and the NAS suggests that the mPFC can have strong modulatory effects on the mesocorticolimbic dopamine (DA) system while itself being influenced by this system. Anatomically, the mPFC sends glutamatergic projections to both the VTA and the NAS (Sesack et al., 1989; Sesack and Pickel, 1992; Berendse et al., 1992) and receives dopaminergic input from the VTA (Fuxe et al., 1972; Emson and Koob, 1978) and glutamatergic input from other cortical areas and the basal ganglia (via the mediodorsal thalamus) (Condé et al., 1990, 1995). Functionally, DA released from mesocortical terminals inhibits mPFC projection neurons (Mora et al., 1976a; Godbout et al., 1991), while stimulation of the mPFC results in an activation of dopaminergic VTA cells and an increase of DA release in the NAS (Gariano and Groves, 1988; Taber et al., 1995). Since activity of the mesoaccumbal DA system is considered to be a core element in the generation of reward (Wise, 1982; Wise and Bozarth, 1987; Wise and Rompré, 1989), electrical or chemical stimulation of the mPFC should be rewarding or should at least facilitate the generation of reward through other mechanisms. Conversely, inactivation or destruction of the mPFC should attenuate the induction of reward through other mechanisms.

There are three paradigms that are widely used to assess the rewarding properties of drugs and other treatments and to examine the relevance of certain brain areas for reward: 1. Conditioned place preference (CPP) (van der Kooy, 1987; Carr et al., 1989; Tzschentke, 1998): the treatment in question is repeatedly paired with a set of distict environmental cues, while a neutral control treatment is repeatedly paired with a different set of distinct environmental cues. If the treatment in question is rewarding for the animal, it will, during this repeated pairing, associate these rewarding effects with the distinct environmental cues paired with the treatment. Subsequently, it will then show a preference for these cues over the neutral cues when given a free choice between them. 2. Intracranial self-stimulation (ICSS) (Stellar and Rice, 1989; Phillips and Fibiger, 1989): a stimulating electrode is implated into the brain region in question. If the electrical stimulation of this region is experienced as rewarding by the animal, it will learn to perform an operant response (usually lever-pressing or nose-poking) to obtain this stimulation. 3. Self-administration (Koob and Goeders, 1989; Richardson and Roberts, 1996): An animal is implanted with an intravenous catheter or an injection canula directly into a discrete brain region. If a peripheral or central drug injection is experienced as rewarding by the animal, it will learn to perform an operant response (again, usually lever-pressing or nose-poking) to obtain drug injections. Results of studies that have examined mPFC function in the context of reward generated with each of these paradigms will now be summarized below.

Place preference conditioning

Only a relatively limited number of studies have directly addressed the involvement of the mPFC in brain reward mechanisms using place preference

conditioning. The following drugs have been directly injected into the mPFC: amphetamine (Carr and White, 1986; Schildein et al., 1998), the D1 receptor antagonist SCH23390 (Shippenberg et al., 1991), morphine (Olmstead and Franklin, 1997), the μ-opiate receptor agonist DAMGO (Bals-Kubik et al., 1993), the μ-opiate receptor antagonist naloxone (Shippenberg and Bals-Kubik, 1995) and the κ-opiate receptor agonist U-50488H (Bals-Kubik et al., 1993). The only effect obtained in these studies was a conditioned place aversion (CPA) produced by the κ-agonist in the last study, whereas all other drugs injected into the mPFC produced neither CPP nor CPA. On the other hand, electrical stimulation of the mPFC has been shown to produce a CPP (Duvauchelle and Ettenberg, 1991). Surprisingly, to our knowledge there is no published report on the CPP effects of intra-mPFC injections of cocaine (see section on self-administration below).

Another approach employed in place conditioning studies is to examine the effects of mPFC lesions on the rewarding effects of systemically administered drugs. Here it has been shown that 6-OHDA lesions of the mPFC did not affect cocaine- (Hemby et al., 1992) and morphine- (Shippenberg et al., 1993) induced CPP and the CPA induced by the κ-agonist U-69593 (Shippenberg et al., 1993). On the other hand, it was reported that in rats bearing aspiration lesions of the mPFC cocaine produced a CPA rather than a CPP (Isaac et al., 1989). Finally, excitotoxic quinolinic acid lesions of the mPFC (destroying the infralimbic [il], prelimbic [pl] and anterior cingulate [cg] subareas) were found to block the development of CPP induced by cocaine, morphine and the competitive NMDA receptor antagonist CGP37849, while they had no effect on amphetamine-induced CPP. In addition, specific lesions of the il mPFC were sufficient to block morphine- and CGP37849-induced CPP, specific lesions of the pl mPFC were sufficient to block cocaine- and CGP37849-induced CPP and lesions of the cg mPFC were sufficient to block CGP37849-induced CPP (Tzschentke and Schmidt, 1998a,b; Tzschentke and Schmidt, 1999).

Taken together, the results of these place conditioning studies demonstrate that even though many drugs may not be able to elicit reward within the mPFC, the mPFC nevertheless is involved in the mediation of the rewarding effects of these drugs, presumably because of its important modulatory influence on the mesolimbic system. The results further show that with respect to its role in reward, the mPFC may be functionally heterogenous, since different subareas appear to be involved in the mediation of reward produced by different drugs.

Intracranial self-stimulation

A powerful tool to assess whether a given brain structure is involved in reward mechanisms is electrical brain self-stimulation. Starting with the classic demonstration of Olds and Milner (1954) that rats will self-stimulate discrete brain areas, many regions have been shown subsequently to support self-stimulation (see Phillips and Fibiger, 1989, for review). Specifically, the mPFC was also shown to support self-stimulation, initially by Routtenberg and Sloan

(1972) and subsequently in many other studies (e.g. Mora et al., 1976b; Corbett et al., 1982a,b; see Mora and Cobo, 1990; Robertson, 1989, for reviews).

The mechanism by which electrical stimulation of the mPFC produces rewarding effects is not well understood. One line of evidence suggests that intra-cortical connections, in particular fiber connections to and from the sulcal prefrontal cortex are important for mPFC self-stimulation (Corbett et al., 1982b; Robertson et al., 1982). Other studies show that the glutamatergic projections of the mPFC to the VTA appear to be important for the rewarding effects of the stimulation. As mentioned above, chemical or electrical stimulation of the mPFC increases the activity of DA cells in the VTA (presumably be increasing glutamate release in the VTA) and causes an increase in extracellular DA levels in the NAS. To our knowledge, there is only one published report on the effects of mPFC *self*-stimulation on subcortical transmitter release in which You et al. (1998) have shown that mPFC self-stimulation increases levels of DA, glutamate and cholecystokinin in the NAS. The stimulation-induced increase in NAS DA was blocked by intra-VTA infusion of the glutamate antagonist kynurenic acid, suggesting that the NAS DA release was mediated by increased glutamate transmission in the VTA. The notion that mPFC self-stimulation involves the mesolimbic system is consistent with the fact that some drugs of abuse which are thought to produce their effects predominantly through the mesolimbic system are able to enhance the rewarding effects of mPFC self-stimulation (Spence et al., 1985; Corbett, 1989, 1991; Moody and Frank, 1990; McGregor et al., 1992).

Self-administration

For some drugs self-administration directly into the mPFC has been demonstrated: cocaine (Goeders and Smith, 1983, 1986, 1993), phencyclidine, the non-competitive NMDA receptor antagonist MK-801, and the competitive NMDA receptor antagonist CPP (Carlezon and Wise, 1996). On the other hand, intra-mPFC self-administration of lidocaine or amphetamine could not be established (Goeders et al., 1986). Dopaminergic innervation of the mPFC has been shown to be important for intra-mPFC self-administration of cocaine since 6-OHDA lesions of the mPFC disrupt cocaine self-administration into the mPFC (Goeders and Smith, 1986) and intra-mPFC injections of SCH23390 also decreased the rewarding effects of i.v. cocaine (McGregor and Roberts, 1995). Surprisingly, 6-OHDA lesions of the mPFC enhanced the rewarding effects of intravenously self-administered cocaine in two studies (Schenk et al., 1991; McGregor et al., 1996) while having no effect in another study (Martin-Iverson et al., 1986) and also having no effect on i.v. amphetamine self-administration (Leccese and Lyness, 1987). Binding of heroin to μ-receptors within the mPFC does not appear to be of relevance for i.v. heroin self-administration, since intra-mPFC injection of the μ-receptor antagonist methyl-naltrexone was without effect on self-administration behaviour (Corrigall, 1987). We are aware of only one study examining the

effects of excitotoxic mPFC lesions on drug self-administration in which Hansen et al. (1995) showed that ibotenic acid lesions of the mPFC did not affect oral ethanol consumption.

Another line of evidence suggesting a role of the mPFC in self-administration derives from electrophysiological and electrochemical studies. When activity of mPFC cells was recorded during drug self-administration, it was found that the firing of mPFC cells can be very closely linked to the i.v. injections of cocaine and heroin (Chang et al., 1997a,b, 1998). Likewise, when DA release in the mPFC or activity of dopaminergic cells in the VTA was monitored during response-contingent delivery of food or liquid reward using voltammetry or electrophysiological recordings, respectively, it was found that the DA signal or DA cell activity showed changes timelocked to the delievery of the reward (Watanabe, 1996; Richardson and Gratton, 1998) [in this context the response-contingent delivery of food or liquid can also be viewed as a self-administration situation].

Conclusions

The available data strongly suggests that the mPFC is part of the brain reward circuitry. However, the role of the mPFC in reward is not uniform for all drugs and not under all experimental conditions. Most notably, the mPFC appears to be very important for cocaine´s rewarding effects, while it seems not to be involved in the mediation of amphetamine reward. Another class of drugs the rewarding effects of which seem to depend heavily on the mPFC are the NMDA receptor antagonists. The reason for these differences are not clear but they may be related to the particularities of the DA innervation of the mPFC (see Tzschentke and Schmidt, 1998a for further discussion). In the case of cocaine reward the action of cocaine in the mPFC is sufficient but not necessary to produce reward.

Since the mPFC has been implicated in higher cognitive functions such as learning and memory (Bubser and Schmidt, 1990), decision making (Granon et al., 1994), temporal sequencing of actions (Muir et al., 1998) and modification of behaviour based on the comparison of the expected and the actual outcome of an event (Watanabe, 1996), ´reward deficits´ observed in the paradigms discussed here may potentially not only be due to genuine reductions in the rewarding effects of a given treatment, but also to impaired detection, computation and representation of the reward signal or to inadequate responding to the rewarding stimuli. For example, the lack of drug-induced CPP after mPFC lesion might also be due to a learning deficit which would also impair the process of conditioning. Careful behavioural analysis and, in particular, the comparison of results from different paradigms is needed to avoid misinterpretation of data. But with the data of the existing paradigms at hand it is clear that the mPFC is, amongst many other functions, also directly involved in reward-related mechanisms and in the mediation of the rewarding effects of at least some drugs of abuse.

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