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A link between role of two prefrontal areas in immediate memory and in long-term memory consolidation

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Abstract

The dorsolateral and medial prefrontal cortex are critical for immediate memory processing. The possibility has been raised that those two areas may also contribute to long-term memory formation. Here, we studied the role of specific receptors in dorsolateral and medial prefrontal cortex in immediate and in long-term memory formation of one-trial inhibitory avoidance. Four different specific receptor ligands were infused into these two areas: the dopamine D1 receptor antagonist, SCH23390, the $GABA_A$ receptor agonist, muscimol, the AMPA glutamatergic receptor antagonist, ciano-nitro-quinoxaline-dione (CNQX), and the NMDA glutamatergic receptor antagonist, aminophosphonovaleric acid (AP5). In all cases the doses used had been previously shown to affect immediate or long-term memory. In the experiments on immediate memory the drugs were given 5 min before training and the animals were tested 3 s post-training. These animals were then also tested 24 h later for long-term memory. The effect of the treatments on long-term memory was studied by their infusion 0, 90, 180 or 270 min post-training, testing the animals 24 h after training. Immediate memory was inhibited by SCH23390, muscimol and CNQX, but not by AP5, given into any of the two subregions. Long-term memory formation was inhibited by SCH23390, muscimol and CNQX, but not by AP5, given pre-training or 0, 90 or 180 but not 270 min post-training into the dorsolateral region; or 90 but not 0 or 180 min post-training into the medial region. Thus, there is a time- and receptor-dependent correlation in the two areas between their role in immediate and in long-term memory processing. Both roles require intact glutamate AMPA and dopamine D1 receptors, are inhibited by GABAergic synapses, and are unaffected by AP5. In the dorsolateral prefrontal cortex the link between immediate and long-term memory appears to be direct; in the medial area the link suffers a 90 min delay.

Keywords: Prefrontal cortex in immediate memory; Prefrontal cortex in long-term memory; Dorsolateral prefrontal cortex; Medial prefrontal cortex; AMPA receptors; Dopamine receptors; GABA receptors

1. Introduction

The dorsolateral (Bailey & Mair, 2004; Goldman-Rakic, 1991) and ventromedial prefrontal cortex (PFC) (Akirav & Maroun, 2006; Fuster, 2001; Runyan & Dash, 2005) are customarily linked to immediate or working memory processing, taking these two terms as synonymous (Goldman-Rakic, 1991). Here, we study the effect of several drugs given into the dorsolateral and ventromedial PFC on immediate memory expression and on long-term memory consolidation. As will be seen the findings suggest a connection between the two functions of the PFC regions.

Memories measured right after training are usually richer and decline more or less exponentially in the next few hours (Ebbinghaus, 1885). Six hours or more after training memory performance usually reaches a plateau, which may last for several days, which corresponds to long-term memory (Izquierdo & Netto, 1985). Since immediate memory (Jacobsen, 1936) is coincident in time with the most labile part of long-term memory formation (Izquierdo et al., 2006; McGaugh, 1966, 1973), treatments

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given at the time of the former may also influence the latter. In addition, there are strong anatomical connections between the dorsolateral, ventromedial and other regions of the PFC with the entorhinal cortex, and, through this, with the hippocampus and other areas involved in long-term memory formation (Hyman, van Heusen, & Damasio, 1990; Izquierdo & McGaugh, 2000; Izquierdo & Medina, 1997; Izquierdo et al., 2006; Phelps, 2006).

Indeed, treatments that affect immediate memory may also influence memory measured at later times (Akirav & Maroun, 2006; Blumenfeld & Ranganath, 2006; Ranganath, Cohen, & Brozinsky, 2005; Ruchkin, Grafman, Cameron, & Berndt, 2003; Rypma & D'Esposito, 2003). In any case, the cognitive content of immediate and long-term memory in terms of sensorimotor input and behavioral output, is basically the same and one would expect similar neuronal networks to be involved in all of them (Izquierdo, Barros, et al., 1998; Izquierdo, Izquierdo, et al., 1998; Izquierdo & Medina, 1997; Quirk, Likhtik, Pelletier, & Pare, 2003; Sakai, 2003; Simon & Spears, 2003).

Recent findings in fact suggest a role of both the ventromedial PFC (Akirav & Maroun, 2006; Liang, Hu, & Chang, 1966) and the dorsolateral PFC (Blumenfeld & Ranganath, 2006) in memory consolidation. Some have ventured the possibility that such a role may result from "working memory maintenance" (Ranganath et al., 2005), or lingering electrophysiological activity in the PFC (Xiang & Brown, 2004).

Pre-training drug administrations may affect acquisition, immediate memory or the consolidation of short- (Izquierdo, Barros, et al., 1998; Izquierdo, Izquierdo, et al., 1998) or long-term memory (McGaugh, 1973). In order to study their effect on immediate memory (Izquierdo, Izquierdo, et al., 1998), which is supposed to last only a few seconds (Goldman-Rakic, 1991; Jacobsen, 1936), drugs must be given prior to training. Therefore, the results do not distinguish influences on fear expression from those on any specific memory type; but, indeed, immediate memory by definition just represents immediate fear expression. Its relation to working memory processes is inferential (Christoff, Ream, Geddes, & Gabrieli, 2003; Goldman-Rakic, 1991; Izquierdo, Barros, et al., 1998; Izquierdo, Izquierdo, et al., 1998). So here we will omit interpretations of such treatments as acting on working memory, or, for that matter, comments on possible influences of working memory on long-term memory. For such inferences, see Ranganath et al. (2005) and Blumenfeld and Ranganath (2006).

Post-training drug administration into defined brain structures at different times from training is classically used in order to determine the molecular mechanisms underlying memory consolidation in those structures (Izquierdo & McGaugh, 2000; Izquierdo et al., 2006). Evidence from one-trial learning indicates that memory consolidation takes 3–6 h at least (Izquierdo & Medina, 1997). It uses glutamate NMDA, AMPA and dopaminergic D1 (Bernabeu et al., 1997) receptors, among others, and is inhibited by $GABA_A$ receptors (Izquierdo et al., 2006) in rat hippocampus. These and other neurotransmitters also play a role in consolidation in basolateral amygdala (Kim and McGaugh (1992), entorhinal, parietal, cingulate, insular and other regions of the cortex (Izquierdo & Medina, 1997; Izquierdo et al., 2006). By giving agonists and antagonists to the corresponding receptors them at different post-training intervals, the processes under study have been timed, and the putative role of a number of brain neurotransmitters in different brain regions in the encoding of one or other type of memory has been ascertained (see Izquierdo & McGaugh, 2000; Izquierdo et al., 2006).

Here, we study the participation of glutamate *N*-methyl-D-aspartate (NMDA) receptors, amino-hydroxymethyl isoxazole propionate (AMPA) receptors, dopamine D1 and γ-amino-butyrate type A ($GABA_A$) receptors in the dorsolateral and medial PFC of rats in immediate memory (Goldman-Rakic, 1991; Jacobsen, 1936), and in long-term memory consolidation of this task. The regions chosen to represent dorsolateral and medial PFC were those used by Bailey and Mair (2004), Izquierdo, Barros, et al. (1998), Izquierdo, Izquierdo, et al. (1998), Milad and Quirk (2002) or Akirav and Maroun (2006). Their role in consolidation of one-trial inhibitory avoidance had not been previously ascertained (Izquierdo et al., 2006; see, however, Liang et al., 1966). We administered either pre-training, or 0, 90 or 180 min after one-trial avoidance training, AP5, CNQX or SCH23390, antagonists of NMDA, AMPA, dopamine D1 receptors, respectively, and muscimol, a $GABA_A$ receptor agonist into the regions mentioned. The animals submitted to pre-training infusions were used for the study of both immediate and long-term memory and those infused post-training were tested for retention 24 h after training.

2. Experimental procedures

2.1. Surgery and drug infusion

Three month old, 220–300 g male Wistar rats purchased at Fundação Estadual de Pesquisa em Saude (FEPS), Brazil were used. They had free access to water and Purina food pellets, were housed 5 to a cage and kept at 21–23 °C under a 12 h light/dark cycle (lights on at 7:00 AM). They were implanted under deep thiopental anesthesia (30–50 mg/kg, ip) with 30-g guide cannulae in the dorsolateral and medial PFC, bilaterally. The stereotaxic coordinates were AP −5.0 mm, ML −2.0 mm (Izquierdo, Barros, et al., 1998; Izquierdo, Izquierdo, et al., 1998; see Bailey & Mair, 2004) and AP +2.9 mm, ML −1.0 mm, CV −4.1 for medial PFC (Lebrón, Milad, and Quirk (2004); Quirk et al., 2003), according to the atlas of Paxinos and Watson (1986).

Animals were allowed to recover from surgery during 4–7 days before submitting them to any other procedure. At the time of drug infusion, a 30-gauge infusion cannula was tightly fitted into the guides. Infusions (0.5 μl/side) were carried out during 60 s, first on one side and then on the other. The infusion cannulae were left in place for an extra 60 s after the infusions in order to minimize backflow. Cannulae placements were verified post-mortem: 2–4 h after the behavioral testing sessions 0.5 μl of a 4% methylene blue solution were infused as described above and the