



Muscarinic cholinergic influences in memory consolidation

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Received 9 July 2003; revised 29 July 2003; accepted 29 July 2003

Abstract

The central cholinergic system and muscarinic cholinergic receptor (mR) activation have long been associated with cognitive function. Although mR activation is no doubt involved in many aspects of cognitive functioning, the extensive evidence that memory is influenced by cholinergic treatments given after training either systemically or intra-cranially clearly indicates that cholinergic activation via mRs is a critical component in modulation of memory consolidation. Furthermore, the evidence indicates that activation of mRs in the basolateral amygdala (BLA) plays an essential role in enabling other neuromodulatory influences on memory consolidation. Memory can also be affected by posttraining activation of mRs in the hippocampus, striatum and cortex. Evidence of increases in hippocampal and cortical acetylcholine (ACh) levels following learning experiences support the view that endogenous ACh release is involved in long-term memory consolidation. Furthermore, the findings indicating that mR drug treatments influence plasticity in the hippocampus and in sensory cortices strongly suggest that mR activation is involved in the storage of information in these brain regions.

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Keywords: Acetylcholine; Basolateral amygdala; Nucleus basalis magnocellularis; Multiple memory systems

1. Introduction

Interest in the role of acetylcholine (ACh) in cognitive processes began just a little over a half-century ago, before ACh was generally accepted as a *bona fide* neurotransmitter. The first reports of studies of the involvement of ACh in learning and memory to our knowledge were studies reporting the effects of the irreversible acetylcholinesterase (AChE) inhibitor di-isopropylfluorophosphate (DFP) on learning in rats (Platt & Wickens, 1950; Russell, 1960) and studies investigating the relationship between brain AChE and maze performance (Krech, Rosenzweig, Bennett, & Krueckel, 1954; McGaugh, 1959). The findings of these early studies suggested that learning performance varied with brain ACh levels at the time of training. Subsequently, several laboratories reported that the cholinergic re-

ceptor antagonists atropine and scopolamine administered before training impaired rats' performance on various types of tasks (Burešová, 1964; Carlton, 1963; Herz, 1960; Whitehouse, 1964). The behavioral effects were likely due to influences on cholinergic functioning within the brain as the peripherally active quaternary compounds methylscopolamine and methylatropine did not impair the rats' performance. Other studies reported that low doses of the reversible AChE inhibitor physostigmine injected systemically before training enhanced learning performance (Bureš, 1962; Cardo, 1959).

These early findings strongly suggested that increases in brain cholinergic functioning enhanced cognitive functioning and that decreases impaired such functioning. But, the findings provide few, if any, insight into the bases of the performance impairing and enhancing effects of drugs affecting cholinergic functioning. As the drugs were administered before behavioral testing they could have acted by influencing sensory processing, attention and motivation as well as by influencing brain processes underlying the storage of new information

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(McGaugh & Petrinovich, 1965; McGaugh, 1989). The introduction of the use of posttraining drug administration (e.g., Breen & McGaugh, 1961) provided a method of investigating drug effects on memory consolidation without the confounding effects of drug effects on acquisition or retention performance (McGaugh, 1966). Many studies reported finding enhancing or impairing effects of drugs administered posttraining. Further, the evidence that the effectiveness of the drugs decreased as the training-injection interval increased provided strong support for the hypothesis that the drugs affected retention by influencing memory consolidation (McGaugh & Herz, 1972).

Stratton and Petrinovich (1963) were the first to report that posttraining administration of physostigmine enhanced memory in rats. Their findings clearly suggested alterations in cholinergic functioning can influence memory by altering memory consolidation. This conclusion was subsequently confirmed by many studies of the effects of posttraining injections of drugs affecting cholinergic functioning (Hunter, Zornetzer, Jarvik, & McGaugh, 1977), including many more recent studies (e.g., Baratti, Huygens, Mino, Merlo, & Gardella, 1979; Kopf, Boccia, & Baratti, 1998; Rudy, 1996; Schroeder & Packard, 2002). Of course, such studies do not address the issue of cholinergic involvement in attention and other processes affecting acquisition and retention performance. But, the findings of the studies using posttraining treatments clearly indicate that, apart from other possible influences on cognitive processes, cholinergic function influences the consolidation of new memories.

The cholinergic hypothesis of Alzheimer's disease greatly increased interest in understanding cholinergic involvement in cognitive functioning (Bartus, Reginald, Dean, Beer, & Lippa, 1982; Coyle, Price, & DeLong, 1983; Davies & Maloney, 1976; Perry et al., 1978). Most of the drugs currently available for treating Alzheimer's disease are AChE inhibitors (Bartus et al., 1982; Drachman & Leavitt, 1974; Mohs et al., 1985). Although these drugs may well improve (modestly) cognitive functioning by enhancing attention and working memory, the findings of the studies briefly discussed above suggest that the drugs may also enhance performance of Alzheimer's patients by aiding the consolidation of long-term memories. This paper focuses primarily on recent research investigating brain systems and processes mediating cholinergic influences on memory consolidation. As studies using systemic drug injections cannot, by themselves, reveal the loci of brain influences, many recent studies have investigated the effects of drug infusions administered locally into brain regions such as the amygdala, hippocampus, striatum and cortical regions. We will first consider the extensively investigated cholinergic influences on memory consolidation in the amygdala.

2. Involvement of amygdalar cholinergic activation in memory consolidation

Considerable evidence indicates that modulation of memory consolidation by posttraining systemic drug treatments depends on the amygdala (Cahill & McGaugh, 1991; McGaugh et al., 1993; Tomaz et al., 1993). Recent findings indicate that these memory modulatory processes are mediated selectively by the basolateral complex of nuclei in the amygdala (BLA) (McIntyre, Power, Roozendaal, & McGaugh, 2003). As found with systemic treatments (Baratti et al., 1979; Introini-Collison, Dalmaz, & McGaugh, 1996), posttraining infusion of a muscarinic cholinergic receptor (mR) agonist into the amygdala or the BLA enhances memory (Barros, Pereira, Medina, & Izquierdo, 2002; Dalmaz, Introini-Collison, & McGaugh, 1993; Introini-Collison, Arai, & McGaugh, 1989; Introini-Collison et al., 1996; Power & McGaugh, 2002a; Vazdarjanova & McGaugh, 1999). Correspondingly, extensive reduction of amygdalar cholinergic activation during consolidation can impair retention. For example, long-term memory for inhibitory avoidance (IA) training can be impaired by posttraining intra-BLA infusions of the mR antagonist scopolamine (Bianchin, Mello e Souza, Medina, & Izquierdo, 1999; Izquierdo et al., 1992) or by lesions of the major amygdalar cholinergic input from the nucleus basalis magnocellularis (NBM) with phthalic acid (PA) (Power & McGaugh, 2002a). Posttraining cholinergic manipulations of the BLA produce comparable effects in a variety of behavioral tasks including IA (Izquierdo et al., 1992), contextual fear conditioning (Vazdarjanova & McGaugh, 1999), reductions in food reward (Salinas, Introini-Collison, Dalmaz, & McGaugh, 1997) and both food and amphetamine motivated conditioned place preference (McIntyre, Ragozzino, & Gold, 1998; Schroeder & Packard, 2002). Moreover, as summarized in Fig. 1, posttraining intra-BLA infusions of the mR agonist oxotremorine enhanced long-term memory in rats for contextual fear conditioning, as evidenced by several indices of memory including latency to enter and number of entries into the shock context, time spent in the shock vs. non-shock arms of the Y-maze training apparatus as well as the conventional measure of time spent freezing (Vazdarjanova & McGaugh, 1999). As retention for both aversive and appetitive training is sensitive to enhancement with posttraining mR agonism in the BLA, these effects can not be attributed to any rewarding or reinforcing properties of the treatments. Additionally, extensive evidence suggests that augmenting muscarinic cholinergic activation in the BLA during consolidation enables enhancement of memory storage processes in other brain regions (McGaugh, McIntyre, & Power, 2002).

The mechanisms and circuitry underlying the critical role for mR activation in the BLA during memory

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