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GLUCOCORTICOIDS INTERACT WITH EMOTION-INDUCED NORADRENERGIC ACTIVATION IN INFLUENCING DIFFERENT MEMORY FUNCTIONS

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Abstract—Extensive evidence from rat and human studies indicates that glucocorticoid hormones influence cognitive performance. Posttraining activation of glucocorticoid-sensitive pathways dose-dependently enhances the consolidation of long-term memory. Glucocorticoid effects on memory consolidation rely on noradrenergic activation of the basolateral amygdala and interactions of the basolateral amygdala with other brain regions. Glucocorticoids interact with the noradrenergic system both at a postsynaptic level, increasing the efficacy of the β-adrenoceptor-cyclic AMP/protein kinase A system, as well as presynaptically in brainstem noradrenergic cell groups that project to the basolateral amygdala. In contrast, memory retrieval and working memory performance are impaired with high circulating levels of glucocorticoids. Glucocorticoid-induced impairment of these two memory functions also requires the integrity of the basolateral amygdala and the noradrenergic system. Such critical interactions between glucocorticoids and noradrenergic activation of the basolateral amygdala have important consequences for the role of emotional arousal in enabling glucocorticoid effects on these different memory functions. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: amygdala, corticosterone, emotional arousal, memory consolidation, memory retrieval, working memory.

Adrenal hormones (i.e. catecholamines and glucocorticoids) are secreted during emotionally arousing events and influence, together with other components of the stress system, the organism's ability to cope with stress. There is extensive evidence that these hormones have also profound effects on cognitive functioning (McGaugh and Roozendaal, 2002). Immediate posttraining systemic injections of epinephrine or norepinephrine to rats enhance the consolidation and/or storage of novel information (Gold and van Buskirk, 1975). Recent evidence indicates that epinephrine also enhances memory consolidation for emotionally arousing material in human subjects (Cahill and Alkire, 2003). It is now also well established that glucocorticoid hormones dose-dependently enhance memory consolidation in animal and human subjects (de Kloet et al., 1999; Roozendaal, 2000). Blockade of glucocorticoid production with the synthesis inhibitor metyrapone impairs memory consolidation (Roozendaal et al., 1996b; Maheu et al., 2004) and prevents stress- and epinephrine-induced memory enhancement (Roozendaal et al., 1996a; Liu et al., 1999), whereas acute systemic administration of glucocorticoids enhances memory when given either before or immediately after a training experience (Flood et al., 1978; Roozendaal and McGaugh, 1996; Sandi and Rose, 1997; Roozendaal et al., 1999b; Buchanan and Lovallo, 2001; Abercrombie et al., 2003). In addition to such enhancing effects of acutely administered glucocorticoids on memory consolidation, elevated levels of glucocorticoids at the time of retention testing impair the retrieval of previously acquired information (de Quervain et al., 1998, 2000; Wolf et al., 2001; Roozendaal et al., 2003, 2004a,b). High levels of glucocorticoids also impair working memory performance (Lupien et al., 1999; Wolf et al., 2001; Roozendaal et al., 2004c).

Research in our laboratory has focused primarily on the brain systems mediating such stress hormone effects on memory. Extensive evidence indicates that the amygdala plays a key role in mediating epinephrine effects on memory consolidation. However, as epinephrine does not readily cross the blood–brain barrier, a peripheral–central pathway is involved in mediating epinephrine effects on amygdala activity in modulating memory consolidation (McGaugh et al., 1996; Williams and Clayton, 2001). Systemic epinephrine can activate peripheral β-adrenoceptors located on vagal afferents terminating in the nucleus of the solitary tract (NTS). In turn, noradrenergic cell groups in the NTS send direct projections to the amygdala (Fallon and Ciofi, 1992), or indirectly via the locus coeruleus (Williams and Clayton, 2001). The evidence that a blockade of β-adrenoceptors in the amygdala prevents memory enhancement induced by systemic injections of epinephrine (Liang et al., 1986) indicates that epinephrine effects on memory consolidation depend critically on noradrenergic activity of the amygdala. There is now extensive evidence that several neuromodulatory and neurotransmitter systems interact with the noradrenergic system of the amygdala in influencing memory consolidation (McGaugh et al., 1996; McGaugh, 2000, 2004). As discussed below the neurobiological mechanisms underlying the acute effects

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Abbreviations: BLA, basolateral complex of the amygdala; cAMP, cyclic AMP; CEA, central nucleus of the amygdala; GR, glucocorticoid receptor; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; NTS, nucleus of the solitary tract; PKA, protein kinase A; RU 38486, mifepristone.

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of glucocorticoids on memory consolidation are highly similar to those of epinephrine in that they require noradrenergic activation within the amygdala that influences memory consolidation via interactions with other brain regions. The findings suggest also that the impairing effects of glucocorticoids on memory retrieval and working memory depend on noradrenergic activation within the amygdala. Such critical interactions between glucocorticoids and noradrenergic activation of the amygdala have important consequences for the role of emotional arousal in enabling glucocorticoid effects on these different memory functions.

Glucocorticoid effects on memory consolidation: involvement of the amygdala

Unlike catecholamines, glucocorticoid hormones readily enter the brain and bind directly to two intracellular types of adrenal steroid receptors (Reul and de Kloet, 1985; de Kloet, 1991). Glucocorticoid receptors (GRs) have a low affinity for corticosterone and become occupied only during stress and at the circadian peak, when circulating levels of glucocorticoids are high. In contrast, mineralocorticoid receptors (MRs) have a 10-fold higher affinity for corticosterone and are almost saturated under basal conditions (Reul and de Kloet, 1985). Extensive evidence indicates that glucocorticoid effects on memory consolidation involve a selective activation of GRs. For example, immediate posttraining i.c.v. or local infusions of a GR antagonist, but not an MR antagonist, impair memory consolidation (Oitzl and de Kloet, 1992; Roozendaal et al., 1996c; 1999a; Roozendaal and McGaugh, 1997a,b). Furthermore, genetic disruption of GR functioning interferes with memory consolidation processes (Oitzl et al., 2001).

Both MRs and GRs are expressed in the brain. In contrast to MRs, which are most densely expressed in limbic areas, GRs are ubiquitous and are found both in neurons and in glial cells (de Kloet, 1991). Recent findings suggest that glucocorticoids may act in many different, though interacting, brain regions to enhance memory consolidation. Our studies have focused primarily on the amygdala, and interactions of the amygdala with other brain regions, as there is extensive evidence that the amygdala is a critical component of the neural circuitry regulating the effects, on memory consolidation, of drugs and hormones affecting several receptor systems (McGaugh et al., 1996; McGaugh, 2000, 2004). Furthermore, as noted above, the amygdala mediates epinephrine as well as glucocorticoid effects on memory consolidation. Selective NMDA-induced lesions of the amygdala restricted to the basolateral complex (BLA; consisting of the lateral, basal and accessory basal nuclei) block 48-h inhibitory avoidance retention enhancement induced by posttraining systemic injections of the synthetic glucocorticoid dexamethasone (Roozendaal and McGaugh, 1996). In contrast, lesions of the adjacent central nucleus (CEA), made with ibotenic acid, do not block the dexamethasone-induced memory enhancement. Selective BLA lesions also block memory impairment induced by an i.c.v. administration of a GR antagonist (Roozendaal et al., 1996c). Posttraining infusions of the specific GR agonist RU 28362 administered into the BLA enhance retention in a dose-dependent fashion, but are ineffective when administered into the CEA (Roozendaal and McGaugh, 1997a), whereas intra-BLA, but not intra-CEA, infusions of the GR antagonist RU 38486 (mifepristone) impair retention in a water-maze spatial task (Roozendaal and McGaugh, 1997a). Moreover, intra-BLA infusions of RU 38486 attenuate the facilitating effects of chronic corticosterone administration on contextual fear conditioning (Conrad et al., 2004). These findings indicate that the modulatory effects of glucocorticoids on memory consolidation are mediated, in part, by direct binding to GRs in the BLA. Such a selective involvement of the BLA in regulating glucocorticoid effects on memory consolidation is consistent with the evidence that the BLA is also the critical subdivision of the amygdala mediating the modulatory effects of drugs affecting several other neurotransmitter systems (McGaugh, 2004).

Many findings from our laboratory indicate that BLA activity enhances memory by influencing consolidation processes occurring in other brain regions, including the hippocampus (McGaugh, 2002, 2004). It is well established that the hippocampus has a high density of adrenal steroid receptors (Reul and de Kloet, 1985) and that the hippocampus is involved in spatial/contextual learning and memory (Morris et al., 1982; Eichenbaum and Otto, 1992). Furthermore, cumulative evidence indicates that hippocampal adrenal steroid receptors are involved in neuroplasticity (Foy et al., 1987; Diamond et al., 1992; Pavlides et al., 1993; Korz and Frey, 2003) and memory consolidation (de Kloet, 1991). We found that posttraining infusions of the GR agonist RU 28362 into the dorsal hippocampus enhance rat's retention of inhibitory avoidance and that pretraining infusions of the antagonist RU 38486 impair retention of water-maze spatial training (Roozendaal and McGaugh, 1997b). Additionally, and most importantly, selective BLA lesions block the memory-modulatory effects of the intra-hippocampal infusions of drugs affecting GRs. These findings parallel those of electrophysiological studies reporting that the BLA modulates long-term potentiation in the hippocampus (Ikegaya et al., 1994, 1997; Akirav and Richter-Levin, 1999, 2002; Frey et al., 2001; Nakao et al., 2004) and that BLA lesions block stress effects on hippocampal long-term potentiation (Kim et al., 2001).

Other recent findings indicate similar interactions of the BLA with other brain regions. Posttraining infusions of RU 28362 into either the medial prefrontal cortex or nucleus accumbens enhance memory consolidation for inhibitory avoidance training; effects that are blocked by lesions of the BLA (B. Roozendaal, J. R. McReynolds, C. K. McIntyre and J. L. McGaugh, unpublished observations). Thus, these findings indicate that although glucocorticoids may act in many different brain regions to enhance memory consolidation, the modulatory effects of such local glucocorticoid administrations on memory consolidation depend on BLA activity. That is, influences from the BLA appear to be essential in enabling glucocorticoid effects on memory consolidation involving other brain regions.