

Cooperation Between Memory Systems: Acetylcholine Release in the Amygdala Correlates Positively With Performance on a Hippocampus-Dependent Task

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The present experiment examined the relationship between release of acetylcholine (ACh) in the amygdala and performance on a hippocampus-dependent spatial working memory task. Using *in vivo* microdialysis, the authors measured ACh release in rats during testing on a spontaneous alternation task. Amygdala ACh release was positively correlated with performance on the hippocampus-dependent task. These findings suggest that activation of the amygdala promotes processing in other neural systems important for learning and memory.

Considerable evidence supports the view that somewhat independent multiple neural systems are responsible for processing and storing information for different classes of memory (cf. Gabrieli, 1998; Kesner, Gilbert, & Lee, 2002; Nyberg & Tulving, 1996; White & McDonald, 2002; Willingham, 1997). These findings indicate that several memory systems are dissociable with specific lesions and specific behavioral tests. However, it is readily apparent that multiple memory systems must interact when the brain is intact and when an animal is faced with a task that requires processing across systems.

Many interactions between memory systems can be characterized as competitive (Gold, McIntyre, McNay, Stefani, & Korol, 2001; Matthews & Best, 1995; Matthews, Ilgen, White, & Best, 1999; Packard, 2001a, 2001b; Squire, Knowlton, & Musen, 1993; White & McDonald, 2002). One set of findings consistent with the view that memory systems can compete is that disruption of hippocampal functions can facilitate acquisition of some tasks (Hirsh, 1974; O'Keefe & Nadel, 1978; Packard, Hirsh, & White, 1989). For example, lesions of the fornix or ventral hippocampus facilitate acquisition of an amygdala-dependent conditioned place preference task and of a nonspatial maze task (Ferbinteanu &

McDonald, 2001; Matthews & Best, 1995; McDonald & White, 1995). Findings like these suggest that an intact hippocampal system, or information acquired by the hippocampal system, may sometimes interfere with learning of or memory for information that depends on other memory systems, including the amygdala.

Because memory systems can make conflicting contributions to the memory of an experience (cf. White & McDonald, 2002), mechanisms must exist to regulate the balance of activation between systems during experiences that engage more than one neural system. Neurochemical modulators of learning and memory are in an ideal position to regulate the relative participation of independent systems during memory formation and retrieval (for reviews, see Gold, 1995; Gold et al., 2001). Acetylcholine (ACh), for example, is found extensively in several anatomical regions that support learning and memory. Systemic injections of cholinergic drugs affect performance on a variety of learning and memory tasks in both human and non-human animals (Disterhoft et al., 1999; Ingram et al., 1994; Riedel & Jolles, 1996; for a review, see Levin & Simon, 1998). When cholinergic drugs are injected directly into discrete regions of the brain, the memory tasks that are affected generally correspond to the location of the drug infusion (Kobayashi & Iwasaki, 2000; Power, Roozendaal & McGaugh, 2000; Ragozzino & Kesner, 1998; Schiltein, Huston, & Schwarting, 2000; Wallenstein & Vago, 2001). For example, manipulations of the cholinergic system within or projecting to the amygdala impair performance on amygdala-dependent tasks, but not hippocampus-dependent spatial maze tasks (McIntyre, Ragozzino, & Gold, 1998; Power & McGaugh, 2002). Thus, cholinergic mechanisms appear to be important in regulating learning and memory processes in several neural systems. However, these findings, among others, suggest that the interactions are not necessarily reciprocal. Although interference with hippocampal functions can enhance learning that is dependent on the amygdala, interference

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with amygdala functions does not appear to enhance performance on hippocampus-dependent learning and memory tasks.

Experiments using *in vivo* microdialysis have provided further support for the idea that release of ACh serves as a marker of activation of different neural systems during learning. Release of ACh in the hippocampus increases significantly while rats perform hippocampus-dependent tasks (Ragozzino, Unick, & Gold, 1996), and the magnitude of release is positively correlated with good performance (Fadda, Cocco, & Stancampiano, 2000; Hironaka, Tanaka, Izaki, Hori, & Nomura, 2001; Thiel, Huston, & Schwarting, 1998). Memory-modulating drugs, administered systemically or directly into the medial septum, have been reported to have parallel effects on performance of memory tasks and hippocampal ACh release (Darnaudéry, Koehl, Piazza, Le Moal, & Mayo, 2000; Hiramatsu, Murasawa, Mori, & Kameyama, 1998; Hiramatsu, Murasawa, Nabeshima, & Kameyama, 1998; Kopf, Buchholzer, Hilgert, Löffelholz, & Klein, 2001; Ragozzino & Gold, 1995). When measured in the training room, release of ACh in the hippocampus has been reported to be greater in rats that have already been trained on a spatial working memory task than in untrained rats (Fadda, Melis, & Stancampiano, 1996). Release of ACh in the amygdala may similarly be related to memory formation. Intra-amygdala injections of histamine H₃ receptor antagonists decrease ACh release and impair fear conditioning (Passani et al., 2001).

By marking the activation of neural systems during learning, patterns of ACh release in different neural systems can also be viewed as providing direct information about the role of ACh in coordinating the relative contributions of separate neural systems during learning. For example, just as an intact septohippocampal system can apparently interfere with learning an amygdala-dependent task (Ferbinteanu & McDonald, 2001; Matthews & Best, 1995; McDonald & White, 1995), recent findings suggest that the magnitude of ACh release in the hippocampus is inversely related to good performance on an amygdala-dependent conditioned place preference task (McIntyre, Pal, Marriott, & Gold, 2002). Moreover, ACh release in the hippocampus and the ratio of ACh release in the hippocampus versus the striatum predict whether rats learn a T maze with a place strategy or a response strategy (McIntyre, Marriott, & Gold, 2003). Relatedly, increases in release of ACh in the hippocampus early during T-maze training and later increases in ACh release in the striatum after extensive T-maze training correspond to a transition of the expression of place solutions to response solutions to the T maze after extensive training (Chang & Gold, *in press*). Such findings suggest that ACh release reflects activation of neural systems during learning and can reflect competition between neural systems for control over learned responses.

In addition to examples of competition between memory systems, there are some instances in which separate neural systems appear to work cooperatively to form new memories. For example, Packard, Cahill, and McGaugh (1994) found that direct administration of amphetamine into the amygdala immediately after training facilitated retention of both hippocampus-dependent and caudate nucleus-dependent tasks, whereas intra-amygdala lidocaine injections did not impair performance on either task. These findings indicate that processing of these forms of memory does not depend on the amygdala, but activation of the amygdala may contribute to memory formation that is supported by other systems.

Similarly, McNay and Gold (1998) found that the memory impairment that resulted from morphine injections into the medial septum was attenuated by glucose infusions into the amygdala, suggesting a cooperative interaction between the amygdala and septohippocampal systems.

The goal of the present study was to examine further the relationship between the hippocampus and amygdala during learning, specifically by assessing release of ACh in the amygdala while rats were tested on a hippocampus-dependent spontaneous alternation task in which the amygdala appears to cooperate with processing in the hippocampus (McNay & Gold, 1998). If the amygdala competes with the hippocampus for control over learning, the extent of ACh release in the amygdala should be inversely related to performance on the hippocampal task. If the relationship is cooperative, ACh release in the amygdala should be positively related to performance on this task.

Method

Subjects

Fourteen adult male Sprague–Dawley rats (Hilltop breeders, Scottsdale, PA), weighing between 275 and 300 g, were housed individually. Rats were maintained on a 12-hr light–dark cycle (on at 0700), with ad-lib access to food and water.

Surgery

All rats were injected with atropine sulfate (0.4 mg/kg ip) prior to being anesthetized with sodium pentobarbital (50 mg/kg ip). Plastic guide cannulas (CMA/12 type; Carnegie Medicin, Stockholm, Sweden) were implanted unilaterally in the right amygdala according to standard stereotaxic procedures. Coordinates were 0.2 mm posterior to bregma, +4.6 mm lateral, and 6.9 mm ventral from dura. The nose bar was set at 5.0 mm above the interaural line according to the atlas of Pellegrino, Pellegrino, and Cushman (1979).

Microdialysis Procedure

A 1-mm dialysis probe (CMA/12; Carnegie Medicin) was inserted through the guide cannula 24 hr prior to sample collection and again 85 min before sample collection. On the second insertion, plastic tubing connected the dialysis tubing to a microinfusion system (CMA/100; Carnegie Medicin). The dialysis probe was perfused continuously at a rate of 1.0 μ l/min with cerebrospinal fluid (128 mM NaCl/2.5 mM KCl/1.3 mM CaCl₂/2.1 mM MgCl₂/21 mM Na₂HPO₄/3.3 mM glucose, brought to pH 7.0 by NaOH), which contained the acetylcholinesterase inhibitor neostigmine (1 μ M). A recent study found that the percent increase in ACh release during testing was comparable at neostigmine concentrations ranging from 1 ng to 1 μ g (Chang & Gold, study in progress). A total of seven samples were collected from each rat. Three baseline samples (1 μ l/min for 25 min) were taken before the rat was placed on the maze (Samples 1–3), one sample was taken while the rat was being tested on the maze (Sample 4), and three samples were collected after the rat was removed from the maze (Samples 5–7).

Apparatus

A plus-maze was used for spontaneous alternation testing. Each arm was 55 cm long and 10 cm wide, with 12-cm-high walls made of poster board. The central platform was 25 cm across. The floor and walls of the central platform and the floors of the arms were made of wood that was

painted flat gray. The ends of the arms were open, and the maze was elevated 90 cm from the floor. The room contained various extramaze cues.

Spontaneous Alternation

One week following surgery, rats were handled for 3 days (5 min/day) prior to behavioral testing. Rats were tested for spontaneous alternation performance on the plus-maze. All arms were accessible, and no food was on the maze. Rats were allowed to explore the maze freely for 25 min. An alternation was recorded if a rat entered all four arms within a series of five consecutive entries. Percent alternation was scored as (total alternations) \div (number of entries - 4) \times 100.

In previous experiments examining ACh release during spontaneous alternation performance, rats were allowed to explore the maze for only 12 min (Ragozzino et al., 1996; Stefani & Gold, 1998). However, because the amygdala is a smaller structure than the hippocampus, a 1-mm dialysis probe was used. Use of such a small membrane surface area required a slower flow rate to increase retention of ACh. Thus, we extended the testing time to 25 min in order to collect a sufficient volume for analysis by high-performance liquid chromatography (HPLC). Percent alternation was analyzed after 12 min and again after 25 min of testing. Percent alternation scores did not differ at either time point; however, the rate of arm entries decreased over time.

ACh Assay

Microdialysis samples (20 μ l) were assayed for ACh content by means of HPLC with electrochemical detection. ACh was separated from choline with a reverse-phase analytical column (Chromspher 5 C18, 100 \times 3 mm; Chrompack, Middleburg, the Netherlands). An enzymatic postcolumn reactor containing acetylcholinesterase (EC 3.1.1.7, Type VI-S; Sigma, St. Louis, MO) and choline oxidase (EC 1.1.3.17; Sigma) converted the ACh to choline and acetate and the choline to betaine. The final conversion to hydrogen peroxide was electrochemically detected by a platinum electrode held at a potential of +525 mV. Mobile phase containing 0.2 mM dibasic potassium phosphate, 1.0 mM tetramethylammonium hydroxide, 0.3 mM EDTA, and 0.005% ProClin 150 Reagent (to prevent bacterial growth; Bioanalytical Systems, West Lafayette, IN) was delivered at a rate of 0.6 ml/min by a solvent delivery system (PM-80; Bioanalytical Systems, West Lafayette, IN). The detection limit was 50 fmol. ACh peaks were quantified by comparison to peak heights of ACh standard solutions.

Histology

After completion of microdialysis and behavioral testing, rats were administered a lethal dose of sodium pentobarbital and were perfused intracardially with 0.9% (wt/vol) saline and a 10% (wt/vol) Formalin solution. Brains were removed and placed in a 30% (wt/vol) sucrose-Formalin solution for storage, frozen at -20°C , and later sectioned on a Leica 1800 cryostat (Leica Microsystems, Wetzlar, Germany). Sections (40 μ m) were taken beginning at the anterior amygdala and continuing through the extent of the cannula damage, mounted onto slides, and stained with Cresyl violet. Figure 1 illustrates an example of an acceptable placement, with the dialysis probe drawn to scale. Rats with probe placements outside of this area were not included in data analysis.

Statistical Analysis

Microdialysis data were converted to percentages from each rat's baseline output. Baseline scores were derived from the mean levels of ACh in the first three samples taken while rats were in their home cages (3.8 ± 0.7 pmol/24 μ l). A two-tailed, matched *t* test was used to compare the percent change between baseline extracellular levels of ACh and mean percent ACh output during spontaneous alternation behavior. Correlations were

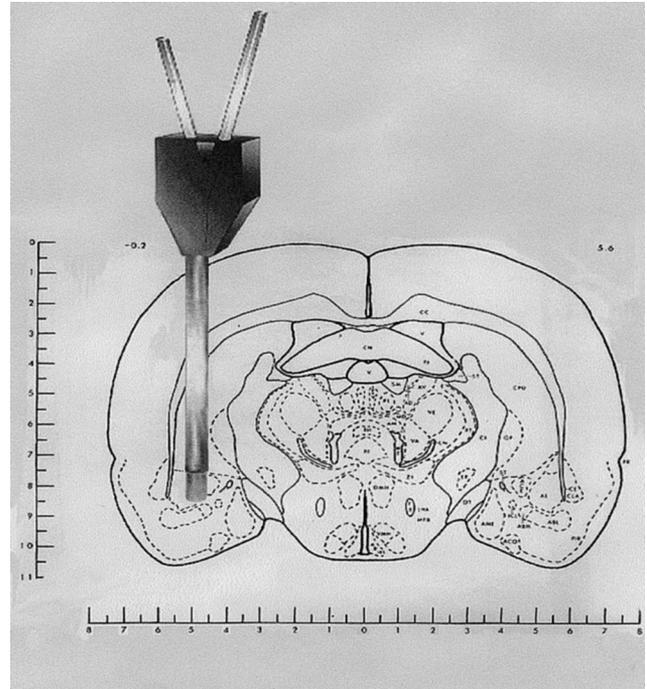


Figure 1. An example of an acceptable probe placement, illustrated on a section from the atlas of Pellegrino et al. (1979). The 1-mm probe membrane is to scale, relative to the brain. Although the probe was directed at the lateral amygdala, dialysis most likely included acetylcholine drawn from much of the amygdala. From *A Stereotaxic Atlas of the Rat Brain* (-0.2 – 5.6), by L. J. Pellegrino, A. S. Pellegrino, and A. J. Cushman, 1979, New York: Plenum Press. Copyright 1979 by Plenum Press. Adapted with permission.

tested to analyze the relationship between percent increase in ACh during behavior and performance (percent alternation score).

Results

Spontaneous alternation scores ranged from 60% to 87%. The mean alternation score was $70.86\% \pm 4.44\%$. Release of ACh in the amygdala increased to a mean of 156% of baseline during spontaneous alternation testing. Release of ACh in the amygdala was significantly greater while rats were performing the hippocampus-dependent spontaneous alternation task than when they were in their home cages, $t(6) = 3.43$, $p < .02$ (see Figure 2). The percent increase in release of ACh was similar to that seen in the hippocampus during spontaneous alternation testing (McIntyre, Pal, et al., 2002; Ragozzino et al., 1996; Ragozzino, Pal, Unick, Stefani, & Gold, 1998).

Of particular importance, the magnitude of increase of ACh release above baseline in the amygdala was positively correlated with performance on the spontaneous alternation task ($r = .77$, $p = .04$; see Figure 3). This relationship is the inverse of the relationship between ACh release in the hippocampus and performance on an amygdala-dependent task.

The relationship between the magnitude of ACh release above baseline and the number of arm entries was not significant ($r = -.70$, $p = .50$). The direction of the nonsignificant relationship

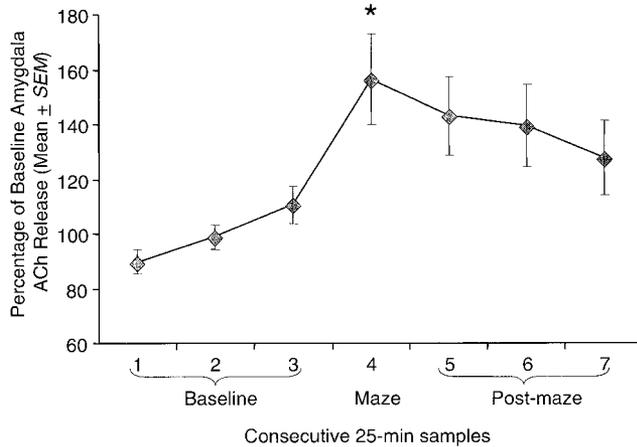


Figure 2. Mean (\pm SEM) percentage of baseline acetylcholine (ACh) release in the amygdala before, during, and after spontaneous alternation testing. ACh release increased significantly in the amygdala when rats were performing the spontaneous alternation task (* $p = .014$).

was opposite that of the relationship between increases in ACh release and alternation scores. These results suggest that the positive correlation between ACh release in the amygdala and performance is not related to increased locomotor activity (see Figure 4).

Discussion

Although the amygdala is not necessary for good performance on this spontaneous alternation task, release of ACh in the amygdala nonetheless increased significantly during testing. Moreover, the magnitude of release of ACh in the amygdala was positively correlated with good performance, indicating that rats with good spatial working memory were also those in which release of ACh in the amygdala was greatest. To the extent that ACh release reflects activation and participation of the amygdala during spontaneous alternation testing, these findings suggest that the amygdala is involved in spontaneous alternation performance. This

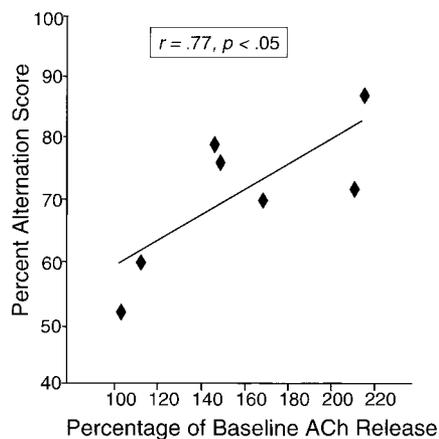


Figure 3. Relationship between the magnitude of increase in acetylcholine (ACh) release over baseline during spontaneous alternation testing and performance on the spontaneous alternation task.

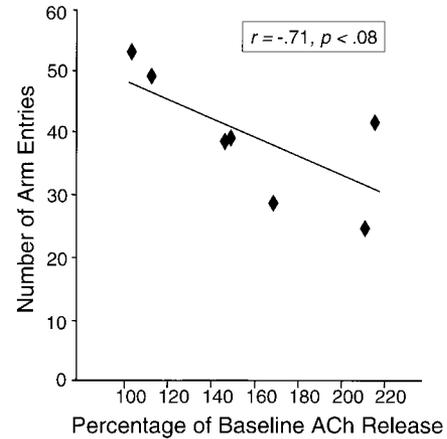


Figure 4. Relationship between the magnitude of increase in acetylcholine (ACh) release over baseline and the number of arm entries during spontaneous alternation testing. The correlation was not significant. Note that the trend was in a negative direction, opposite that of the relationship between alternation scores and ACh release shown in Figure 3.

conclusion is contrary to what one would expect on the basis of evidence obtained with lesions, but it is consistent with evidence that glucose injections into the amygdala enhance performance on a spontaneous alternation task (McNay & Gold, 1999).

An alternative possibility is that high levels of ACh release in the amygdala might inactivate that system, that is, reflecting an inverted-U function commonly found in studies of memory modulation. According to this view, the cooperation suggested by the present results may instead reflect release of competition of the amygdala with hippocampal processing. Although it is an interesting possibility, this interpretation seems unlikely. First, our studies of ACh in the hippocampus do not suggest an inverted-U relationship between ACh release and memory, but instead, a positive monotonic relationship with learning and memory on hippocampus-dependent tasks and a negative monotonic relationship with learning and memory on amygdala- or striatum-dependent tasks (Chang & Gold, in press; McIntyre, Marriott, & Gold, 2003; McIntyre, Pal, et al., 2002; Ragozzino & Gold, 1995). In addition, the inverted-U dose-response relationship between glucose and spontaneous alternation performance was mirrored by an inverted-U dose-response relationship between glucose and ACh release, not the monotonic relationship predicted by this interpretation. Nonetheless, the possibility that high levels of ACh release might down-regulate the contribution of a neural system to learning and memory is clearly worthy of future investigation.

Because microdialysis in the amygdala has not been paired with spontaneous alternation performance in the past, one consideration was that the correlation seen between percent alternation scores and ACh release was due to an increase in locomotion in the rats that performed more alternations. However, because release of ACh in the amygdala was not significantly related to the total number of arm entries, differences in locomotion per se do not account for the present results. In fact, a trend toward a negative correlation was observed in this analysis.

The positive correlation between amygdala ACh release and spontaneous alternation performance seen here supports the view

that the amygdala serves as a modulator of multiple forms of memory, and therefore of multiple memory systems, even when it is not required for the formation of such memories (McGaugh, 2000; McGaugh, Cahill, & Roozendaal, 1996). It is interesting that although the amygdala is often associated with memory for emotionally arousing experiences (Cahill, 2000; Davis, 1992; Gold & McGaugh, 1975; LeDoux, 2000; Weiskrantz, 1956), the present findings suggest that the amygdala also modulates learning and memory under relatively lower levels of arousal, such as exposure to a novel maze.

Other findings indicate that the amygdala modulates memory processing in multiple neural systems. For example, injections of memory-enhancing drugs into the amygdala attenuate impairment induced by infusions of memory-impairing drugs into the hippocampus or medial septum (McNay & Gold, 1999; Roozendaal & McGaugh, 1997). In addition, infusions of memory-enhancing drugs into the amygdala enhance performance on both spatial and cued versions of the water maze (Packard et al., 1994; Packard & Teather, 1998). Moreover, electrophysiological data indicate that the basolateral nucleus of the amygdala plays a role in long-term potentiation in the dentate gyrus of the hippocampus (Ikegaya, Saito, & Abe, 1996a, 1996b).

According to one model of amygdala modulation of multiple systems of memory, cholinergic activation is the last step in a neurochemical organizational scheme within the amygdala that acts shortly after a learned experience or after injection of a drug to enhance memory formation (Dalmaz, Introini-Collison, & McGaugh, 1993; Introini-Collison, Dalmaz, & McGaugh, 1996; Power et al., 2000). Although adrenergic drugs affect memory when injected systemically or within the amygdala, administration of cholinergic drugs into the amygdala attenuates these effects. However, intra-amygdala infusions of GABAergic or opioid drugs do not block the effects of adrenergic drugs. Therefore, the present findings provide support for the hypothesis that release of ACh within the amygdala reflects activation of the amygdala that is important for modulating other neural systems, such as the hippocampus, during learning.

The present findings are also important because they provide evidence that the relationship between the hippocampal system and the amygdala system is not one of mutual competition. When considering interactions among neural systems, the role of the amygdala in supporting processing for a hippocampus-dependent task stands in marked contrast to the role of the hippocampal system, in which competition with other neural systems appears to be a dominant characteristic. Thus, as more information is acquired about the interactions between multiple memory systems, several features are becoming clear:

1. Different neural systems, which have been shown by lesion studies to support different types of memory, appear to interact when the brain is whole.
2. There may be a hierarchical organization to the systems whereby some systems compete more successfully than others for control over learning.
3. Although some relationships between memory systems are competitive, others are cooperative.

4. The relationships between systems are not reciprocal.

Previous results have shown that hippocampal activation can have a negative influence on amygdala-dependent memory (McIntyre, Pal, et al., 2002; White & McDonald, 1993). The present findings suggest that cholinergic activation of the amygdala apparently does not have the reciprocal effect on hippocampus-dependent memory but instead is positively correlated with performance on a hippocampus-dependent task.

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