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Review

Regulation of memory – From the adrenal medulla to liver to astrocytes to neurons☆

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ABSTRACT

Epinephrine, released into blood from the adrenal medulla in response to arousing experiences, is a potent enhancer of learning and memory processing. This review examines mechanisms by which epinephrine exerts its effects on these cognitive functions. Because epinephrine is largely blocked from moving from blood to brain, it is likely that the hormone's effects on memory are mediated by peripheral actions. A classic effect of epinephrine is to act at the liver to break down glycogen stores, resulting in increased blood glucose levels. The increase in blood glucose provides additional energy substrates to the brain to buttress the processes needed for an experience to be learned and remembered. In part, it appears that the increased glucose may act in the brain in a manner akin to that evident in the liver, engaging glycogenolysis in astrocytes to provide an energy substrate, in this case lactate, to augment neuronal functions. Together, the findings reveal a mechanism underlying modulation of memory that integrates the physiological functions of multiple organ systems to support brain processes.

This article is part of a Special Issue entitled 'Memory enhancement'.

Contents

1. Memory consolidation and memory modulation

Many treatments enhance memory when administered soon after an experience and do so in retrograde time-dependent manner (McGaugh and Petrinovich, 1965; McGaugh, 1966, 2000; McGaugh and Roozendaal, 2009; Gold, 2008; Gold and Korol, 2012). These findings complement the extensive evidence that amnestic treatments can also act in time-dependent retrograde fashion.

Retrograde enhancement of memory studies, together with retrograde amnesia studies, provided much of the bases for ideas about memory consolidation, i.e. that the temporal properties of post-training treatments revealed the time needed to form new memories. Similar ideas come from examination of the time courses of cell molecular responses, and manipulations of those responses, during the time after a training experience. In these studies too, the temporal functions for different responses differ widely. Some of these findings are described and discussed below.

While the findings are clear, the interpretation of these findings as a basis to define temporal properties of memory formation is not clear (Gold and McGaugh, 1975; Gold, 2006, 2008). Beginning with

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a consideration of retrograde amnesia and memory enhancement gradients, if there were a time-constant for memory formation, one would expect a rather narrow range of times after training when treatments were effective. However, there are very different temporal gradients across tasks, species and treatments. Differences by tasks and species might of course reflect real differences in the time needed to form memory under different conditions. Less readily incorporated into memory consolidation frameworks are the many findings that a single treatment can affect memory across widely different times after training depending on the dose or intensity of the treatment (cf. Gold and McGaugh, 1975; Gold, 2008), suggesting that such differences in the temporal characteristics of retrograde amnesia represent properties of the treatments rather than those of an underlying memory process (Gold and McGaugh, 1975). Similarly, anterograde amnesia gradients are often taken as evidence of decay of a short-term memory process that can be seen in the absence of impaired long-term memory formation. (A few of many examples: Bourtchouladze et al., 1998; Wang et al., 2006; Taubenfeld et al., 2001). However, in these instances too the time-course varies with the specific treatment and often with the dose or intensity of that treatment (cf. Gold, 2008), sometimes even revealing non-monotonic decay functions (Schafe and LeDoux, 2000).

The vastly different functions for the temporal gradients of anterograde and retrograde impairments and enhancements of memory suggest that, while the underlying construct of memory consolidation may be valid, the literature does not provide direct support for a unitary function that represents the time necessary for memory formation.

Instead, it appears on the basis of the results above that there may be multiple biological factors responsible for the formation of new memories. Some of these factors may occur soon after an experience while others have rather long times to onset (Izquierdo et al., 2006) and still others appear in waves after training (Bekinschtein et al., 2007; Bourtchouladze et al., 1998; Nader et al., 2000; Igaz et al., 2002; Abel and Lattal, 2001). For example, as described by Izquierdo et al. (2006), cGMP levels peak within minutes of inhibitory avoidance training and PKC levels peak about 2 h after training. PKA levels peak within minutes of training, return toward baseline at 1 h, and then peak again at 3 h, returning to baseline at 8–9 h after training. Moreover, some molecular responses, e.g. pCREB (Taubenfeld et al., 2001) and pERK (Trifilieff et al., 2007) have durations that peak early, decrease, and then increase and remain increased beyond 24 h. In addition, the duration of these responses to experience can themselves be short or long. These multiple temporal properties for amnesia contribute important information about the sensitivity of memory to pharmacological and other manipulations but also complicate the interpretation of the effects of post-training treatments on memory processes. It seems likely that molecular mechanisms of memory involve a network of serial and parallel molecular responses with multiple time courses to regulate memory processing (Izquierdo et al., 2006).

Given the diverse temporal characteristics of anterograde and retrograde treatment effects on memory and of molecular players in the formation of memory, questions about the neurobiology may gain focus by studying how the multiple changes are initiated and regulated by physiological responses to experiences. This view captures the distinction between modulation and consolidation of memory. Consolidation of memory refers to the formation of a neural product of memory while modulation of memory refers to up- and down-regulation of processes that participate in the storage of new memories. While modulation of memory is often used to describe enhancement of memory formation, the term applies as readily to down- as well as up-regulation of memory processing.

2. Epinephrine and memory

The multiple time courses seen for retrograde and anterograde enhancement and impairment of memory led directly to the development of early ideas about modulation of memory. The question became: what was the purpose of changes in memory and in susceptibility to treatments that enhanced and impaired memory? One answer is that there are endogenous responses to an experience – arousal, neuroendocrine changes, etc. – that regulate memory processes (for reviews: Gold and McGaugh, 1975; Korol and Gold, 2007, 2008; McGaugh and Roozendaal, 2009).

One of the earliest identified and most potent hormonal regulators of memory is epinephrine (Gold and van Buskirk, 1975, 1978a). Epinephrine is released from the adrenal medulla into blood in response to training experiences in a graded manner related to the arousal and emotion of the triggering experience (McCarty and Gold, 1981). Many of the demonstrations of enhancement of memory with epinephrine have used inhibitory avoidance tasks. In these tasks, epinephrine is particularly effective at enhancing memory for training with low footshock intensities, apparently by mimicking a physiological response seen with an experience of higher arousal (McCarty and Gold, 1981). In addition to inhibitory avoidance tasks, the efficacy of epinephrine as a treatment with which to enhance memory has also been demonstrated using active avoidance, conditioned emotional response, one-trial water-motivated appetitive, visual discriminated avoidance, spatial working memory, and object recognition memory tasks (Sternberg et al., 1985; Introini-Collison and McGaugh, 1986; Stone et al., 1992; Talley et al., 2000; Dornelles et al., 2007). Epinephrine also enhances memory in humans (Cahill and Alkire, 2003; Cahill et al., 2003). This broad base of findings likely represents the involvement of multiple memory systems, providing evidence that epinephrine enhancement of learning and memory is itself probably mediated by effects at multiple memory systems.

The relationship between circulating levels of epinephrine and memory is not a monotonic function. Low doses of epinephrine have little effect on memory, moderate doses enhance memory, and high levels impair memory. The dose-dependent profile for epinephrine effects on memory may be a biological instantiation of the inverted-U function relating arousal to learning and memory characterized long ago by Yerkes and Dodson (1908). The inverted-U dose-response curve, with enhancement and impairment of memory at different doses, applies to most treatments that modulate memory, apparently including even protein synthesis inhibitors (Gold and Wrenn, 2012), suggesting that a wide range of treatments my act on memory through shared cellular mechanisms.

Although the inverted-U is most directly shown with dose-response curves, interactions of exogenous treatments with endogenous arousal are also evident. A single dose of epinephrine enhances 24-h memory for inhibitory avoidance training with a single footshock of low intensity but impairs 24-h memory for training with a single footshock of high intensity (Gold and van Buskirk, 1978a). Results like these suggest that endogenously released epinephrine may be additive with exogenously administered epinephrine to produce the inverted-U relationship with memory. The results suggest further that epinephrine, as well as other endogenous modulators of memory including glucose described below, may provide elements of the biological underpinnings of for both memory enhancement and impairment.

The ways by which high doses of modulators of memory produce amnesia are unclear and at present quite speculative (cf. Gold, 2006; Calabrese, 2008; Mattson, 2008; Gold and Korol, 2012). One suggestion is that the memory is erased by overly active mechanisms of plasticity, making and breaking connections too rapidly to retain memory for a new experience. Another is that there is too much