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Review

Forgetfulness during aging: An integrated biology ☆,☆☆

Paul E. Gold *, Donna L. Korol

Department of Biology, Syracuse University, Syracuse, NY 13244, United States

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ABSTRACT

Age-related impairments in memory are often attributed to failures, at either systems or molecular levels, of memory storage processes. A major characteristic of changes in memory with increasing age is the advent of forgetfulness in old vs. young animals. This review examines the contribution of a dysfunction of the mechanisms responsible for modulating the maintenance of memory in aged rats. A memory-modulating system that includes epinephrine, acting through release of glucose from liver glycogen stores, potently enhances memory in young rats. In old rats, epinephrine loses its ability to release glucose and loses its efficacy in enhancing memory. Brain measures of extracellular levels of glucose in the hippocampus during memory testing show decreases in glucose in both young and old rats, but the decreases are markedly greater in extent and duration in old rats. Importantly, the old rats do not have the ability to increase blood glucose levels in response to arousal-related epinephrine release, which is retained and even increased in aged rats. Glucose appears to be able to reverse fully the increased rate of forgetting seen in old rats. This set of findings suggests that physiological mechanisms outside of the brain, i.e. changes in neuroendocrine functions, may contribute substantially to the onset of rapid forgetting in aged animals.

1. Introduction

Aging is accompanied by rapid forgetting in humans (e.g., Craik, Anderson, Kerr, & Li Karen, 1995; Craik & Salthouse, 1992; Davis et al., 2003; Kausler, 1994; Mary, Schreiner, & Peigneux, 2013) and increased forgetfulness with aging is also evident in animals other than humans, as detailed below. In particular, studies using laboratory rodents show age-related increases in rates of forgetting and provide reliable and valid models with which to study the biological bases of forgetfulness during aging. The issue of the rapid forgetting that characterizes memory in aged animals is the focus of this paper.

2. Background: epinephrine and glucose modulation of memory processing

It has been known since at least the early 20th century that there is an optimal level of arousal that facilitates information processing and promotes memory formation (Yerkes & Dodson, 1908). Epinephrine is perhaps the best-studied example of a hormonal mediator of the modulation of memory by arousal. Epinephrine administered near the time of behavioral testing enhances learning and memory across a wide spectrum of tasks in rodents (cf. Gold, 2008, in press) and also enhances the durability of long-term potentiation (Korol & Gold, 2008). Administration of epinephrine also enhances memory in humans (Cahill & Alkire, 2003; Cahill, Gorski, & Le, 2003). Together, the results suggest that the conditions under which epinephrine enhances cognitive functions are very broad.

Epinephrine is released from the adrenal medulla in graded fashion during times of arousal and thus is physiologically well-positioned to play an important role in the sequelae that modulate memory (Gold & McGaugh, 1975). Plasma levels of the hormone increase about twofold above baseline when rats are placed in a novel environment, increasing several fold after footshock or after immersion in water, as in inhibitory avoidance and swim tasks, respectively (Mabry, Gold, & McCarty, 1995a, 1995b). The large dynamic range of the physiological responses of epinephrine support

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* Corresponding author. Address: Department of Biology, Syracuse University, Life Sciences Complex, 107 College Place, Syracuse, NY 13244, United States. Fax: +1 315 443 2012.

E-mail address: pegold@syr.edu (P.E. Gold).

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a role for regulating brain functions across a range of arousing and emotional situations that can readily match the many instances when epinephrine enhances memory.

Because circulating epinephrine is largely excluded from the brain (Axelrod, Weil-Malherbe, & Tomchick, 1959; Hardebo & Owman, 1980; Weil-Malherbe, Whitby, & Axelrod, 1961), a peripheral mechanism likely serves as an intermediate step between increases in plasma epinephrine levels and the hormone's effects on brain functions such as learning and memory. There is now substantial evidence, as reviewed recently (Gold, in press; Gold & Korol, 2012), showing that increased blood glucose levels in response to increases in epinephrine levels reflects a key mechanism linking epinephrine to memory. In a set of fundamental and classic experiments in biology, Sutherland and Rall (1960) showed that epinephrine activates hepatic adrenergic receptors to initiate the breakdown of glycogen to glucose with subsequent release of glucose into blood; it is these experiments that provided the first evidence for second-messenger systems in response to activation of cell membrane receptors.

The evidence that glucose mediates epinephrine effects on memory takes several forms (Gold, in press). Like epinephrine, systemic administration of glucose enhances memory on a wide variety of tasks (cf.: Gold, 2008, in press; Korol & Gold, 2007; Messier, 2004). The glucose doses that enhance memory result in blood glucose levels comparable to those seen after epinephrine doses that enhance memory. Also, peripheral adrenergic receptor antagonists block epinephrine effects on memory and also block the associated increases in blood glucose levels; however, the adrenergic receptor antagonists do not block glucose enhancement of memory (Gold, Vogt, & Hall, 1986; Hall & Gold, 1992). Additional evidence supporting the view that increases in blood glucose contribute importantly to and are downstream from epinephrine enhancement of memory is that epinephrine loses its ability to enhance memory in rats that are deprived of food, with subsequent loss of liver glycogen stores and of the ability to generate glucose in response to epinephrine injections (Talley, Kahn, Alexander, & Gold, 2000). In contrast, glucose effects on memory are retained in food-restricted rats (e.g., Messier & Destrade, 1988; Packard & White, 1990; Winocur & Gagnon, 1998). Additional evidence derived from studies of aging and memory is described below.

3. Rapid forgetting in aged rats and mice

Across many studies, the findings show that aged rats and mice exhibit learning and memory performance comparable to that of young adults when tests are administered soon after training but show poor memory relative to young animals when tests are administered at later times after training (Barnes, 1991; Foster, 1999; Gold, 2001, 2005; Gold & Stone, 1988; Korol, 2002; Morris, Chang, Mohler, & Gold, 2010; Morris & Gold, 2012, 2013; Wimmer, Hernandez, Blackwell, & Abel, 2012; Winocur, 1988). While there are many examples of accelerated forgetting in aged rodents, it is of interest that the specific time courses of forgetting differ by task. Memory for inhibitory avoidance training, which remains stable for weeks after training in young rats, is intact soon after training but then deteriorates over the next several days in aged rats; middle-aged rats have intermediate rates of forgetting (Gold, McGaugh, Hankins, Rose, & Vasquez, 1982). A clear example of age-related increases in forgetting rates can be seen across young adult (70-day-old), middle-aged (1-yr-old), and senescent (2-yr-old) male rats trained on an inhibitory avoidance task (Fig. 1). After a single training trial, independent groups of rats were tested for memory at different post-training times. As shown in Fig. 1, young adult rats showed good memory for several weeks after training, with some forgetting appearing after a 6-week delay between the training trial and the memory test. Forgetting was evident at 7 days of training in 1-year-old rats and reached the low latencies of untrained rats (not shown) at 21 days. In 2-yr-old rats, forgetting emerged after 1 day and was considerable at 7 days after training. As mentioned before, rapid forgetting is also evident after training in many other tasks, including swim (Gage, Dunnett, & Bjorklund, 1984; Lindner, Balch, & VanderMaelen, 1992; Mabry, McCarty, Gold, & Foster, 1996; Rapp, Rosenberg, & Gallagher, 1987), reward reduction (Salinas & Gold, 2005), visual discriminated avoidance (Gold et al., 1982), spatial (Barnes & McNaughton, 1985; Markowska, 1999), spatial reversal (Zornetzer, Thompson, & Rogers, 1982), odor-reward association (Roman, Alescio-Lautier, & Soumireu-Mourat, 1996), social transmission of food preference (Countryman & Gold, 2007) tasks, and object location (Wimmer et al., 2012) tasks.

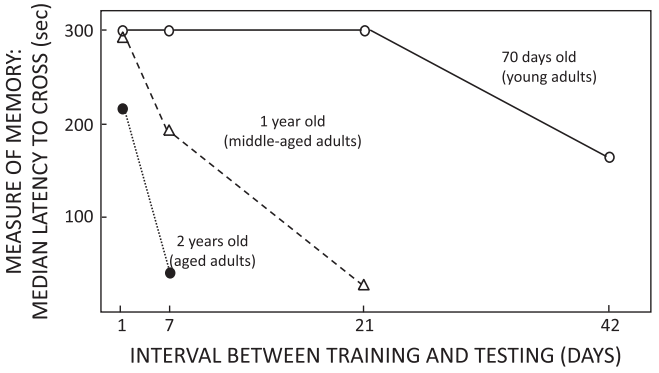

Fig. 1. Age-related differences in forgetting rates. Rats were trained on a one-trial inhibitory avoidance task and memory was assessed at different times after training. Note that the rate of forgetting increased with age (from Gold et al., 1982).

In experiments examining age-related differences in memory across time after training, forgetting rates are often assessed after 24-h or longer intervals between training and test trials and therefore can be characterized as a failure of long-term maintenance of new memories. However, the same general principle of rapid forgetting is also evident in tasks that tap working memory and that, by their nature, have shorter forgetting times even in young rats. For example, in a test of spatial working memory, spontaneous alternation scores in a Y-maze are similar in young and two-year-old mice permitted to move freely through the maze but not when an interval of 60 s was imposed between arm choices (Stone, Rudd, & Gold, 1992). Rapid deterioration of spatial working memory, tested in a swim task, can also be observed after 3-min delays in 2-yr-old females shown to be reproductively senescent (Markowska, 1999).

Rapid forgetting may also explain results seen in classical conditioning experiments. These experiments show that trace conditioning, with a delay between the conditioned and unconditioned stimuli, is more impaired by aging in both laboratory animals and humans than is delay conditioning, where the unconditioned stimulus occurs at the end of a conditioned stimulus (e.g., Graves & Solomon, 1985; Solomon & Groccia-Ellison, 1996; Thompson, Moyer, & Disterhoft, 1996). Moreover, the age-related impairment increases as the time between the conditioned and unconditioned stimulus increases, suggestive of rapid forgetting of the conditioned stimulus. The fleeting quality of memory for new information in old animals, evident for both short- and long-lasting types of memories, suggests that there is impaired maintenance – or enhanced forgetting – of new information that transcends the classically defined stages of memory formation, e.g. short- and long-term memory.

The pervasiveness of rapid forgetting across many tasks and across species also suggests age-related changes across different

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