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FORGETFULNESS DURING AGING: AN INTEGRATED BIOLOGY

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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, potentially 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.

Keywords

aging; age-related memory impairments; epinephrine; glucose; astrocytes; brain metabolism and memory; memory consolidation and modulation

INTRODUCTION

Aging is accompanied by rapid forgetting in humans (e.g., Craik, Anderson, Kerr and Li, 1995; Craik and Salthouse, 1992; Kausler, 1994; Davis et al., 2003; Mary et al., 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

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forgetfulness during aging. The issue of the rapid forgetting that characterizes memory in aged animals is the focus of this paper.

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 and 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, 2014) and also enhances the durability of long-term potentiation (Korol and Gold, 2008). Administration of epinephrine also enhances memory in humans (Cahill and Alkire, 2003; Cahill et al., 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 and McGaugh, 1975). Plasma levels of the hormone increase about two-fold 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 et al., 1995a,b). The large dynamic range of the physiological responses of epinephrine support 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 (Weil-Malherbe et al., 1961; Axelrod et al., 1959; Hardebo and Owman, 1980), 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 and Korol, 2012; Gold, 2014), 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, 2014). Like epinephrine, systemic administration of glucose enhances memory on a wide variety of tasks (cf.: Messier, 2004; Korol and Gold, 2007; Gold, 2008, 2014). 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 et al., 1986; Hall and 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 et al., 2000). In contrast, glucose effects on memory are retained in food-restricted rats (e.g., Winocur and Gagnon, 1998; Packard and White, 1990; Messier and Destrade, 1988). Additional evidence derived from studies of aging and memory is described below.

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; Winocur, 1988; Foster, 1999; Gold, 2001; Korol, 2002; Morris et al., 2010; Morris and Gold 2012, 2013; Wimmer et al., 2012; Gold and Stone, 1988; Gold, 2005). 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 et al., 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 (Figure 1). After a single training trial, independent groups of rats were tested for memory at different post-training times. As shown in Figure 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 et al., 1984; Rapp et al. 1987; Lindner et al., 1992; Mabry et al. 1996), reward reduction (Salinas and Gold, 2005), visual discriminated avoidance (Gold et al., 1982), spatial (Barnes and McNaughton, 1985; Markowska, 1999), spatial reversal (Zornetzer et al., 1982), odor-reward association (Roman et al., 1996), social transmission of food preference (Countryman and Gold, 2007) tasks, and object location (Wimmer et al., 2012) tasks.

In experiments examining age-related differences in memory across time after training, forgetting rates are often assessed after 24-hour 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 sec was imposed between arm choices (Stone et al., 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 and Solomon, 1985; Solomon and Groccia-Ellison, 1996; Thompson et al., 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 brain areas that are employed for different tasks. In many experiments, there has been an emphasis on age-related changes in hippocampal functioning, with many using the hidden-platform version of the swim task for behavioral assessments (cf. Robitsek et al., 2008). These experiments have resulted in a wide array of biological correlates of individual differences in learning on this task. As assessed by neuroendocrine responses to stress, some of which are discussed below, immersion in water is more stressful than is training-related footshock and substantially so in older rats (Mabry et al., 1995a). Differential stress responses across ages, such as elevated epinephrine release to water immersion, may therefore alter learning strategies in the swim task by increasing thigmotaxis. Thus, age-related memory loss may reflect an age difference in stress responses, age differences in learning strategies, age differences in mechanisms of memory formation, or all of these. Whether the focus on a single task, e.g. the swim task, and the derived focus on a single brain area, e.g. the hippocampus, is a good strategy is somewhat unclear (cf. Lindner, 1997; Nicolle et al., 2003). This is an especially important issue when viewed in the context of evidence that age-related deficits are also evident under behavioral conditions of low stress as in spatial reversal, social transmission of food preference, and object location tasks noted above. Moreover, it is clear that brain areas other than the hippocampus also exhibit changes during aging and these may contribute to the broad spectrum of tasks in which memory changes are evident. The intersection of research on the neurobiological underpinnings of age-related memory impairments with information from research based on approaches of multiple memory systems (cf.: White and McDonald, 2002; Poldrack and Packard, 2003; Korol et al., 2013; Mizumori and Jo, 2013; Kathirvelu and Colombo, 2013; Gold et al., 2013; Packard and Goodman, 2013; Konishi et al., 2013) needs more attention.

AGE-RELATED FORGETFULNESS AS A FAILURE OF MEMORY MODULATION: PERIPHERAL MECHANISMS

The extensive neurobiological changes during aging, together with the similar failures to hold new memories across tasks and species, suggest that the underlying mechanisms may

involve processes that are pervasive across brain areas and across neurochemical mediators of memory formation. An outcome of this perspective is the possibility that the dysfunctions in memory may be mediated by impairments not in the anatomical or neurochemical substrates of memory but instead in the modulators of memory formation, i.e. processes responsible for up-regulating the substrate mechanisms of memory, thereby engaging and amplifying the neural mechanisms of memory formation.

Both classes of research – on substrates and on modulators of substrates – have considered changes in the brain to be the key elements responsible for age-related memory impairments. At a level of analysis examining the machinery of memory formation, changes in brain function are undoubtedly appropriate targets for research. However, it is important to note that modulation of memory involves, in part at least, hormones such as epinephrine that are released outside the brain. Therefore, it is possible that physiological changes that initiate brain dysfunctions may reside outside the brain. This review will describe findings suggesting that an important locus of dysfunction may involve epinephrine regulation of memory processing specifically via an uncoupling between epinephrine and subsequent release of glucose from hepatic stores. The results demonstrate that a loss of arousal-initiated increases in blood glucose levels is associated with rapid forgetting in aged rats. The rapid forgetting can apparently be reversed by glucose administration. These results suggest that the brain mechanisms needed to form and to maintain memories are intact in aged rats but are not effectively engaged by modulators of memory to promote optimal memory formation. The perspective offered here is that alterations in brain functions that underlie rapid forgetting are secondary to loss of adequate blood glucose responses to arousing events.

UNCOUPLING OF EPINEPHRINE AND GLUCOSE IN AGED RATS

One way in which epinephrine and glucose modulation of memory might contribute to age-related accelerated forgetting would be if the neuroendocrine system were dysregulated in aged rats. Perhaps, release of epinephrine from the adrenal medulla during and after training is impaired in aged rats. However, the findings indicate exactly the opposite is true: Release of epinephrine is exaggerated in aged rats. In undisturbed young adult and aged (2-yr-old) rats, baseline levels of epinephrine were about the same. Despite similar baseline values, epinephrine levels in old rats rose about twice as much as in young rats when rats were placed in a water tank (Mabry et al., 1995a) (Figure 2).

Results consistent with greater release of epinephrine in old rats were also obtained using footshocks during inhibitory avoidance training (Mabry et al., 1995b). In this experiment, baseline epinephrine levels (~100 pg/ml) were again similar at both ages (not shown). As illustrated in Figure 3 (left), plasma epinephrine levels increased markedly more in aged rats than in young rats at all shock levels. Note that there is a difference by age evident even in the non-shocked rats after they were placed in the novel training apparatus (i.e., 0 mA footshock level). Thus, circulating epinephrine responses to training and to training-related arousal are markedly *increased*, not decreased, in aged rats. When viewed alone, these results suggest that if anything these adrenal modulatory processes shown to support memory in young adults are increased, not decreased with age.

However, even in the face of increased epinephrine release into the circulation, blood glucose responses to training or stress are severely attenuated in aged rats (Mabry, McCarty and Gold, 1995a; Morris et al., 2010). An example of the discrepant responses of epinephrine and glucose is shown in Figure 3 (compare left and right panels) particularly at the 1.0 mA shock level. Similarly, as shown in Figure 4, increases in blood glucose levels in response to epinephrine injections are severely depleted in aged rats. Blood glucose levels hardly increase after injections of a memory-enhancing dose (0.1 mg/kg) of epinephrine. These results suggest that epinephrine release may be increased by loss of negative feedback from the absent rise in glucose levels. In terms of modulation of memory, it may be the case then that deficient glucose production by the liver represents the impaired step in modulation of memory, contributing to the relative inability of aged rats to retain new memories.

Supporting this possibility are results showing that epinephrine is less effective at enhancing memory in old vs. young rats while glucose is effective at both ages. Rats were trained on a one-trial inhibitory avoidance task and memory was tested 48 hours later. Epinephrine or glucose was administered immediately after the training footshock (Figure 5). In this experiment, the shock intensity and the 48-hour training-test interval were selected to compare directly the efficacy of epinephrine and glucose in enhancing memory in young vs. old rats, requiring comparable memory at both ages to address the question clearly. Therefore, the control memory scores did not differ by age after 48 hours although rapid forgetting in aged rats as compared to young rats may have emerged at later times with these training conditions. In addition, the doses of epinephrine (0.1 mg/kg) and glucose (100 mg/kg) were selected to match enhancement scores in young rats. As shown in Figure 5, epinephrine significantly enhanced memory in young but not aged rats while, in contrast, glucose enhanced memory in rats at both ages.

Systemic injections of glucose enhance memory in aged rodents not only for inhibitory avoidance tasks, but also in reward reduction (Salinas and Gold, 2005), spatial (Winocur and Gagnon, 1998), and spontaneous alternation (McNay and Gold, 2001) tasks, fully reversing age-related memory deficits on each of these tasks and in some cases enhancing memory scores to the glucose-enhanced levels of young rats. Importantly, studies in healthy young, aged, and cognitively impaired humans using orally administered glucose have shown complementary results, with glucose enhancement characterized by an inverted-U dose-response curve and enhancing memory on a range of tasks (cf. Korol, 2002; Gold, 2005; Messier, 2004). Some of the largest effects of glucose on memory in humans have been seen in healthy elderly people and in people with Alzheimer's Disease, with enhancement of memory for a narrative prose passage of 30–40% in healthy individuals and 100% in Alzheimer's patients above their individual baselines (Manning et al., 1990, 1993; cf.: Gold, 2001; Korol, 2002).

In these multiple tasks and from rodents to humans, the enhancement of memory by glucose in aged subjects resulted in scores equal to or higher than those of the young subjects. These findings support the view that the aged brain apparently retains the ability to form and to maintain new memories but that the storage mechanisms are not effectively engaged by endogenous modulators of memory, such as glucose. The ability of exogenous systemically administered glucose to improve memory, together with a failure of epinephrine to initiate

release of glucose into blood from hepatic glycogen stores, suggests that a primary cause of rapid forgetting in aged rats is a peripheral one. Consistent with this view, we have preliminary findings indicating that glycogen levels in the liver are substantially lower in old vs. young rats. Moreover, epinephrine injections reduce liver glycogen concentrations in young rats, presumably by signaling the conversion of glycogen to glucose, but do not lower the already depleted glycogen concentrations in old rats. If confirmed, the decreased ability of epinephrine to initiate the release of glucose from hepatic glycogen stores in aged rats may explain why epinephrine very effectively enhances memory in young rats but is less effective at doing so in old rats.

AGE-RELATED FORGETFULNESS AS A FAILURE OF MEMORY MODULATION: CENTRAL MECHANISMS

Glucose availability

The findings reviewed above show that circulating glucose levels are not responsive to arousal and stress in aged rats and that old rats exhibit rapid forgetting. These results are coupled with evidence that exogenous glucose treatments enhance memory in aged rats. The collective evidence suggests either that circulating glucose, like epinephrine, augments memory processes via peripheral actions or that the brain requires the additional circulating glucose to support cognitive processes. These are certainly not mutually exclusive views. The first possibility - that glucose has peripheral signaling or other actions that contribute to memory enhancement in aged animals has not received much attention. However, the second possibility - that glucose acts directly on brain mechanisms - now has considerable support.

Using zero-net flux methods, glucose levels in brain ECF are ~1 mM in hippocampus and lower in other brain regions and do not saturate neuronal glucose transporters (Fellows et al., 1993; McNay and Gold, 1999, 2002). Because in normal states the glucose transporter is not saturated, brain extracellular levels of glucose are likely to fluctuate in response to changing need and are therefore positioned to regulate neuronal function (McNay and Gold, 2002).

In the absence of blood glucose increases in response to epinephrine release, brain functions in aged rats may be compromised by depressed glucose availability. As seen on many tests of spatial working memory, aged rats exhibited a memory deficit when tested on a 4-arm spontaneous alternation task (Figure 6); injections (i.p.) of glucose restored memory to the levels seen in young rats treated with glucose. Performance on this task is impaired by lesions of the hippocampus and is sensitive to pharmacological manipulations of the hippocampus. The memory deficit in aged rats was accompanied by depletion of ECF glucose in the hippocampus during testing that was greater and of longer duration in aged than in young rats, dropping to nearly 50% of baseline values during memory testing in aged rats (Figure 7). At the same time, the substantial depletion of hippocampal ECF glucose seen during memory testing in aged rats, and the smaller depletion seen in young rats, was fully prevented by injections of glucose (McNay and Gold, 2001). As noted above, basal blood glucose levels in aged rats were comparable to those of young adult rats, but aged rats did not exhibit a significant increase in blood glucose levels in response to training. Thus, in

failing to provide sufficient glucose to the brain under demand, the absence of a blood glucose response to the arousal of placement in a novel environment appears to be a major contributor to the greater depletion of ECF glucose, the slower return of ECF levels to baseline, and the cognitive deficits observed in old rats.

To test whether glucose in the hippocampus is critical to memory processing, Morris and Gold (2013) examined the effects of post-training intra-hippocampal injections of glucose. As shown in Figure 8, the infusions of glucose prevented forgetting after inhibitory avoidance training in aged rats, resulting in memory scores like those seen in young rats. Together with the neurochemical evidence that hippocampal glucose is depleted during memory testing in aged rats, the results support the view that the conditions for maintenance of memory, i.e. the absence of forgetting, include availability of extracellular glucose to support neural functions. The enhancement of memory in aged rats is similar to that seen in young rats and shares a task x brain target interaction, i.e., intracerebral infusions of glucose are only effective when glucose injected into selective structures shown to play a primary role in the task (e.g., Parent et al., 1997; McNay and Gold, 1998; McNay et al., 2000; Stefani and Gold, 2001; Canal et al., 2005; Pych et al., 2006). Therefore, while it is possible that peripheral actions of glucose contribute to memory enhancement, the efficacy of central injections in a task by memory system manner indicates that peripheral actions are not necessary for glucose enhancement of memory.

Acetylcholine

In young rats, glucose augments acetylcholine release in a manner related to enhancement of spatial working memory (Ragozzino et al., 1996, 1998). We compared acetylcholine release after inhibitory avoidance training in young and old rats that received post-training injections of epinephrine or glucose. The training was conducted under low footshock conditions that would reveal rapid forgetting in aged but not young rats. Microdialysis samples were collected for measurements of acetylcholine release every 10 min for 40 min before training to 60 min after training. Young and old rats were trained on an inhibitory avoidance task and received systemic injections of epinephrine (0.1 mg/kg), glucose (100 mg/kg) or saline (1 ml/kg) immediately after training. The effects on acetylcholine release were consistent with the effects on memory shown above. Epinephrine and glucose similarly augmented the duration of acetylcholine release after training in young rats, mirroring their comparable efficacy in enhancing memory. However, in old rats, glucose was substantially more effective than was epinephrine in augmenting release of acetylcholine after training, again paralleling the relative effects of the two treatments on memory. These findings suggest that the age-related deficiency in the ability of epinephrine signaling to increase blood glucose levels may contribute to diminished neurotransmitter responses to training and thereby contribute to rapid forgetting in aged rats.

The augmented release of acetylcholine in response to glucose and training, as seen in both aged and young rats (Morris et al., 2010; Ragozzino et al., 1996, 1998) is consistent with evidence that acetylcholine release may contribute to glucose effects on memory. In particular, nicotinic receptors and associated signaling processes have become important targets for experiments addressing mechanisms of memory function and dysfunction. Many

of these experiments have shown that the specific $\alpha 7$ and $\alpha 4\beta 2$ nicotinic receptor antagonists, methyllycaconitine (MLA) and dihydro-beta-erythroidine (DHBE), respectively, impair memory (e.g. Addy et al., 2003; Bettany and Levin, 2001; Chan et al., 2007; Levin et al., 2002; Nott and Levin, 2006). Recent findings using young adult rats provide pharmacological evidence that glucose enhancement of memory may be mediated, in part, by nicotinic receptors (Morris et al., 2012). Young adult rats received injections (I.P.) of either MLA or DHBE 30 min prior to inhibitory avoidance training or spontaneous alternation testing. Both drugs impaired memory in these tasks. In the inhibitory avoidance task, the memory impairment was evident as an instance of rapid forgetting similar to observations in aged rats: Memory was intact at 1 hour after training but impaired by 7 days. When injected directly into the hippocampus, these drugs also impaired working memory assessed in a spontaneous alternation task, a task in which age-related memory impairments are also evident in rats. Additional treatment with intrahippocampal glucose was used to challenge the efficacy on memory of the two nicotinic antagonists. The findings indicated that glucose did not attenuate the effects of the $\alpha 7$ antagonist but did reverse the effect of the $\alpha 4\beta 2$ antagonist in both tasks; the spontaneous alternation results are shown in Figure 9.

Thus, glucose is very effective at reversing age-related impairments in memory and glucose enhancement of memory appears to include augmented release of acetylcholine as a mediating mechanism, with pharmacological evidence suggesting involvement of nicotinic $\alpha 7$ receptors. However, as described below, recent findings show that glucose may also act more generally than through cholinergic actions, i.e. supporting metabolic demands of learning and memory that may be important in the mechanisms by which glucose reverses memory impairments during aging.

Astrocytes, Glycogen and Lactate

Findings described above provide evidence that glucose reverses the rapid forgetting that characterizes memory in aged animals and that glucose replenishes extracellular glucose levels that are severely depleted in aged rats by memory testing. While the evidence of a poor blood glucose response to training or to epinephrine suggests that peripheral glycogen stores and production of glucose, i.e. in the liver, may be a basis for these effects, the issue remains about the brain actions of glucose that mediate the effects on both brain signaling mechanisms and on cognition. Recent findings suggest that glucose enhances memory by providing a substrate for astrocytic generation of lactate (Suzuki et al., 2011; Newman et al., 2011; see Gold et al., 2014, for recent review). Although neurons do not have the capability to store glycogen, astrocytes do (Maxwell and Kruger, 1965; Petersen, 1969; Pfeiffer-Guglielmi et al. 2003; Brunet et al., 2009; Newman et al., 2011), providing stores that can supplement glucose availability. In the brain, astrocytic glycogen is metabolized to lactate, which can be shuttled to neurons to provide an additional energy reserve when needed (Magistretti et al., 1999). Measured in somatosensory cortex, glucose uptake by neurons and astrocytes is similar at baseline but glucose uptake increases in astrocytes and not neurons during times of activation (Chuquet et al., 2010). In memory tests, glucose levels in the hippocampus decrease upon activation (McNay et al., 2000, 2001; McNay and Gold, 2001; McNay and Sherwin, 2004) (as in Figure 7). The decrease is accompanied by an increase in extracellular levels of lactate (McNay and Sherwin, 2004; Newman et al., 2011). The

increase in lactate levels is likely generated by glycogenolysis and glycolysis in astrocytes with release of lactate into the extracellular space (Sampol et al., 2013).

An example of the fluxes in extracellular lactate and glucose during spontaneous alternation tests is shown in Figure 10. In this experiment (Newman et al., 2011), biosensors were used to measure lactate and glucose levels in the hippocampus, a method that permits 1-second sampling of the analytes; however, 10-sec averages were used in Figure 10 for display purposes. As seen in earlier studies using microdialysis methods, extracellular levels of glucose decreased after the start of training before recovering later. Previous work showed that the recovery of extracellular glucose levels during testing in young rats, which is not seen in aged rats, is coincident with increases in blood glucose levels (McNay et al., 2001). The main new finding was that lactate levels increased at times that mirrored the decrease in glucose values, suggesting that lactate may supplement glucose as a reserve for energy metabolic demand in support of neural processing needed for optimal cognitive functions. Genetic and pharmacological manipulations support this view (Suzuki et al, 2011; Newman et al. 2011). As shown in Figure 11, direct injections of lactate into the hippocampus enhance memory, similar to results obtained with intrahippocampal injections of glucose. In addition, intrahippocampal infusions of a drug, α -cyano-4-hydroxycinnamate, that blocks the entry of lactate into neurons impairs memory (Newman et al., 2011). That impairment is not rescued by coadministration of either glucose or lactate. Astrocytes contain a host of neurotransmitter receptors, including both nicotinic receptors noted above (Xiu et al., 2005), that might initiate glycogen breakdown to lactate, perhaps opening an opportunity to integrate neurotransmitter functions with glucose enhancement of memory.

These recent findings point to a key role of astrocytes in mediating the enhancement of memory by glucose. Thus far, the work has not been extended to aged rats but the findings open clear avenues for investigation within the realm of glucose reversal of forgetfulness during aging. In particular, it is possible that astrocytes will demonstrate age-related deficits in glycogen storage and carbohydrate delivery for energy use by neurons in a manner similar to what is seen in the periphery.

CONCLUSIONS

Across tasks, glucose administration appears to fully reverse the effects of aging on memory. Therefore, the results show that an old brain can learn and store new information as well as a young brain but apparently does not readily do so because the modulation of memory is dampened or absent. This conceptual approach is very different from that guiding much of aging research in memory, in which the presumption is that the aged brain has limited capacity. That perspective includes the ideas that compensatory mechanisms are engaged with less efficiency, and that cognitive enhancers therefore can only act on limited residual functions or by effecting downstream molecular cascades. Replacing single signaling molecules may be technically and conceptually challenging. Most memory molecules participate in multiple converging pathways, making it difficult to alter any one molecular pathway and function. Moreover, the pervasiveness of forgetfulness across many tasks and their related neural systems suggests a mechanism with more comprehensive

functions. Addressing such a mechanism, as that described here, may offer a promising approach to ameliorate age-related increases in forgetting.

Our results suggest that cognitive functions in older adults are remediable simply if adequate glucose is provided to the brain. This research may open new avenues for development of drug treatments or lifestyle interventions for age-related memory loss that target regulation of neuroendocrine response. The application of endocrine studies to examine bases for age-related memory impairments will likely propel these developments, as might experiments that point to altered mechanisms of glycogen storage, metabolism, and delivery of intermediary substrates in the periphery or in the brain.

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HIGHLIGHTS

- A major characteristic of memory change during aging is the onset of rapid forgetting.
- Forgetting is blunted and memory is enhanced by glucose.
- The physiological basis for rapid forgetting in aged rats may be a failure of epinephrine to release glucose from the liver.

FIGURE 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.]

FIGURE 2.

Plasma levels of epinephrine (EPI) at baseline and at timed intervals after swimming for 15 min. Values are means for groups of 7–10 rats. Old rats had substantially greater levels of epinephrine after immersion in water than did young rats. [From Mabry et al., 1995a.]

FIGURE 3.

Plasma epinephrine (left panel) and glucose (right panel) levels after administration of a single footshock at the intensity shown. Note that old rats exhibited exaggerated release of epinephrine compared to young rats but diminished increases in blood glucose levels across the same shock intensities. * $P < 0.05$ vs. young. [From Mabry et al., 1995b.]

FIGURE 4.

Effects of epinephrine injections on blood glucose levels in aged vs. young rats. Epinephrine injections increased glucose levels more substantially in young than in old rats, particularly at an epinephrine dose (0.1 mg/kg) that is effective at enhancing memory in young rats.

[From Morris et al., 2010.]

FIGURE 5.

Enhancement of inhibitory avoidance memory (48 hr) by immediate posttraining injections of epinephrine and glucose. Although the treatments were equally effective at enhancing memory in young rats, glucose was more effective than epinephrine in old rats. [From Morris et al., 2010.]

FIGURE 6.

Alternation scores in rats tested for working memory on a 4-arm spontaneous alternation task. Young adult rats performed significantly better than chance on this task, but 24-month-old rats did not; the aged rats had scores significantly lower than those of young adult controls. Glucose enhanced memory in both young and old rats, bringing the memory scores in old rats to values near those of the glucose-enhanced memory of young rats. [From McNay and Gold, 2001.]

FIGURE 7.

In vivo microdialysis measurements of extracellular glucose levels in the hippocampus before, during, and after testing on a spontaneous alternation task. Extracellular glucose levels decreased significantly at both ages, but significantly more so in aged rats. [From McNay and Gold, 2001.]

FIGURE 8.

Effects of intrahippocampal injections of glucose on memory. Immediately after training on an inhibitory avoidance task, young and old rats received injections of aCSF containing either 1 mM or 33.4 mM glucose. These groups are designated aCSF and GLUCOSE, respectively, in this figure. The 1 mM glucose concentration in aCSF matches baseline extracellular glucose levels in the hippocampus, as measured with zero-net-flux microdialysis methods (McNay and Gold, 1999). Memory was assessed 7 days after training. Glucose enhanced memory in aged rats, bringing the latencies to the ceiling scores of 600 sec. [From Morris and Gold, 2013.]

FIGURE 9.

Effects of intrahippocampal infusions of glucose and nicotinic receptor antagonists on working memory assessed in young adult rats using a 4-arm spontaneous alternation task. Chance performance is 44% on this task. Rats pretreated with either an $\alpha 7$ (MLA) or an $\alpha 4\beta 2$ (DH β E) nicotinic receptor antagonist exhibited significantly impaired memory. Co-administration of glucose reversed the impairments produced by the $\alpha 4\beta 2$ antagonist but not the $\alpha 7$ antagonist. * $P < 0.05$ vs. aCSF. MLA: methyllycaconitine; DH β E: dihydro-beta-erythroidine; GLU: glucose; aCSF: artificial cerebrospinal fluid. [From Morris et al., 2013.]

FIGURE 10.

Effects of spontaneous alternation testing on extracellular glucose (black diamonds) and lactate (gray circles) levels in the hippocampus of young adult rats. These levels were measured using bioprobes with 1-sec sampling periods, summarized here as 10-sec sampling epochs. Note first that glucose levels decreased near the start of alternation testing, as shown before with microdialysis methods. In contrast, lactate levels increased during testing, mirroring the changes in glucose. Not shown here, pharmacological manipulations that block and restore lactate availability impair and enhance memory, respectively. [From Newman et al., 2011.]

FIGURE 11.

Effects of intrahippocampal injections of lactate on working memory scores in a 4-arm spontaneous alternation task. Lactate enhanced memory in an inverted-U manner, as seen also with glucose. [From Newman et al., 2011.]