Glucose modulates recently reactivated memories

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A passive avoidance to active avoidance negative transfer paradigm was used to investigate the effects of glucose on recently acquired and recently reactivated memories. Immediate post-passive avoidance training injections of glucose (100 mg/kg s.c.) improved memory and thus interfered with the rats' ability to learn the one-way active avoidance task 24 h later. Rats receiving a memory reactivation treatment 24 h after passive avoidance training showed greater negative transfer to the active avoidance task presented 24 h later than did nonreactivated control animals. Furthermore, the administration of glucose (32, 100, or 320 mg/kg) following memory reactivation proactively interfered with the acquisition of the active avoidance; this effect followed an inverted U-shaped dose–response function. The ability of glucose (100 mg/kg) to alter the reactivated passive avoidance memory decreased as the interval between reactivation and glucose treatment was increased up to 30 min. These results demonstrate that glucose modulates the processing of old memories that have been recently reactivated, just as it modulates the processing of new memories that have been recently acquired.

The administration of drugs and hormones after training influences subsequent performance (Martinez, Schulteis, & Weinberger, 1991). One of the first hypotheses to account for this result suggests that drugs administered post-training directly affect memory consolidation processes and thus lead to a stronger and more persistent neural representation of the training episode (McGaugh, 1966). However, studies showing that the effects of drugs and hormones depend not only on the strength and nature of the treatment (drug or hormone), but also on the strength of training (e.g., the unconditioned stimulus [US] intensity and the amount of training) and the treatment/training interaction, have led to a more modest hypothesis. According to this hypothesis, many drugs that enhance and impair memory do so by selectively promoting the processing of emotionally significant events, perhaps by mimicking the effects produced endogenously by naturally occurring substances (Gold & McGaugh, 1975; Gold & Zornetzer, 1983; Martinez et al., 1991; McGaugh, 1989). Drugs that operate in this way are called memory modulators (Gold, 1989; Schulteis & Martinez, 1992).

Messier and White (1984) were the first to show that glucose administered posttraining could function as a cognitive enhancer. Subsequently, Gold (1986) showed that posttraining administration of glucose resulted in changes in performance characteristic of those produced by memory modulators, since the dose–response curve for the effect of glucose on conditioning was found to be U shaped (maximally effective dose: 100 mg/kg) and the ability of glucose to influence conditioned performance was found to be time dependent. Further evidence that glucose is an important memory modulator comes from studies showing that the maximally effective dose of glucose changes with US intensity (footshock) intensity (Gold, Vogt, & Hall, 1986), and that blood glucose levels after inhibitory avoidance training correlate with later performance (Hall & Gold, 1986). Subsequently to these initial studies, the conditions under which glucose influences memory have been found to include not only aversive learning situations in animals (Messier & White [1987], White & Messier [1988], conditioned suppression; Gold [1986], single-trial inhibitory avoidance), but also appetitive learning situations in animals (e.g., Packard & White [1990], radial arm maze; Messier & Destrade [1988], operant response) and human cognitive processing (for a review, see Gold, 1991).

Gold (1991), Wenk (1989), and White (1991) all suggest that biologically significant events alter learning and memory via a common mechanism, and that an important component of this mechanism is the release of glucose from the liver and the subsequent effect of glucose on central neuromodulators. Glucose may be part of the
reinforcement system that marks the importance of an event by changing the level or duration of active processing (cf. Martinez et al., 1991; White & Milner, 1992) and thereby increasing associative strength (Wagner & Brandon, 1989; Wickelgren, 1976). Gold (1991), Wenk (1989), and White (1991) argue that both appetitive and aversive stimuli normally cause the release of epinephrine from the adrenal medulla, which in turn causes the release of glucose into the blood from the liver. It is suggested that peripheral glucose affects the central nervous system either directly by active uptake into the brain (Gold, 1991; Wenk, 1989) or indirectly by hepatic detection of glucose levels that are relayed to the central nervous system by the celiac ganglion (White, 1991). These researchers all argue that central glucose selectively influences the neural systems involved in learning and memory. Glucose interacts both with central opioid peptide systems, which modulate (frequently impairing) learning and memory, and with central cholinergic systems, which modulate (frequently enhancing) learning and memory (Gallagher, 1984; Gold & Zornetzer, 1983; McGaugh, 1989; Squire & Davis, 1981; Stone, Cottrill, Walker, & Gold, 1988; Stone, Walser, Gold, & Gold, 1991). Because glucose attenuates the actions of opioidergic mechanisms and augments the actions of cholinergic mechanisms, Wenk (1989) terms glucose a "cognitive enhancer."

Important to the study of memory processing is the finding that re-presenting some features of the training episode following conditioning and before testing affects subsequent performance of a large number of tasks, under a variety of prompting or prior-cuing conditions (Spear, 1976, 1981; Spear, Miller, & Jagielo, 1990). Effective retrieval cues are believed to recreate in active memory many of the conditions that existed at the time of acquisition; the resulting enhancement in performance is consistent with Tulving’s encoding specificity hypothesis (Tulving & Thompson, 1973). Following training with an aversive US, an especially effective reactivation treatment is the reintroduction of the US in the presence of original learning contextual cues (Rescorla & Heth, 1975; Richardson, Riccio, & Mowrey, 1982; Spear, Hamberg, & Bryan, 1980). New memories recently acquired and old memories previously acquired but recently reactivated or retrieved share many functional similarities (Gordon, 1981; Riccio & Ebner, 1981; Spear, 1976, 1981; Spear & Mueller, 1984). It has been suggested that just like recently acquired memories, recently reactivated memories are in a labile state and thus highly susceptible to modification (Gordon, 1981; Lewis, 1979; Miller & Marlin, 1984; Miller & Springer, 1973; Spear, 1976, 1981). That is, the decoding and subsequent retrieval of a memory trace constitutes an opportunity for its modification. Memory reactivation treatments are believed to affect subsequent performance either by stabilizing the retrieval route or by updating and reconstructing the original memory (Izquierdo, 1989; Miller & Marlin, 1984; Sara, 1991; Spear & Mueller, 1984; Wickelgren, 1976).

Drugs and hormones affect not only memory storage; they also affect memory retrieval (Quartermain, 1983; Riccio & Ebner, 1981; Rodriguez, Phillips, Rodriguez, & Martinez, in press; Sara, 1991). Preretention testing injections of catecholamines (Quartermain, 1983; Sara, 1985) attenuate forgetting. Recently, Stone, Rudd, and Gold (1990) showed that glucose produces a dose-dependent attenuation of forgetting of an inhibitory avoidance response when it is administered 30 min prior to the retention test. However, when drugs and hormones are administered shortly before testing they may influence not only memory retrieval but also sensory, motor, and motivational task-relevant factors. Further, long-term effects on performance cannot be assessed when the drug-test interval is short.

The present study was designed to extend the findings of Gold (1991) and White (1991) that demonstrate that glucose is an important memory modulator by investigating the effects of glucose on recently acquired and recently reactivated memories. Importantly, we selected an experimental approach for these studies that permitted assessment of glucose’s memorial effects independently of any possible effects on nonassociative memorial variables. For these studies, we conducted passive avoidance training and 24 h later we reactivated the rats’ memory with a noncontingent footshock delivered in the experimental context. We administered glucose after the reactivation treatment and tested the rats 24 h later on a reversal (active avoidance) task. This approach not only reduced the likelihood that glucose was affecting nonassociative memorial variables, but by testing the rats 24 h after the reactivation treatment, we were able to measure persistent drug effects on recently reactivated memories and retrieval mechanisms (Gordon, 1977; Gordon & Spear, 1973).

The purpose of Experiment 1 was to extend to a new experimental paradigm, passive to active avoidance negative transfer, the finding that administration of glucose (100 mg/kg) modulates recently acquired memories. Experiment 2 was designed to demonstrate the presence of a reactivation effect and to enable the investigation of its dose-dependent modulation by glucose. In Experiment 3, we investigated the time period during which old memories, once reactivated, remain vulnerable to modification by glucose administration.

**EXPERIMENT 1**

**Effects of Glucose on Recently Acquired Memories**

**Method**

Subjects. The subjects were 48 experimentally naive male Sprague-Dawley rats, approximately 100 days of age at the beginning of training. They were housed individually in a temperature-controlled room and were maintained on a 12:12-h light:dark cycle (0700 h on). Food and water were available ad lib. Behavioral testing was performed between 1200 and 1600 h. All animal use and testing procedures were approved in advance by the Animal Care and Use Committee at New Mexico Highlands University.
Apparatus. A single avoidance apparatus, similar to that described by Spear et al. (1980), was used for both passive and active avoidance conditioning. It consisted of adjacent white and black Plexiglas chambers of identical dimensions (27 x 14.5 x 14 cm). The chambers were separated by a guillotine door that could be lowered to a height of 2.5 cm. The grid floor of both chambers consisted of stainless steel bars 6 mm in diameter and spaced 1.7 cm between centers. A scrambled footshock (0.5 mA) could be delivered to either chamber by a Lafayette shock generator (S2404/5.SS). A 2-Hz flashing light (7.5 W) was mounted on the outside of the end wall of the white chamber. Lowering the guillotine door activated the flashing light and a timer, both of which were deactivated when the rat crossed a photobeam located in the middle of the dimly illuminated black chamber. A wire mesh cage (25 x 20 x 18 cm) was used both to transport subjects and to hold them during the intertrial intervals. Constant background noise (63 dB) was provided by a white noise generator. Stimulus presentation and response recording were programmed with computer and solid-state modules.

Design and drugs. The subjects were assigned randomly to either a saline or a glucose treatment group. Glucose (100 mg/kg) was prepared in saline. Injections were delivered subcutaneously in the back of the neck, 1 to 2 cm posterior to the base of the skull. All injections were blind coded.

Procedure. At the start of each passive avoidance training trial, the rat was placed in the white chamber, facing the black chamber. After 3 sec, the guillotine door opened, which started a 60-sec clock and the flashing light. If the rat crossed into the black chamber within 60 sec, the guillotine door closed and the rat received a mild footshock (0.5 mA, 1 sec). Crossing to the black chamber was scored as an incorrect response. If the rat remained in the white chamber for 60 sec, a correct (passive) avoidance response was recorded. After making a correct or incorrect response, the rat was placed in the holding cage for a 30-sec intertrial interval. All subjects were trained to a criterion of five consecutive correct responses. Immediately after reaching criterion, the rat was removed from the apparatus and given a glucose or saline injection. It was then returned to its home cage in the colony room for the retention interval.

Active avoidance training occurred 24 h later. At the start of each active avoidance training trial, the rat was placed in the white chamber, facing the black chamber; 3 sec later, the guillotine door opened, and the flashing light and a 5-sec timer were started. If the rat did not cross into the black chamber within 5 sec, a 0.5-mA footshock was activated; it continued until the rat entered the black chamber. This was scored as an incorrect response. A correct response was recorded if the rat entered the black chamber before 5 sec had elapsed (i.e., before the footshock was activated). The subject remained in the black chamber for 10 sec and then was placed into the holding cage for the 30-sec intertrial interval. All rats were trained to a criterion of five consecutive (active) avoidancees (30-trial maximum). Animals not reaching criterion were assigned a score of 30.

Data analysis. The number of trials to passive and active avoidance was analyzed by means of analyses of variance (ANOVA). All a priori hypotheses were evaluated by standard methods described by Keppel (1991). Correspondence between the data and the general linear model assumptions was confirmed by exploratory ANOVA techniques described by Hoaglin, Mosteller, and Tukey (1991). For all statistical tests, the rejection criterion was \( p < .05 \).

Results and Discussion

The glucose and saline treatment groups did not differ significantly on the mean number of trials to reach criterion on the passive avoidance task \( [M = 7.52; F(1,46) < 1.0] \), indicating that both groups of animals acquired the initial passive avoidance response at similar rates.

Figure 1 shows that rats receiving an immediate post passive avoidance training injection of glucose (100 mg/kg) took significantly more trials to reach criterion on the active avoidance task than did saline-injected control rats \( [F(1,46) = 22.37, p < .001] \), indicating that glucose produces greater proactive interference than saline administration with the negative transfer active avoidance test. These results are consistent with those of many other studies, in demonstrating that a posttraining injection of glucose (100 mg/kg) improves the retention of a recently acquired response (Gold, 1986; Hall & Gold, 1986; White, 1991).

EXPERIMENT 2

Dose-Response Function for the Effect of Glucose on Recently Reactivated Memories

Method

Subjects and Apparatus. The subjects were 77 male Sprague-Dawley rats, 75 days of age at the start of the experiment. The housing and maintenance conditions were the same as in Experiment 1. The avoidance apparatus was identical to that described in Experiment 1, although Experiments 1 and 2 were conducted in different experimental rooms. A clear Plexiglas chamber (28 x 21 x 20 cm) with a grid floor identical to that in the avoidance apparatus served as the reactivation chamber.

Procedure. In order to avoid response ceiling effects, all subjects in this experiment were trained to a criterion of three con-
secutive passive avoidance responses. In all other respects, passive and active avoidance training followed the procedures used in Experiment 1. Twenty-four hours after passive avoidance training, the rat was returned to the experimental room for the reactivation treatment. Once in the experimental room, the rat was removed from its holding cage, placed into the clear Plexiglas reactivation chamber, and 3 sec later given a mild footshock (0.5 mA, 1 sec). After 10 sec, the subject was removed from the reactivation chamber, given an injection of glucose (32, 100, or 320 mg/kg) or saline, and then returned to its home cage in the colony room. A separate control group of animals received neither the reactivation treatment nor an injection. Twenty-four hours later, all animals were trained on the active avoidance task. Assignment to the five treatment groups was random.

Results and Discussion

Rats in the five treatment groups did not differ significantly on the number of trials required to reach criterion on the passive avoidance task \([M = 4.65; F(4,72) = 1.04, p = .39]\). Thus, as in Experiment 1, the subjects in each group learned the passive avoidance response at the same rate.

Figure 2 depicts the number of trials required for each group to reach criterion during active avoidance training. The omnibus one-way ANOVA was significant \([F(4,72) = 11.03, p < .0001]\); planned comparisons revealed that the subjects that did not receive the reactivation treatment acquired the active avoidance response faster than did the postreactivation, saline-injected control animals \([F(1,72) = 4.85, p < .03]\). This finding demonstrates increased retention of passive avoidance training when it is followed 24 h later by a reactivation treatment, since the reactivation treatment produced greater negative transfer on the reversal (active avoidance) task. This result is consistent with the findings of Spear et al. (1980), who report that reintroducing rats to the conditioning context and the US (shock) affects the memory of the original training episode.

Figure 2 also shows that glucose produces a dose-dependent enhancement of recently reactivated memories. Planned comparisons between the reactivation saline control treatment and each glucose dose revealed the presence of a U-shaped dose–response function, since a glucose dose of 100 mg/kg \([F(1,72) = 17.60, p = .0001]\), but not of 32 mg/kg \([F(1,72) = 0.16, p = .69]\) or 320 mg/kg \([F(1,72) = 0.13, p = .72]\), given after the reactivation treatment, increased significantly the number of trials required to reach criterion on the negative transfer (active avoidance) task. Further corroborating the presence of a U-shaped dose–response function for the effects of postreactivation glucose treatment was a significant quadratic component for the glucose effect \([F(1,47) = 5.29, p = .026]\).

Together, these results indicate that the reactivation treatment increased the retention of the passive avoidance response and thus led to proactive interference during the acquisition of the reversed (active avoidance) response. The results also indicate that glucose enhances the retention of a recently reactivated memory, and that this effect is dose dependent and follows a U-shaped function.

EXPERIMENT 3

Time Dependency of the Effect of Glucose on Recently Reactivated Memories

Method

Subjects and Apparatus. The subjects were 160 male Sprague-Dawley rats, 75 days of age at the start of the experiment. The apparatus, housing, and maintenance conditions were the same as in Experiment 2.

Procedure. The passive avoidance training, reactivation treatment, and active avoidance training procedures were identical to those used in Experiment 2. However, in this experiment, glucose (100 mg/kg) or saline was administered either immediately 2, 5, or 30 min after the reactivation treatment. The subjects were assigned randomly to the eight treatment conditions.

Results and Discussion

A one-way ANOVA of the trials to criterion on the passive avoidance task showed that rats in the eight treatment groups did not differ significantly \([M = 4.2; F(7,152) = 1.09, p = .37]\). Figure 3 presents the mean number of trials to criterion for the glucose- and saline-treated animals at each of the four reactivation–injection intervals. Planned comparisons between the glucose and saline treatments at each reactivation–injection interval showed that at both the immediate \([F(1,152) = 6.18, p =

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GLUCOSE AND REACTIVATED MEMORIES

Figure 3. Time dependency of the effect of glucose (100 mg/kg s.c.) on reactivated memories. When compared with saline (open squares) treatment (n = 16, immediate; n = 13, 2 min; n = 23, 5 min; n = 24, 30 min), administration of glucose (filled diamonds) immediately (n = 17) or 2 min (n = 13) after reactivation, but not 5 min (n = 28) or 30 min (n = 26) after reactivation, resulted in significantly more trials (*p < .05) to reach criterion on the negative transfer one-way avoidance task presented 24 h later.

An orthogonal polynomial analysis of trend across the reactivation-injection intervals was conducted separately for the glucose- and saline-treated subjects. This analysis indicated that the effects of postreactivation glucose injections at varying time intervals were linear [F(1,80) = 5.03, p = .03, accounting for 92.8% of the interval variance], whereas the effects of postreactivation saline treatment at varying time intervals followed a more complex quadratic trend [F(1,72) = 5.48, p = .02, accounting for 76.4% of the interval variance]. These results indicate that it is only when glucose (100 mg/kg) is administered shortly after the context-shock reactivation treatment that differences in the subsequent acquisition of the active avoidance response are evident. Thus the data in Experiment 3 replicate (immediate treatment) and extend (2-min reactivation-injection interval) the conditions under which glucose modulated recently reactivated memories are linearly time dependent across the 30-min postreactivation interval. The quadratic nature of the effect of postreactivation saline treatment at varying time intervals is somewhat more difficult to explain. The unexpected interference observed at the 5-min reactivation–saline injection interval was replicated three times. Because so little is known about the way in which the conditions of reactivation interact (Spear et al., 1990), it is possible that the shape of this function may be specific to situations in which the US (footshock) is a component of the reactivation treatment.

GENERAL DISCUSSION

It has been found in previous studies that glucose modulates recently acquired appetitively and aversively motivated memories (see Gold, 1991, and White, 1991, for reviews). The present data provide additional evidence that glucose (100 mg/kg) enhances newly acquired aversively motivated memories. However, this study is the first demonstration that glucose can enhance memory in a passive avoidance to active avoidance negative transfer design. Our results also are consistent with prior findings that a context-footshock reactivation treatment can attenuate forgetting (Richardson et al., 1982; Spear et al., 1980). Most importantly, our results suggest that glucose modulates recently reactivated memories, and that just as with recently acquired memories (Gold, 1986), the modulation by glucose of recently reactivated memories follows a U-shaped dose–response function. We also demonstrated that the modulation by glucose (100 mg/kg) of a reactivated, 24-h-old, passive avoidance memory de-
increases monotonically as the interval between reactivation and glucose administration increases. Because we found the effects of glucose on reactivated memories to be time dependent, it is unlikely that the effects of glucose administered immediately after reactivation are due to nonspecific negative transfer. Thus our results suggest that glucose, when administered after reactivation, acts as a memory modulator (Gold, 1989; Gold & Zornetzer, 1983; Schulteis & Martinez, 1992), because the dose–response function for this effect is U shaped, and because the effect is time dependent.

Only one other study in animals demonstrated that glucose affects the processing of old memories (Stone et al., 1990). However, in that study, glucose was administered 30 min prior to testing, and there was no independent verification that the glucose was acting on a reactivated memory. The present study showed in three ways that glucose can modulate reactivated memories. First, because we tested the animals 24 h after glucose administration, and because glucose injections produce only a short-lived elevation of plasma glucose levels (Hall & Gold, 1986), alterations by glucose administration of nonmemorial performance factors can be assumed to be absent during testing. Second, because the interval between glucose administration and testing in our study was 24 h, we were able to demonstrate long-term or persistent effects of glucose on reactivated memories. To our knowledge, this is the first study describing the dose–response function for the long-term effects of a drug on a reactivated memory. Third, in this study, we have reported both a primary context-footshock reactivation effect and its susceptibility to modulation by glucose. This is noteworthy because none of our glucose doses themselves interfered with the primary reactivation effect; that is, in no case did glucose-injected animals perform like nonreactivated rats. Thus our results are consistent with the prior findings that, when compared with saline injections, glucose does not interfere with learning and memory (Gold [1986], 1.0–500 mg/kg glucose; White [1991], 0.1–4 g/kg glucose), and with the suggestion that glucose may be a cognitive enhancer (Wenk, 1989).

In the present study, we reintroduced the US (footshock) within the context of the original learning episode. When compared with nonreactivated control animals, rats receiving the reactivation treatment took longer to acquire the active avoidance response measured 24 h later. This suggests that the context–US reactivation treatment affected the rats’ memory for the original training episode. It has been suggested that reactivation treatments modify, and hence will not lead to the development of a distinctive memory. Interestingly, an inverted U-shaped relationship is also observed between learning and the interval between the conditioned stimulus (CS) and the US. The latter function is explained by behavioral theories of associative learning (see, e.g., Wagner & Brandon, 1989) as being the result of conjoint rehearsal of the CS and US traces in active or working memory, and this coprocessing is thought to be optimized at certain CS–US intervals. If drugs modulate CS and/or US processing, perhaps a common mechanism can account for both the U-shaped nature of the dose–response function for drug effects on learning and the U-shaped relationship between learning and the CS–US interval.

Gold (1991) and Wenk (1989) suggest that as a result of increasing central cholinergic and decreasing central opioidergic activity, glucose administration can mark the salience or importance of an episode or event. Recent evidence for glucose facilitation of hippocampal cholinergic activity (Durkin, 1989), especially under conditions of high acetylcholine demand (Messier, Durkin, Mrabet, & Destrade, 1991), may be important to the interpretation of our results for two reasons. First, the hippocampus is hypothesized to have an important role in the processing of
of contextual information (e.g., Hirsh, 1980; Kim & Fanselow, 1992; Selden, Everitt, Jarrard, & Robbins, 1991; Teveler & DiScenna, 1986; Winocur & Gilbert, 1984; Winocur, Rawlins, & Gray, 1987), and we used the learning context as a retrieval cue. Second, the hippocampus is posited to be the site for retrieval cue-encoding interaction and modification (Moscovitch & Umlit, 1991; Teveler & DiScenna, 1986), and we believe that the study of reactivated memories and of their modification by drugs and lesions can elucidate the site(s) at which retrieval cues are brought into interaction with stored representations. Thus studies such as ours may lead to an understanding of the mechanism(s) common to the effects of glucose on recently acquired and recently reactivated memories, as well as help to uncover the mechanism(s) underlying memory storage and retrieval.

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