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Brief Report

The enhancing effects of hippocampal infusions of glucose are not restricted to spatial working memory

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Abstract

Extensive evidence shows that hippocampal infusions of glucose enhance spontaneous alternation (SA) performance or reverse deficits in this task. The current experiments determined whether the enhancing effects of hippocampal infusions of glucose are restricted to spatial working memory. Specifically we tested whether hippocampal infusions of glucose would reverse deficits in an emotional reference memory task (continuous multiple trial inhibitory avoidance [CMIA]) produced by septal infusions of the γ-aminobutyric acid agonist muscimol. Male Sprague–Dawley rats were given septal infusions of vehicle or muscimol (0.15 nmol: SA; 5 nmol: CMIA) combined with hippocampal infusions of vehicle or glucose (50 nmol) 15 min prior to assessing SA or CMIA training. CMIA retention was tested 48 h later. Muscimol infusions decreased percent alternation scores and avoidance retention latencies. Importantly, hippocampal infusions of glucose reversed the deficits produced by the septal muscimol infusions on both tasks. These findings show for the first time that hippocampal glucose infusions also influence emotional memory, indicating that the enhancing effects of glucose generalize to memory tasks that vary in motivational and cognitive demand.

Keywords: Septum; Hippocampus; Glucose; GABA; Memory; Avoidance; Spontaneous alternation

Extensive evidence indicates that glucose influences memory processes (Korol & Gold, 1998; Messier & Gagnon, 2000). For instance, in rodents, systemic injections of glucose facilitate memory on tests of emotional and spatial memory (Degroot, Kornecook, Quirion, DeBow, & Parent, 2003; Kopf & Baratti, 1996a; Rashidy-Pour, 2001). The effects of glucose on memory are mediated, at least in part, by an influence on the brain. Glucose readily crosses the blood–brain barrier (Takata, Hirano, & Kasahara, 1997) and direct injections of glucose into specific brain regions, including the septum or hippocampus, enhance spontaneous alternation (SA) performance (Ragozzino & Gold, 1995; Ragozzino, Pal, Unick, Stefani, & Gold, 1998; Stefani & Gold, 1998). Septal or hippocampal infusions of glucose also reverse drug-induced deficits in SA (Parent, Laurey, Wilkniss, & Gold, 1997; Ragozzino & Gold, 1995; Stefani & Gold, 1998).

SA is a measure of spatial working memory that is dependent on the hippocampus (Lalonde, 2002). Although the effects of systemic infusions of glucose have been examined in a variety of behavioral tasks (Blanchard & Duncan, 1997; Gold, Vogt, & Hall, 1986; Kopf, Buchholzer, Hilgert, Loffelholz, & Klein, 2001; Kopf & Baratti, 1996a; Li et al., 1998; Messier & Destrade, 1988), to our knowledge, research examining the effects of *hippocampal* infusions of glucose on memory has been restricted to SA. Consequently, it is not clear whether the ability of hippocampal infusions of glucose to reverse memory deficits is restricted to spatial working memory. If glucose is part of a general mechanism in the hippocampus that influences memory, then the effects of glucose should be observed in other memory paradigms. Consequently, the goal of the present experiment was to determine whether hippocampal infusions

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of glucose would also reverse shock avoidance retention deficits produced by septal infusions of muscimol. Unlike SA, shock avoidance is a commonly used measure of emotional, long-term memory that is less dependent on spatial processes (McGaugh, 2004), but is still dependent on the hippocampus (Lovely, Grossen, Moot, Bauer, & Peterson, 1971; Martinez, Quirarte, Diaz-Cintra, Quiroz, & Prado-Alcala, 2002).

Fifty-two ($n = 11$–15 per group; SA) and 41 ($n = 8$–14 per group; shock avoidance) male Sprague–Dawley derived rats weighing 200–250 g upon arrival (Charles River, Wilmington, MA) were used. The rats were housed individually on a 12 h light–dark cycle (lights on at 7:00 a.m.) with food and water ad libitum. The Georgia State University Institutional Animal Care and Use Committee (IACUC) approved all procedures involving rats.

At least 1 week after arrival, the rats were given atropine sulfate (0.4 mg/kg, ip), anesthetized with sodium pentobarbital (50 mg/kg, ip), and given an injection of penicillin (1500 U, im, Crystiben). Stereotaxic (David Kopf Instruments, Tujunga, CA) surgical procedures were used to implant one 22-gauge stainless-steel guide cannulae (Plastics One, Roanoke, VA) aimed at the medial septum (0.5 mm anterior [AP] to bregma, 4.9 mm ventral to dura [DV]) and one guide cannula aimed at the dorsal hippocampus [4.5 mm AP, 1.6 mm DV, and 4.0 mm from the interaural line; (Paxinos & Watson, 1986)]. The hemisphere in which the unilateral hippocampal cannulae were implanted was counterbalanced. After surgery, the rats were given an injection of 0.9% sterile saline (3.0 cm^3, sc) and kept under a warm lamp until recovery from anesthesia.

Behavioral testing occurred at least 1 week after surgery. All rats performed in the SA task and then a minimum of 3 days later were given continuous multiple trial inhibitory avoidance (CMIA) training. Fifteen minutes prior to behavioral testing, different groups of rats were given hippocampal infusions of vehicle (1 μl, 0.5 μl/min; phosphate-buffered saline (PBS), pH 7.4) or glucose (50 nmol). The dose of glucose was selected based on previous experiments showing that it reversed SA deficits produced by septal muscimol infusions (Parent et al., 1997). One minute later, the rats were given a septal injection of vehicle (PBS; 0.5 μl, 0.5 μl/min) or muscimol (0.15 nmol; SA; 5 nmol; CMIA). The 0.15 nmol dose of muscimol was selected based on pilot data showing that it decreased percent alternation scores without affecting the number of arms rats entered in the maze. The 5 nmol dose of muscimol was selected on the basis of previous findings indicating that this dose impaired avoidance retention performance without affecting acquisition (Degroot & Parent, 2001). Drug treatments were counterbalanced across the two behavioral tasks.

Fifteen minutes after the injections, SA performance was assessed by placing each rat in a Y-shaped maze and allowing the rat to explore the maze for 8 min. The experimenter, who was blind to drug treatment, recorded the sequence and number of arms entered. A percent alternation score was computed for all rats that entered at least 10 arms. The number of arms each rat entered was used as a measure of activity. An alternation was defined as entering three different arms consecutively. The percent alternation score was computed by dividing the number of alternations made by the number of arms entered minus two (i.e., the number of alternations possible), and then multiplying that quotient by 100.

The avoidance apparatus consisted of a trough-shaped alley divided into a lighted and a dark compartment by a retractable door. For training, each rat was placed in the lighted compartment with its head facing away from the door. Once the rat faced the door, it was opened. After the rat entered the dark compartment with all four paws, it was given a foot shock (1.2 mA) until it returned to the lighted compartment (maximum 4 s). This sequence constituted one training trial. Training continued until the rat remained in the lighted compartment for 100 consecutive seconds or for a maximum of 5 trials. The number of trials needed to reach the criterion was used as a measure of acquisition.

On the retention test 48 h later, each rat was placed in the lighted compartment with its head facing away from the closed door. After the rat faced the door, the door was opened and the latency (s) to cross over to the dark (shock) compartment was recorded and used as a measure of retention. Each rat was given a maximum of 600 s to enter the dark compartment. Foot shock was not delivered on the retention test.

After behavioral testing, the rats were euthanized with an overdose of sodium pentobarbital (400 mg/kg, ip) and perfused intracardially with 0.9% saline followed by 10% formalin. Their brains were stored in 10% formalin for at least 2 days before they were sectioned (45–60 μm) on a cryostat (Leica CM 30510S) through the septal and hippocampal cannulae tracts. The sections were stained with thionin and an unbiased observer determined the cannulae placement using a light microscope (Olympus BX41). Acceptable medial septal cannulae placement was defined as injection tips located within the medial septum, but not within the lateral septum or the ventral diagonal band of Broca, and the cannula must not have penetrated the fimbria. Acceptable placement for hippocampal cannulae were injection sites located within hippocampal fields CA1, CA2, CA3, or dentate gyrus. Only rats with acceptable cannulae placements in both brain regions were included in the statistical analyses. The SA data were expressed as means and standard errors of the mean (*SEM*) and analyzed using 2 (septal drug treatment) × 2 (hippocampal drug treatment) univariate analysis of variance and Tukey post hoc tests. The number of trials to criterion during acquisition and the retention latency scores were not normally distributed. This was because several rats required the maximum number