Neuropsychologia 49 (2011) 1052–1066

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Glucose administration enhances fMRI brain activation and connectivity related to episodic memory encoding for neutral and emotional stimuli

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ARTICLE INFO

Article history:
Received 1 August 2010
Received in revised form 7 February 2011
Accepted 9 February 2011
Available online 16 February 2011

Keywords:
Hippocampus
Amygdala
Prefrontal cortex
Functional connectivity

ABSTRACT

Glucose enhances memory in a variety of species. In humans, glucose administration enhances episodic memory encoding, although little is known regarding the neural mechanisms underlying these effects. Here we examined whether elevating blood glucose would enhance functional MRI (fMRI) activation and connectivity in brain regions associated with episodic memory encoding and whether these effects would differ depending on the emotional valence of the material. We used a double-blind, within-participants, crossover design in which either glucose (50 g) or a saccharin placebo were administered before scanning, on days approximately 1 week apart. We scanned healthy young male participants with fMRI as they viewed emotionally arousing negative pictures and emotionally neutral pictures, intermixed with baseline fixation. Free recall was tested at 5 min after scanning and again after 1 day. Glucose administration increased activation in brain regions associated with successful episodic memory encoding. Glucose also enhanced activation in regions whose activity was correlated with subsequent successful recall, including the hippocampus, prefrontal cortex, and other regions, and these effects differed for negative vs. neutral stimuli. Finally, glucose substantially increased functional connectivity between the hippocampus and amygdala and a network of regions previously implicated in successful episodic memory encoding. These findings fit with evidence from nonhuman animals indicating glucose modulates memory by selectively enhancing neural activity in brain regions engaged during memory tasks. Our results highlight the modulatory effects of glucose and the importance of examining both regional changes in activity and functional connectivity to fully characterize the effects of glucose on brain function and memory.

1. Introduction

Extensive evidence indicates that glucose enhances memory in a variety of species, including rodents (Gold, 1986; Messier & White, 1987), pigeons (Parkes & White, 2000), chickens (Gibbs & Summers, 2002), and humans (Benton, 2001; Korol & Gold, 1998; Messier, 2004; Riby, Meikle, & Glover, 2004). 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 via glucose transporters (Pardridge, Boado, & Farrell, 1990; Rahner-Welsch, Vogel, & Kuschinsky, 1995; Takata, Hirano, & Kasahara, 1997). Moreover, direct infusions of glucose into the ventricles or specific brain regions, such as the hippocampus, enhance memory or attenuate drug-induced deficits in rodents (Canal, Stutz, & Gold, 2005; Dash, Orsi, & Moore, 2006; Krebs-Kraft & Parent, 2008; Lee, Graham, & Gold, 1988; Ragozzino & Gold, 1995; Ragozzino, Pal, Unick, Stefani, & Gold, 1998; Stefani & Gold, 1998, 2001; Stefani, Nicholson, & Gold, 1999).

Converging lines of evidence suggest that the memory-enhancing effects of glucose are mediated, at least partially, by an effect on hippocampal function. In both humans and rodents, glucose administration enhances memory when given pre-training, post-training, or pre-retrieval (Manning, Stone, Korol, & Gold, 1998; Messier, 2004; Korol & Gold, 1998). In humans, glucose preferentially enhances performance in memory tasks that depend critically on the hippocampal region (Riby et al., 2006; Riby, Sunram-Lea et al., 2008; Sunram-Lea, Dewhurst, & Foster, 2008; Sunram-Lea, Foster, Durlach, & Perez, 2002). Many reports have shown that glucose administration enhances the encoding of verbal episodic memory (consciously retrievable memory for events; Tulving,

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doi:10.1016/j.neuropsychologia.2011.02.013

2002) but has weak or no effects on short-term, working memory tasks (Foster, Lidder, & Sunram, 1998; Korol & Gold, 1998; Riby et al., 2004, 2006). Glucose may also enhance memory in part by influencing amygdala activity. Infusions of glucose into the amygdala enhance memory (McNay & Gold, 1998; Ragozzino & Gold, 1994; Schroeder & Packard, 2003) and pharmacological stimulation of the amygdala enhances hippocampal-dependent spatial reference memory (McGaugh, Cahill, & Roozendaal, 1996).

In contrast to the extensive literature on the behavioral effects of glucose in humans and the related work examining neural mechanisms in nonhuman animal models, relatively little is known regarding the neural mechanisms underlying the effects of glucose on episodic memory in humans. To date, only one small pilot study has examined the effects of glucose administration on memory encoding with functional magnetic resonance imaging (fMRI). Stone, Thermenos, Tarbox, Poldrack, and Seidman (2005) scanned seven medicated patients with schizophrenia or schizoaffective disorder as they encoded blocks of novel and repeated verbal paired associates (noun pairs) in a double-blind, within-participants, crossover design with participants receiving either 50 g glucose or saccharin on alternate testing days conducted approximately 1 week apart. Although glucose administration did not significantly affect any of the memory measures, glucose administration increased fMRI activation in the left parahippocampal cortex, a region strongly implicated in episodic encoding and retrieval. A trend towards increased activity was also found in the left dorsolateral prefrontal cortex, a region strongly implicated by previous studies in semantic elaborative processes and successful episodic memory encoding.

The results from Stone et al. (2005) and related findings from studies of event-related potentials (ERPs) showing that glucose administration alter the P3b ERP component linked to episodic memory updating and hippocampal and prefrontal function (Riby, Sunram-Lea et al., 2008; Smith, Riby, Sunram-Lea, van Eekelen, & Foster, 2009) suggest that glucose administration enhances brain activity in regions involved in successful encoding of episodic memory. To our knowledge, however, there are no published fMRI studies investigating the effects of glucose administration on regional brain activation during episodic memory encoding in healthy control participants. Consequently, the goal of the present study was to assess the effects of glucose administration on regional brain activity and functional connectivity during encoding of picture stimuli, and to examine the effects of glucose on the neural correlates of successful episodic encoding.

We scanned healthy young male participants as they passively viewed blocks of emotionally arousing negative pictures and emotionally neutral pictures, intermixed with a baseline fixation task. We hypothesized that increases in blood glucose would enhance fMRI activation in regions associated with successful episodic memory encoding, including the hippocampus and its associated neocortical regions in the parahippocampal gyrus, and specific prefrontal and parietal cortical regions that interact closely with the hippocampal memory system during episodic encoding (Eichenbaum, Yonelinas, & Ranganath, 2007; Gabrieli, Brewer, Desmond, & Glover, 1997; Squire & Zola-Morgan, 1991).

Another major goal of this study was to examine whether the effects of glucose on brain activation would differ depending on whether the encoded pictures were emotionally arousing or neutral. A substantial literature has established that episodic memory for emotionally arousing stimuli is typically enhanced. The neural basis for this enhancing effect of emotion has been linked to increased activity in the amygdala, hippocampus, and specific prefrontal regions (Hamann, 2001; Kensinger & Corkin, 2003; LaBar & Cabeza, 2006). In line with previous studies, we predicted that successful episodic encoding of emotional stimuli would engage the amygdala, hippocampus, and prefrontal cortex relatively more than encoding of neutral stimuli.

The evidence regarding the effects of glucose administration on emotional memory is mixed. Specifically, there are reports indicating that glucose administration has no effect on memory for emotional material (Brandt, Sünram-Lea, & Qualtrough, 2006; Brandt, Sunram-Lea, Jenkinson, & Jones, 2010; Ford, Scholey, Ayre, & Wesnes, 2002), impairs emotional memory (Mohanty & Flint, 2001), or prevents the memory-enhancing effects of emotion (Parent, Varnhagen, & Gold, 1999). Moreover, the findings of some studies suggest that emotional arousal may enhance memory through a process that involves increases in peripheral glucose levels (Korol & Gold, 1998; Wenk, 1989). However, the findings of other studies suggest that increases in blood glucose levels are not necessary for the memory-enhancing effects of emotion (Brandt et al., 2010; Gore, Krebs, & Parent, 2006). Given this mixed evidence, we did not have a specific prediction regarding how glucose administration would affect the neural correlates of encoding for emotional stimuli. However, our examination of these potential effects focused on the regions preferentially engaged in episodic encoding for emotional material in prior studies.

In the present study, we used a double-blind, within-participants, crossover design in which either glucose (50 g) or saccharin placebo were administered prior to scanning, on days approximately 1 week apart. Across scanning sessions, participants completed the same picture encoding tasks twice in the scanner, with different stimuli. After scanning ended for each session, participants' memory for the picture stimuli was assessed after a brief 5-min delay with a free recall task, and free recall was tested again 1 day later. We assessed the effects of glucose on brain activity in a series of analyses. We first examined glucose's effects on regional activation changes during encoding, and next examined glucose effects on encoding that were specifically related to successful subsequent episodic memory, as assessed by free recall. Free recall was selected as the memory measure to avoid potential ceiling effects frequently encountered with picture recognition tests (particularly emotional pictures) at short retention intervals, and because recall measures frequently exhibit more robust emotional memory enhancement effects than recognition tests (Hamann, 2001).

Finally, we examined potential effects of glucose on patterns of functional connectivity between brain areas linked to episodic memory and emotion by conducting seed-region based correlational analyses with the hippocampus and amygdala. The hippocampus was selected as a seed region to assess connectivity related to episodic encoding, independent of emotion, based on the large literature supporting that function of the hippocampus. The amygdala seed region was selected as an additional, independent seed region to assess possible modulation of episodic memory by emotional arousal, based on the considerable literature supporting a modulatory role for the amygdala in emotional memory encoding (LaBar & Cabeza, 2006).

2. Methods

2.1. Participants

The Georgia State University and Emory University Institutional Review Boards approved all study procedures, which were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Fourteen healthy, right-handed male volunteers (age = 19–34 years, $M = 24.1$ years; 9 White, 3 Asian, 2 Black) were recruited via an online bulletin board and then screened in a phone interview. Only male participants were tested due to sex differences in glucoregulatory response (Craft, Murphy, & Wemstrom, 1994; Hale, Wright, & Nattrass, 1985; Paula et al., 1990).

The participants were screened with a questionnaire pertaining to history of serious medical conditions, neurological disorders, diabetes or other abnormal glycemic conditions, and current psychotropic medication. Exclusion criteria included any history of substance abuse, diabetes, endocrine disorder (e.g. Cushing's