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Research report

Insulin modulates hippocampally-mediated spatial working memory via glucose transporter-4

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ABSTRACT

The insulin-regulated glucose transporter, GluT4, is a key molecule in peripheral insulin signaling. Although GluT4 is abundantly expressed in neurons of specific brain regions such as the hippocampus, the functional role of neuronal GluT4 is unclear. Here, we used pharmacological inhibition of GluT4-mediated glucose uptake to determine whether GluT4 mediates insulin-mediated glucose uptake in the hippocampus. Consistent with previous reports, we found that glucose utilization increased in the dorsal hippocampus of male rats during spontaneous alternation (SA), a hippocampally-mediated spatial working memory task. We previously showed that insulin signaling within the hippocampus is required for processing this task, and that administration of exogenous insulin enhances performance. At baseline levels of hippocampal insulin, inhibition of GluT4-mediated glucose uptake did not affect SA performance. However, inhibition of an upstream regulator of GluT4, Akt, did impair SA performance. Conversely, when a memory-enhancing dose of insulin was delivered to the hippocampus prior to SA-testing, inhibition of GluT4-mediated glucose transport prevented cognitive enhancement. These data suggest that baseline hippocampal cognitive processing does not require functional hippocampal GluT4, but that cognitive enhancement by supra-baseline insulin does. Consistent with these findings, we found that in neuronal cell culture, insulin increases glucose utilization in a GluT4-dependent manner. Collectively, these data demonstrate a key role for GluT4 in transducing the procognitive effects of elevated hippocampal insulin.

1. Introduction

In peripheral tissues, insulin's canonical effect is to regulate GluT4-mediated glucose uptake and glucose utilization [1]. Although neurons express both GluT4 and insulin receptors (IRs), the role of insulin signaling in controlling neuronal glucose utilization is less clear [2–6]. Because insulin stimulates GluT4 translocation from intracellular storage pools [via GluT4 vesicles (GSVs)] in neuronal cells [4,6], it is possible that insulin can affect glucose transport and hence fuel supply in the brain through GluT4.

Insulin's effects on memory are PI3K-dependent, but downstream mechanisms following PI3K-activation are not clear [7]. While some studies have shown an effect of insulin signaling on glucose utilization in the brain as a whole, others found no effect [7–9]. Because intrahippocampal glucose administration has similar cognitive effects as intrahippocampal insulin [7,10–22], and insulin's well-established action in the periphery is to facilitate glucose utilization, it is possible that insulin's cognitive effects are mediated through enhanced GluT4-mediated glucose uptake and subsequent glucose utilization in the brain.

GluT4 shows primarily neuronal localization in specific brain regions in rat, and its expression is greatest in the perikarya. The hippocampus has high expression of GluT4 in pyramidal cells [23–26]. GluT4 translocation occurs following stimulation by a variety of kinases including PI3 K, several atypical protein kinase c (aPKC) isoforms, and Ca^{2+}/calmodulin kinase II [CaMKII; [27–30]]. Intriguingly, many of these proteins are necessary for memory formation [31–42]. Thus, it is likely that GluT4 activation occurs during hippocampally-mediated memory formation, which is known to be sensitive to glucose supply and metabolism [43,44]. In this study, we used pharmacological inhibition of GluT4-mediated glucose uptake to assess the involvement of hippocampal GluT4 in insulin-mediated memory enhancement and neuronal glucose utilization.

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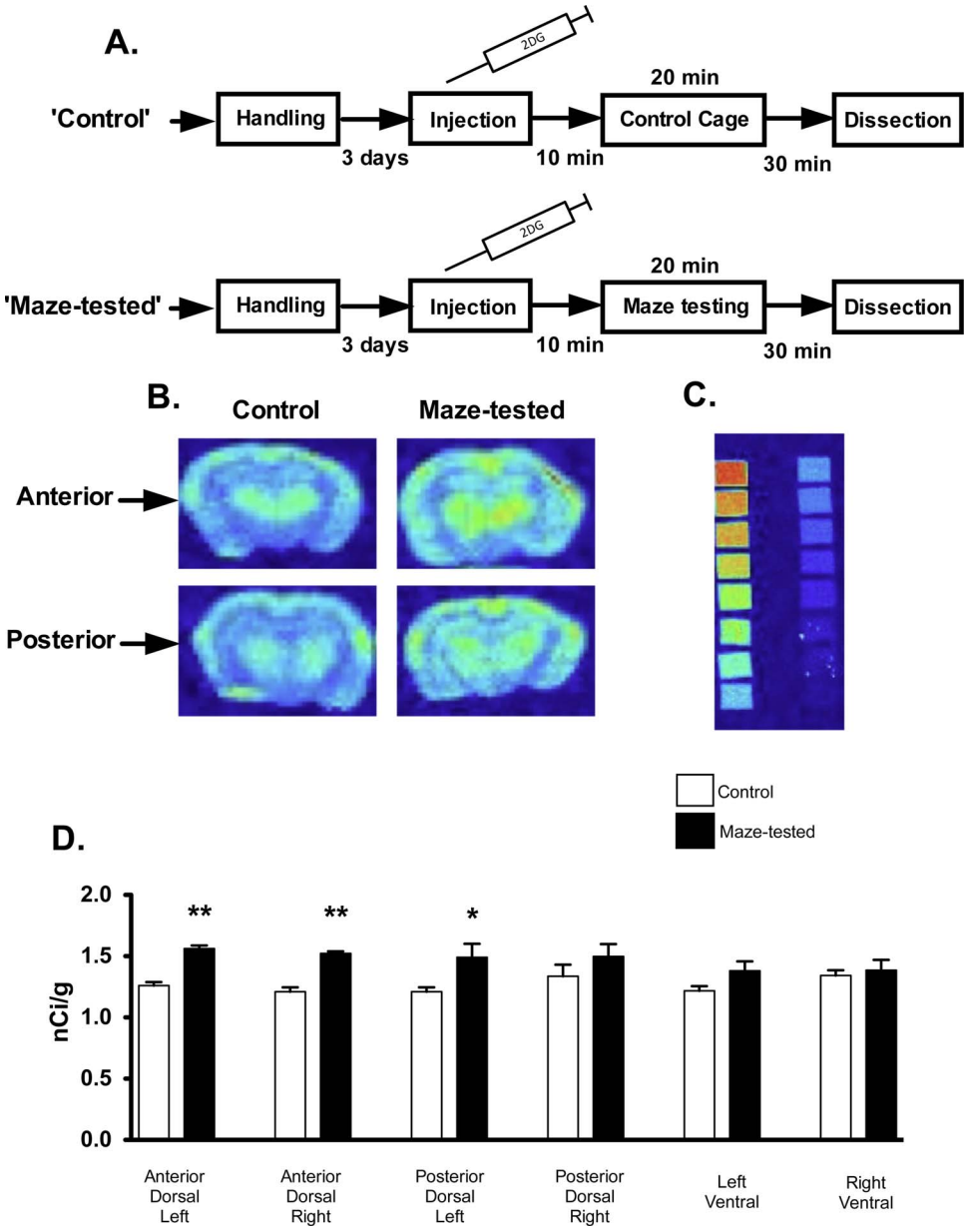

Fig. 1. Regional distribution of glucose utilization in the hippocampus during SA testing. A, Experimental outline for injections of [^{14}C]-2DG. B, Heat maps from representative phosphorimaging of [^{14}C]-2DG phosphorylation. C, [^{14}C] Standards showing standard curve used. D, Regional analysis of [^{14}C]-2DG phosphorylation during SA testing confirming role of dorsal hippocampus in SA behavior ($n = 4$ per group) * $p < 0.05$, two-tailed.

2. Materials and methods

2.1. Animals

All procedures were approved by the University at Albany Institutional Animal Care and Use Committee prior to experimentation.

For *in vivo* experiments, adult male Sprague-Dawley rats (Charles River, Wilmington, MA), approximately 300 g at time of arrival, were housed in pairs on a 12:12 h light:dark schedule with food and water available *ad libitum*. Rats were given at least one week to acclimate prior to any surgery and again after surgery but prior to testing, during which time they were handled extensively. Rats were housed singly following surgery. Each rat was used only once. All testing was done during the light cycle, including generation of hippocampal cell cultures. For generation of hippocampal cell cultures used for *in vitro* experiments, brains were dissected on the day of birth, from postnatal day 1 (P1) rats.

2.2. Surgeries

Rats were anaesthetized with isoflurane and a single microinjection cannula (Plastics One) was stereotaxically implanted in the dorsal hippocampus using aseptic surgical technique. Cannulae coordinates were 5.6 mm posterior to bregma, +4.6 lateral, and 3.3 ventral from dura. The coordinates correspond to the left dorsal hippocampus. Rats received the analgesic acetaminophen in their drinking water following surgery and were then allowed a two-week long recovery period prior to testing.

2.3. Drug treatments and microinjections

Indinavir sulfate (IND) and atazanavir (ATZ) were purchased from Toronto Research Chemicals, Inc. Nelfinavir mesylate (NFV) and insulin were purchased from Sigma, Inc. All drugs and controls were brought to final concentrations in artificial extracellular fluid (aECF; 153.5 mM Na, 4.3 mM K, 0.41 mM Mg, 0.71 mM Ca, 139.4 mM Cl, buffered at pH 7.4; [45]) and fresh stocks were prepared immediately prior to testing. Microinjections were administered to the dorsal hippocampus 10 min

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