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Research Report

Glucose-induced inhibition of the appetitive brain response to visual food cues in polycystic ovary syndrome patients

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ABSTRACT

We postulate that insulin regulation of food intake is compromised when insulin resistance is present. In order to investigate the effect of insulin sensitivity on appetitive brain responses, we conducted functional magnetic resonance imaging studies in a group of women diagnosed with polycystic ovary syndrome (PCOS) in which insulin sensitivity ranged from normal to resistant. Subjects ($n=19$) were imaged while viewing pictures of high calorie (HC) foods and low calorie (LC) foods after ingesting either 75 g glucose or an equivalent volume of water. The insulin sensitive group showed reduced blood oxygen level dependent (BOLD) signal in response to food pictures following glucose ingestion in numerous corticolimbic brain regions, whereas the insulin resistant group did not. There was a significant interaction between insulin sensitivity (sensitive vs resistant) and condition (water vs glucose). The largest clusters identified included the left insula, bilateral limbic/parahippocampal gyrus/culmen/midbrain, bilateral limbic lobe/precuneus, and left superior/mid temporal gyrus/parietal for HC and LC stimuli combined, the left parahippocampal gyrus/fusiform/pulvinar/midbrain for HC pictures, and the left superior/mid temporal gyrus/parietal and middle/inferior frontal gyrus/orbitofrontal cortex for LC pictures. Furthermore, BOLD signal in the anterior cingulate, medial frontal gyrus, posterior cingulate/precuneus, and parietal cortex during a glucose challenge correlated negatively with insulin sensitivity. We conclude the PCOS women with insulin resistance have an impaired brain response to a glucose challenge. The inability of postprandial hyperinsulinemia to inhibit brain responsiveness to food cues in insulin resistant subjects may lead to greater non-homeostatic eating.

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1. Introduction

Insulin is an important signal of energy balance (Benoit et al., 2004). Positive and negative energy states are associated with increased and decreased insulin concentrations respectively. Insulin concentrations in cerebrospinal fluid fluctuate in parallel with peripheral insulin concentrations (Strubbe et al., 1988). Insulin gains access to the brain through a saturable transport process via the endothelial cells of the blood brain barrier (Baura et al., 1993; Banks et al., 1997). Insulin receptors and insulin receptor substrate-2 are present in brain regions known to control food intake including the ventral tegmental area (VTA)/substantia nigra, olfactory bulb, hippocampus, hypothalamus, area postrema, medial nucleus of the solitary tract, and dorsal motor nucleus of the vagus nerve (Schulingkamp et al., 2000). Intracerebral ventricular administration of insulin reduced food intake and induced weight loss in baboons and sheep (Woods et al., 1979; Foster et al., 1991). Conversely, targeted disruption of neuronal insulin signaling resulted in hyperphagia and weight gain (Bruning et al., 2000; Obici et al., 2002).

Insulin resistance results in a reduced ability of insulin to stimulate glucose uptake in muscle and fat and to inhibit gluconeogenesis in the liver. Because glucose uptake by the brain is independent of insulin action, the idea that insulin resistance extends to the brain has been dismissed. However, it has been postulated that insulin signaling in the brain may be impaired when insulin resistance is present (Plum et al., 2005; Pagotto, 2009). Insulin-induced glucose metabolism as measured by positron emission tomography was reduced in the ventral striatum and prefrontal cortex of men with insulin resistance (Anthony et al., 2006). Insulin-induced cortical activity measured by magnetoencephalography during a euglycemic clamp correlated with insulin sensitivity (Tschritter et al., 2006). Hypothalamic activity as measured by functional magnetic resonance imaging (fMRI) was inhibited by a glucose challenge in healthy men, but not in men with type 2 diabetes (Vidarsdottir et al., 2007). Food picture-induced activation of the anterior cingulate, dorsolateral prefrontal cortex (DLPFC), midbrain, and lateral orbitofrontal cortex in women with polycystic ovary syndrome (PCOS) was negatively correlated with insulin sensitivity (Van Vugt et al., 2013).

The objective of the current study was to determine if appetitive brain responses to a glucose challenge are affected by insulin sensitivity. We postulated that a glucose challenge would reduce appetitive brain responses, but this response would be compromised in insulin resistant subjects. To accomplish this goal, we characterized the BOLD response in a group of women diagnosed with PCOS in which insulin sensitivity ranged from normal to resistant. We chose to study this question in the clinical setting of PCOS because of the high incidence of insulin resistance in PCOS (Dunaif et al., 1989; Dunaif, 1997; Lo et al., 2006).

2. Results

2.1. *Demographics*

Mean age and endocrine/metabolic measurements (±SD and range) for all subjects combined and for subjects divided into insulin sensitive and insulin resistant groups are shown in Table 1. Eight of 19 subjects had a 2 h G:I<1.5 and a HOMA2 sensitivity <60% and were designated insulin resistant. The 11 remaining subjects were classified as insulin sensitive. Eight of eleven had a 2 h G:I>1.5 and a HOMA2 >60%, whereas the remaining three had a 2 h G:I>1.5 but a HOMA2 <60%. Based on body mass index (BMI), 6 subjects (5 sensitive) were normal or overweight (23.5–29.7 kg/m^2), 7 subjects (4 sensitive) were obese (30.7–39.7 kg/m^2), and 6 subjects (2 sensitive) were morbidly obese (42.6–55.5 kg/m^2). Two subjects in the resistant group were prescribed metformin and one subject in the sensitive group was prescribed an oral contraceptive pill. BMI, waist circumference, 2 h G:I, HOMA2,

Table 1 – Clinical and biochemical features of study subjects.

	Overall (n=19)	Sensitive (n=11)	Resistant (n=8)
Age	27.6±5.24 (18.0–39.0)	26.5±4.72 (20.0–36.0)	29.3±5.80 (18.0–39.0)
BMI (kg/m^2)	36.1±9.16 (23.5–55.5)	32.5±7.75 (23.5–47.6)	41.2±8.93* (26.7–55.5)
Waist circumference (inches)	41.6±7.8 (32.0–60.0)	37.5±5.32 (32.0–48.0)	47.1±7.40** (35.0–60.0)
2 h OGTT G:I (mg/dl/μU/ml)	2.57±2.202 (0.5–8.9)	3.7±2.35 (1.5–7.4)	1.1±0.26** (0.5–1.3)
HOMA2-IR (% Sensitive)	81±52.8 (29–212)	109±54.7 (50–212)	43±7.1*** (29–53)
Fasting glucose (mg/dl)	89.8±9.72 (70.3–106.3)	89.0±11.65 (70.3–106.3)	90.8±7.27 (77.5–97.3)
Fasting insulin (μU/ml)	12.9±6.51 (3.5–26.6)	8.2±3.87 (3.5–15.0)	18.8±3.61*** (14.7–26.6)
Testosterone (nmol/L)	2.2±0.82 (1.0–4.0)	2.1±0.91 (1.0–3.6)	2.5±0.94 (1.2–4.0)

* $p<0.05$ resistant vs sensitive;
** $p<0.01$ resistant vs sensitive;
*** $p<0.001$ resistant vs sensitive.