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Brief report

Positron emission tomography with fluorodeoxyglucose-F18 in an animal model of mania

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Abstract

Intracerebroventricular (ICV) administration of ouabain to young adult rats has been suggested to model human bipolar mania. In the human condition, mania and bipolar depression are both associated with reductions in frontal cerebral metabolism. We utilized [^{18}F]-fluorodeoxyglucose [^{18}FDG] positron emission tomography (PET) to visualize glucose uptake in animals receiving ICV ouabain. Animals received 5 μl of 10^{-3} M ouabain ICV, were anesthetized with isoflurane inhalation, and administered intraperitoneally with 0.5 mCi of ^{18}FDG. PET data were collected over 20 min 1 hour later. Additionally, the effect of lithium was examined in animals receiving lithium in their diet for 1 week before the ICV ouabain injection. Data were analyzed with IDL Virtual Machine software. Brain glucose utilization as measured by ^{18}FDG uptake was significantly reduced in animals receiving ICV ouabain compared with those receiving equal volumes of artificial cerebrospinal fluid. Pretreatment with lithium normalized ^{18}FDG uptake. These results mirror human studies.

Keywords: Bipolar disorder; microPET; Animal model; Ouabain; Rat; [^{18}F]-Fluorodeoxyglucose [^{18}FDG]; Glucose uptake; Cerebral metabolism

1. Introduction

Bipolar disorder is an illness that afflicts approximately 1% of the world's population (Goodwin and Jamison, 1990). Individuals affected by this disorder may suffer devastating manias or paralyzing depressions. Treatment with lithium (El-Mallakh, 1996), mood-stabilizing anticonvulsants or antipsychotics (Ketter et al, 2006) is effective in only 50–75% of patients, and many experience adverse side effects so that compliance is a frequent problem (Ketter et al 2006; El-Mallakh, 1996). There is a remarkable need for more effective, less problematic drug treatments. Unfortunately, the search for these agents is greatly hampered by the lack of an availability of an adequate animal model for mania or manic-depression.

Intracerebroventricular (ICV) administration of the sodium pump inhibitor ouabain can produce lithium-

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preventable motoric hyperactivity and hypoactivity in rats, to model mania and depression, respectively (El-Mallakh et al., 1995, 2003; Li et al., 1997; Goldstein et al., 2006; Herman et al., in press). A single injection of ICV ouabain is associated with prolonged motoric hyperactivity (Ruktanochai et al., 1998). The model was created in response to early observations that human mania and depression are associated with elevated intracellular sodium (Shaw, 1966), reduced erythrocyte sodium pump activity (reviewed in Looney and El-Mallakh, 1997), and reduced expression of the alpha2 subunit of the sodium pump in post mortem human temporal cortex (Rose et al., 1998). Additionally, several investigators have noted that endogenous ouabain-like and bufodienolide-like compounds (believed to be endogenous regulators of sodium and potassium transport) are dysregulated in bipolar illness (Goldstein et al., 2006; Grider et al., 1999). Ion regulatory abnormalities have been proposed to be important to the pathogenesis of the ill phases of bipolar illness (El-Mallakh and Wyatt, 1995).

Brain imaging may be useful in understanding the neurobiology of mood disorders, targeting appropriate therapeutics, and aiding in relating brain function to clinical features and treatment response (Ketter and Wang, 2002). Imaging of ill bipolar patients has revealed several consistent findings. Buchsbaum et al. (1986) used positron emission tomography (PET) employing [^{18}F]fluorodeoxyglucose (^{18}FDG) as a tracer to reveal relative hypofrontality (lower frontal to occipital glucose metabolic rate ratios), as well as lower metabolic rates in the basal ganglia than observed in normal controls. Al-Mousawi et al. (1996) also found relative hypofrontality in acute mania. Baxter et al. (1985) found that bipolar depressed and mixed patients had whole brain reductions in glucose metabolic rates compared with normal controls. Buchsbaum et al. (1997) reported reductions in the cingulate gyrus, the frontal white matter, the putamen, and the thalamus in the region of the medial dorsal nucleus. Brooks et al. (2006) found that decreased dorsolateral prefrontal ^{18}FDG uptake was associated with more errors in a continuous performance task in depressed bipolar patients compared with normal controls, but that metabolic rates were not different from those in controls. Conversely, Kishimoto et al. (1987) showed an increase in ^{11}C-glucose uptake in manic subjects compared with normal controls. However, since glucose can be metabolized in various ways, ^{11}C-glucose is not as accurate as ^{18}FDG, which accumulates unmetabolized in tissue in which it is taken up. These findings collectively suggest that there is a reduction in glucose metabolism in many parts of the brain. Consequently, if the ouabain animal model of mania is an accurate reflection of the human disease, one would expect reduced glucose uptake in ouabain-treated animals.

2. Methods

2.1. Animals

Twenty-three male Sprague–Dawley rats between 2 and 3 months old weighing 150–200 g were used, and after methodological exclusions 18 were available to generate the data. These animals are at an equivalent human age of the late teens or early twenties – the age of onset of bipolar illness. They were maintained in 12 h:12 h light:dark cycles at 26 °C for 7 days after shipping from the supplier (Harlan, Indianapolis, Indiana) prior to inclusion in the studies. All procedures were approved by the institutional animal studies committee.

2.2. Surgical procedures

As previously described (Changaris et al., 1988; El-Mallakh et al., 1995), ICV cannulae were surgically implanted under sterile conditions into the left lateral cerebral ventricle following total anesthesia (IM ketamine 60.0 mg/kg and xylazine 15 mg/kg) 3–5 days prior to the imaging studies. Cannulae were advanced to a depth of 3.5 mm through a number-60 hole drilled 1.3 mm lateral and 0.6 mm caudal to the bregma while the animal was fixed in a stereotactic setup.

2.3. Treatments

There were the following four groups: 1) ICV artificial cerebrospinal fluid (aCSF) (Changaris et al., 1988) only, 2) ICV ouabain only, 3) ICV aCSF plus oral lithium, and 4) ICV ouabain plus oral lithium. Lithium was mixed into the Purina rodent chow (2.5 g/kg of food for 1 week before the day of investigation. This lithium dose has been validated by the manufacturer to yield plasma lithium levels in the therapeutic range. ICV ouabain was administered at 5 μl of 10^{-3} M and aCSF was administered in an equal volume via cannulae surgically implanted into the left lateral ventricle as previously described (Changaris et al., 1988). [Please note that in El-Mallakh et al. (2003) the report of ouabain 10^{-5} M is erroneous; the actual concentration used for those experiments and the current experiments is 10^{-3} M].

2.4. PET studies

A rodent microPET-R4 scanner (Siemens Preclinical Solutions, Knoxville, TN) was used for all the imaging studies. On the day of investigation, the animals were brought to the lab and received an IP injection of 0.1 ml containing 750 μCi ^{18}FDG 1 h before being scanned