Elevated Brain Lactate Response during Visual Stimulation in Panic Disorder

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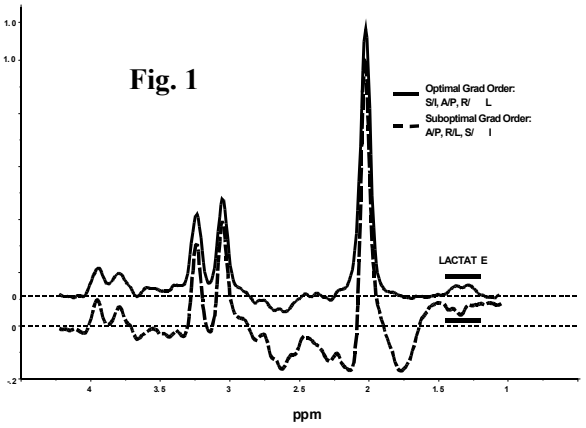
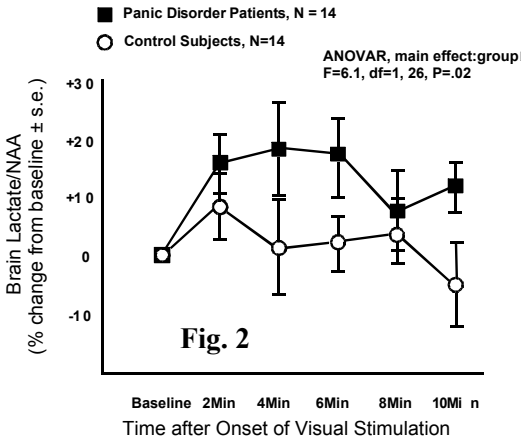
Abnormalities involving lactate, an end-product of glycolysis, have long been associated with panic disorder (PD). Since the 1950's, exaggerated increases in serum lactate have been observed in PD patients following metabolic challenges (e.g. exercise, caffeine, hyperventilation) (1). More recently, 1H-MRS studies have shown significantly elevated brain lactate responses to metabolic challenges in PD patients (1,2). This effect has been attributed to an abnormal cerebrovascular response in PD patients. In this model, exaggerated cerebral vasoconstriction leads to hypoxia and lactate accumulation as a result of anaerobic metabolism. However, this model does not take into account recent findings demonstrating a broader role for lactate in aerobic brain energy metabolism.

Evidence from microsensor studies in animals (3) and 1H-MRS studies during sensory stimulation in humans (4) support the view that lactate is a normal product of glycolysis during times of increased neuronal energy demand under fully aerobic conditions. Dynamic measures of brain lactate with 1H-MRS allow a critical test of the cerebral vasoconstriction model of elevated lactate responses in PD. Since sensory stimulation leads to localized cerebral vasodilation, the vasoconstriction model predicts that an exaggerated lactate response to visual stimulation will not be observed in PD patients. We now provide evidence disconfirming this prediction.

Fourteen untreated PD patients (5 males, mean age 38) and 14 volunteers (5 males, mean age 38) were scanned during a 5 minute baseline condition (eyes closed) and a 10 minute activation condition (viewing an 8 Hz flickering radial checkerboard stimulus). Proton spectra were acquired with a 1.5 Tesla MRI system (GE Signa Horizon NV/I) from an 18.75 cc voxel placed in the primary visual cortex using a 3 inch surface coil and a PRESS sequence (TE=288, TR=1500, reps=640). The order of the slice-selective gradients (for defining the spectroscopy voxel) had a pronounced effect on the extent of contamination by artifact originating outside the voxel. This artifact was minimized with a gradient order of S/I, A/P, R/L (Figure 1). Spectra were zero-filled, phase aligned, time-averaged and apodized using MRUI software (5). After setting the NAA peak frequency to 2.01 ppm, the lactate/NAA ratio was quantified by peak integration (lactate = sum from 1.20 to 1.43 ppm, NAA = sum from 1.87 to 2.15 ppm). The percent change in lactate/NAA from baseline was quantified for five consecutive 2 minute intervals during visual stimulation and statistically analyzed with ANOVAR. The prediction of a greater increase in lactate/NAA during visual stimulation in PD was tested by a main effect for group.





Results: No subjects reported panic attacks during scanning. The lactate doublet centered at 1.32 ppm was visible in all spectra. The PD patients showed a significantly greater increase in lactate/NAA during visual stimulation than the control subjects (F=6.1, df=1,26, P=.02; Figure 2 shows means and standard deviations). There were no group differences in NAA, NAA/Cr ratio, or changes in these values during visual stimulation. There were no group differences in end-tidal pCO2 during scanning.

Conclusions: Our results extend a consistent literature showing elevated brain lactate responses in PD. The cerebral vasoconstriction model proposes that this effect results from ischemic hypoxia. However, ischemic hypoxia cannot account for the current results. In contrast, our results support a metabolic model in which a metabolic disturbance increases lactate production or decreases lactate oxidation under aerobic conditions in PD patients. Preliminary data show persistence of elevated lactate responses to visual stimulation in clinically remitted PD patients, suggesting it may be a trait feature of patients with this condition. Further study is needed to clarify the clinical significance of this abnormality and its possible role in the pathophysiology of PD.

1) Maddock RJ (2001) *J Neuropsychiatry Clin Neurosci* 13:22-34. **2)** Dager SR, Friedman SD, Heide A, Layton ME, Richards T, Artru A, Strauss W, Hayes C, Posse S: (1999) *Arch Gen Psychiatry* 56:70-77. **3)** Hu Y, Wilson GS (1997)*J Neurochem* 69:1484-90. **4)** Prichard J, Rothman D, Novotny E, et al (1991) *Proc Natl Acad Sci USA* 88:5829-5831. **5)** MRUI (2003): Magnetic Resonance User Interface.