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Original article

Increased ventricular cerebrospinal fluid lactate in depressed adolescents

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ABSTRACT

Background: Mitochondrial dysfunction has been increasingly examined as a potential pathogenic event in psychiatric disorders, although its role early in the course of major depressive disorder (MDD) is unclear. Therefore, the purpose of this study was to investigate mitochondrial dysfunction in medication-free adolescents with MDD through in vivo measurements of neurometabolites using high-spatial resolution multislice/multivoxel proton magnetic resonance spectroscopy.
Methods: Twenty-three adolescents with MDD and 29 healthy controls, ages 12–20, were scanned at 3 T and concentrations of ventricular cerebrospinal fluid lactate, as well as N-acetyl-aspartate (NAA), total creatine (tCr), and total choline (tCho) in the bilateral caudate, putamen, and thalamus were reported.
Results: Adolescents with MDD exhibited increased ventricular lactate compared to healthy controls [$F(1,41) = 6.98$, $P = 0.01$]. However, there were no group differences in the other neurometabolites. Dimensional analyses in the depressed group showed no relation between any of the neurometabolites and symptomatology, including anhedonia and fatigue.
Conclusions: Increased ventricular lactate in depressed adolescents suggests mitochondrial dysfunction may be present early in the course of MDD; however it is still not known whether the presence of mitochondrial dysfunction is a trait vulnerability of individuals predisposed to psychopathology or a state feature of the disorder. Therefore, there is a need for larger multimodal studies to clarify these chemical findings in the context of network function.

1. Introduction

Major depressive disorder (MDD) is a debilitating mental illness and major public health concern that remains poorly understood. MDD often emerges in adolescence with devastating consequences, including suicide, the second leading cause of death in this age group [29,45,58]. However, there is a paucity of research targeting adolescents early in the course of illness. Nearly all pathophysiological models of adolescent MDD are based on evidence derived from research in adults, which may be confounded by disease chronicity, antidepressant exposure, and aging.

Recently, mitochondrial dysfunction has been increasingly scrutinized as a potential pathogenic event in MDD [54]. In support of this emerging model are phosphorous magnetic resonance spectroscopy (^{31}P MRS) studies of high-energy phosphate neurometabolites in adults with MDD, which have documented decreased levels of adenosine triphosphate (ATP) – the cell's energy currency – whose production is the primary biological function of the mitochondria [30,39]. Additionally, recent proton magnetic resonance spectroscopy (^{1}H MRS) studies of brain lactate levels have reported elevations in adult patients with MDD [50], schizophrenia, and bipolar disorder [5,47] compared to healthy control subjects. Brain lactate, the end product of anaerobic glycolysis, increases as a result of decreased mitochondrial energy production (Fig. 1), and is thus a sensitive index of mitochondrial dysfunction. However, these prior in vivo MRS assessments of the potential involvement of mitochondrial dysfunction in MDD were conducted in adult patients, so their relevance to depression in adolescence is unclear.

The primary aim of the present study was to investigate the potential role of mitochondrial dysfunction in depressed adolescents through in vivo measurements of neurometabolites using a high-spatial resolution multislice/multivoxel ^{1}H MRS technique,

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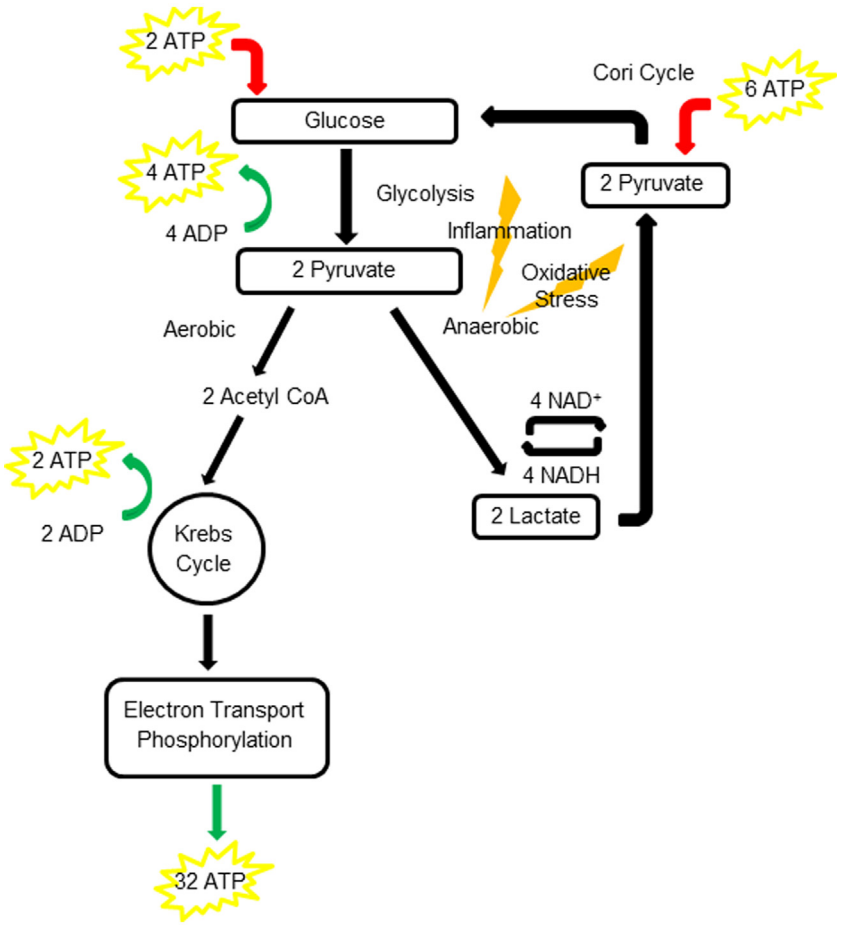

Fig. 1. Anaerobic formation of lactate and aerobic energy production. Lactate is the end product of anaerobic glycolysis. ATP: adenosine triphosphate; ADP: adenosine diphosphate; NAD+: oxidized nicotinamide adenine dinucleotide; NADH: reduced nicotinamide adenine dinucleotide.

commonly referred to as MRS imaging or MRSI [8]. Specifically, based on our prior finding of elevations of ventricular cerebrospinal fluid (CSF) lactate in adults with MDD compared to healthy control subjects [50], we hypothesized that this metabolic marker of mitochondrial dysfunction would be similarly elevated in depressed adolescents. Secondarily, we aimed to assess whether there were significant regional abnormalities (i.e., bilateral caudate, putamen, and thalamus) in the levels of other neurometabolites, including N-acetyl-aspartate (NAA), total choline (tCho), and total creatine (tCr), which are simultaneously measured with lactate by our MRSI technique. We specifically focused on metabolite concentrations within the striatum given mounting evidence linking this region to the reward circuitry, motivation [11–13], and anhedonia [20,28].

In the context of the present study, NAA was of particular interest because it is synthesized in neuronal mitochondria and localized almost exclusively in neuronal elements [2]. Reductions in NAA are generally interpreted as reflecting neuronal injury, dysfunction or loss and, germane to the present study, impaired mitochondrial function [44,55]. Total choline is associated with cell membrane integrity, with increases indicative of membrane peroxidation and breakdown (Urenjak et al., 1993, [49]). Thus, we hypothesized that depressed adolescents would show decreased NAA and increased tCho in the striatum. Conversely, tCr is often constant and functions as an internal standard for comparison in MRSI investigations [31], thus, no differences between groups were hypothesized. Lastly, potential associations between the neurometabolites and depressive symptoms (e.g., anhedonia and fatigue) previously documented in MDD [50,17], were also explored.

2. Methods

2.1. Participants

Participants in this study consisted of 23 adolescents with MDD (mean age = 17.08, SD = 2.53, 14 females) and 29 healthy controls (HC; mean age = 15.86, SD = 1.96, 20 females). Groups were not specifically matched on age and gender, so these factors were explored as covariates in the statistical models.

Depressed adolescents and HC participants were recruited from academic institutions and by media advertisements in the New York City metropolitan area. Participants provided written informed consent, or parental consent and assent for subjects younger than 18 years old, before all procedures. Approval to conduct the study was granted by the institutional review boards of the participating institutions.

2.2. Inclusion and exclusion criteria

All adolescents with MDD met the DSM-IV-TR diagnosis of MDD with a current episode $\geq$ 6 weeks duration, and a raw severity score $\geq$ 36 on the Children's Depression Rating Scale-Revised (CDRS-R). Moreover, all participants with MDD were either medication naïve or psychotropic medication-free for at least 7 half-lives of the medication. In the MDD group, co-morbid