Brief communication

MOLECULAR METABOLISM

# Role of mitochondrial uncoupling protein-2 (UCP2) in higher brain functions, neuronal plasticity and network oscillation

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## ABSTRACT

**Background/Purpose:** Major psychiatric illnesses, affecting 36% of the world's population, are profound disorders of thought, mood and behavior associated with underlying impairments in synaptic plasticity and cellular resilience. Mitochondria support energy demanding processes like neural transmission and synaptogenesis and are thus points of broadening interest in the energetics underlying the neurobiology of mental illness. These experiments interrogated the importance of mitochondrial flexibility in behavior, synaptic and cortical activity in a mouse model.
**Methods:** We studied mice with ablated uncoupling protein-2 expression (UCP2 KO) and analyzed cellular, circuit and behavioral attributes of higher brain regions.
**Results:** We found that mitochondrial impairment induced by UCP2 ablation produces an anxiety prone, cognitively impaired behavioral phenotype. Further, NMDA receptor blockade in the UCP2 KO mouse model resulted in changes in synaptic plasticity, brain oscillatory and sensory gating activities.
**Conclusions:** We conclude that disruptions in mitochondrial function may play a critical role in pathophysiology of mental illness. Specifically, we have shown that NMDA driven behavioral, synaptic, and brain oscillatory functions are impaired in UCP2 knockout mice.
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**Keywords** Mental illness; Mitochondria; Uncoupling proteins; Auditory gating; NMDA receptor antagonism; Behavioral phenotype

## 1. INTRODUCTION

Major psychiatric illnesses are profound disorders of thought and emotion, which are strongly associated with underlying impairments in synaptic plasticity and cellular resilience. Mitochondria support energy demanding processes like neural transmission, and synaptogenesis, and are thus promising points of broadening interest in the energetics underlying the neurobiology of mental illness [1]. A case report of patients with mitochondrial cytopathy documented that 54% of study participants had major depressive disorder (MDD), 17% bipolar disorder, 11% panic disorder and 60% reported a family history of psychiatric illness [2]. Evidence from functional assays, protein expression studies and linkage analyses, points to a specific role for mitochondria in psychotic illnesses [1]. Patients with bipolar disorder have been shown to have impaired brain energy metabolism and increased mitochondrial DNA mutations [1]. A recent report on major depressive disorder demonstrated significantly reduced mitochondrial energy production in neurons of patients compared to controls [3].

With this in mind, we turned to a genetic model in which mitochondrial responses to energy demands are impaired. The mouse model presented here includes a deletion of uncoupling protein 2 (UCP2), a mitochondrial membrane protein that separates oxidative phosphorylation from ATP synthesis via controlled proton re-entry into the mitochondrial matrix [4]. In neurons, sustained UCP2 mediated uncoupling leads to increased mitochondrial proliferation and greater ATP production, making neurons more adaptive to dynamic fluctuations in neuronal activity [4]. We have shown that in the absence of UCP2, neurons are less plastic in response to stress. The translational value of this line of inquiry is clear as UCP2 is widely distributed in the central nervous system of humans including in basal ganglia, hippocampus, and cortex. Early evidence of UCP2's potential importance for mental illness has been demonstrated through post-mortem studies of

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patients with schizophrenia and bipolar disorder showing reduced mRNA expression of UCP2 in cortex [5].

In published preclinical studies, using an UCP2 +/+ mice, we demonstrated that voluntary exercise induced UCP2 mRNA expression and oxygen consumption in the hippocampus [6]. These changes in metabolic demands resulted in increased mitochondrial number and dendritic spine synapses. Importantly, these changes in plasticity, mitochondrial and synaptic, did not occur in UCP2 KO animals, a further confirmation of the important role of UCP2 in neuronal and mitochondrial flexibility [6]. At the outset of the current studies, we hypothesized that the importance of mitochondria may be particularly salient for the cortex, where sustained recurrent neuronal firing has particularly high metabolic demands. Inadequate metabolic resources in the UCP2 KO model over a sustained period of time potentially contribute to abnormalities in the dendritic tree, architectural changes that underlie the deteriorating long-term course of mental illness.

Here we use an UCP2 KO mouse model to probe the role of reduced mitochondrial function in measures relevant to mental illness—emotionality, cognition, and activity in response to NMDA receptor blockade (psychotomimetic), synaptic plasticity and brain oscillatory and sensory gating activities, these latter measures considered endophenotypes of mental illness.

## 2. MATERIALS AND METHODS

### 2.1. Animal subjects

The Institutional Animal Care and Use Committee of Yale University approved all experiments. Mice were kept under standard laboratory conditions with free access to standard chow food and water except during behavioral testing periods. The generation of ucp2$^{-/-}$ mice has been previously described [7]. Animals included in behavioral studies were between 3 and 5 months of age.

### 2.2. Behavioral assessments

A series of behavioral assessments was used to establish the behavioral phenotype of UCP2 KO mice and its relevance as a model for aspects of neuropsychiatric illness. All behavioral testing was done in the light phase.

#### 2.2.1. Elevated plus maze (EPM)

The maze is elevated 50 cm from the floor and has four 16 cm × 5 cm arms. Two arms are enclosed by 12-cm walls and the other 2 arms have a 3-mm edge to prevent the animals from slipping off the maze. The maze is illuminated equally on all four arms. Mice were placed on an open arm facing away from the center and were allowed to explore the maze for 5 min. Behavioral performance was recorded by overhead camera equipment and Any-MAZE™ software. Animals were carefully monitored and observed throughout testing.

#### 2.2.2. Tail suspension test (TST)

Mice were suspended from a metal hanger inside of a tail suspension chamber (PHM-300; MED Associates, Inc. [3]; St. Albans, VT) for five minutes. A load cell and amplifier (ENV-50TS; MA) interfaced with data collection software (SOF-821; MA) was used to measure activity with a lower threshold value set at 2. Time immobile was defined as any period below the lower threshold value. Mice were acclimated to the behavior room with white noise for at least one hour prior to testing, and all equipment were cleaned with 60% ethanol between mice.

#### 2.2.3. Open field

The open field test apparatus was a square, polyurethane arena (36.5 cm × 36.5 cm × 30 cm, Plexiglas). The animal was placed in corner of the apparatus locomotion speed, distance traveled, entries into the central zone, and time spent in contact with the outer walls, were recorded for 5 min. Behavioral testing took place from 1000 to 1400 h (i.e. in the light phase of the light—dark cycle). The apparatus was cleaned with 10% ethanol after each animal exposure. ANY-Maze Software™ (Stoelting Company, Wood Dale, IL) was used to record and analyze behavioral data.

#### 2.2.4. Lashley maze

The Lashley III maze is a complex task that can be solved by learning the correct sequence of right—left responses, or extra-maze cues, or both [8]. Each day, animals were moved to the behavior testing room for thirty minutes prior to testing to allow them to acclimate to the testing environment. At that time, food and water was removed from all home cages. At the beginning of maze testing, mice were placed in the start box. Recorded test time begins when the door of the start box is opened. A mouse is considered to enter a new zone or arm of the maze when its body has crossed into that area. The trial is completed when the mouse has completely entered the pseudo-home cage at the end of the maze. Testing is repeated, with one trial per testing day per animal, until all mice reach a learning criteria defined as two consecutive trials with zero or one errors or until 14 days have elapsed [9]. Using overhead camera equipment and Any-MAZE™ software, Lashley maze activity was recorded and analyzed.

#### 2.2.5. Y-maze

Spatial memory was assessed using the two-trial Y-maze task previously developed to study memory and recognition in rats [10]. A single Y-maze was made of black Plexiglas and consisted of three arms with an angle of 120° between each of the two arms. Each arm was 8 cm × 30 cm × 15 cm (width × length × height). The three arms were randomly designated: start arm, in which the mouse started to explore (always open), novel arm, in which the mouse started to explore (always open), novel arm, which was blocked during the first trial but open during the second trial. The maze was placed on a flat surface within the behavioral testing room. Proximal visual cues (pictures within the arms of the apparatus) and distal visual cues (the configuration of the room, curtain, and wall art) remained constant throughout testing. The floor of the maze was covered with white chip bedding. Between each trial the apparatus was cleaned with 10% ethanol and new bedding was added. Behavioral testing took place from 1000 to 1400 h (i.e. in the light phase of the light—dark cycle). The Y-maze test consisted of two trials separated by an inter-trial interval (ITI) of 60 min to assess spatial memory. The first trial had a five-minute duration and allowed the mouse to freely explore only two arms (start arm and other arm) while the third arm was blocked. After a 60 min ITI, the second trial also of five minutes duration was conducted during which all three arms were accessible and novelty vs. familiarity was compared in all three arms. ANY-Maze Software™ (Stoelting Company, Wood Dale, IL) was used to record and analyze behavioral data.

### 2.3. Response to NMDA receptor antagonist (MK 801)

Mice from were brought from the animal colony to the behavioral testing room. They were first habituated to the testing room for thirty minutes and then habituated to recording chambers for two hours prior to challenge. These chambers were opaque plexi-glass chambers measuring 24 cm W × 20 cm H × 46 cm L with alpha-dri™ bedding in the floor of the testing chambers. At the end of the habituation period, mice received an injection of the NMDA receptor antagonist MK 801 (0.25 mg/kg in saline, i.p.). Using overhead camera equipment

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