Available online at www.sciencedirect.com

SCIENCE DIRECT®

Brain Research Reviews 48 (2005) 1–15

BRAIN RESEARCH REVIEWS

www.elsevier.com/locate/brainresrev

Review

Behavioral correlates of differences in neural metabolic capacity

Jon T. Sakata[a], David Crews[a], F. Gonzalez-Lima[a,b,*]

[a]*Institute for Neuroscience, University of Texas at Austin, Austin, TX 78712, United States*
[b]*Department of Psychology, University of Texas at Austin, Austin, TX 78712, United States*

Accepted 26 July 2004
Available online 1 September 2004

Abstract

Cytochrome oxidase is a rate-limiting enzyme in oxidative phosphorylation, the major energy-synthesizing pathway used by the central nervous system, and cytochrome oxidase histochemistry has been extensively utilized to map changes in neural metabolism following experimental manipulations. However, the value of cytochrome oxidase activity in predicting behavior has not been analyzed. We argue that this endeavor is important because genetic composition and embryonic environment can engender differences in baseline neural metabolism in pertinent neural circuits, and these differences could represent differences in the degree to which specific behaviors are 'primed.' Here we review our studies in which differences in cytochrome oxidase activity and in behavior were studied in parallel. Using mammalian and reptilian models, we find that embryonic experiences that shape the propensity to display social behaviors also affect cytochrome oxidase activity in limbic brain areas, and elevated cytochrome oxidase activity in preoptic, hypothalamic, and amygdaloid nuclei correlates with heightened aggressive and sexual tendencies. Selective breeding regimes were used to create rodent genetic lines that differ in their susceptibility to display learned helplessness and in behavioral excitability. Differences in cytochrome oxidase activity in areas like the paraventricular hypothalamus, frontal cortex, habenula, septum, and hippocampus correlate with differences in susceptibility to display learned helplessness, and differences in activity in the dentate gyrus and perirhinal and posterior parietal cortex correlate with differences in hyperactivity. Thus, genetic and embryonic manipulations that engender specific behavioral differences produce specific neurometabolic profiles. We propose that knowledge of neurometabolic differences can yield valuable predictions about behavioral phenotype in other systems.

Topic: Neural basis of behavior
Theme: Neural plasticity

Keywords: Cytochrome oxidase; Individual differences; Sexual differentiation; Aggression; Courtship behavior; Depression; Learned helplessness; Hyperactivity; Attention deficit

Contents

* Corresponding author. Department of Psychology, 1 University Station A8000, University of Texas at Austin, Austin, TX 78712-0187, United States. Tel.: +1 415 502 3279; fax: +1 415 476 4929.
E-mail address: gonzalez-lima@psy.utexas.edu (F. Gonzalez-Lima).

0165-0173/$ - see front matter © 2004 Elsevier B.V. All right reserved.
doi:10.1016/j.brainresrev.2004.07.017

1. Introduction

Neural activity is the basis of all behaviors. All sensory stimuli impinging on the individual are translated into neural activity, and neural activity governs our actions and understanding of our surroundings. It is not surprising, therefore, that a fundamental parameter of interest in neuroscience is the activity of single neurons or populations of neurons. How neurons in different brain areas respond to different exogenous stimuli and code for different behaviors, and how activity in pertinent brain areas underlie learning and memory are questions of great interest and major importance. Documenting and understanding the plasticity of the brain, or more specifically how the encoding of different stimuli or behaviors changes as a function of experience, and the constraints to this plasticity have significant implications for medicine, psychology, and physiology.

Neural activity is constrained, in part, by the availability of cellular energy, primarily ATP. Furthermore, the production of ATP is constrained by pertinent enzymes involved in oxidative phosphorylation, the major energy-synthesizing pathway utilized by the central nervous system [35,36]. The enzyme, cytochrome oxidase (cytochrome *aa*3 or ferrocytochrome *c*), is a terminal enzyme of the electron transport chain (complex IV) located in the inner mitochondrial membrane, and it catalyzes the transfer of electrons to oxygen to form water and ATP; thus, cytochrome oxidase is a rate-limiting enzyme in oxidative phosphorylation [139]. In this respect, the activity of cytochrome oxidase determines the amount of ATP available in a neuron, which could constrain the amount of activity that a neuron can sustain. Therefore, cytochrome oxidase activity can serve as a marker of metabolic capacity that could be correlated to behavior [41].

Wong-Riley et al. [146] have elegantly documented the series of molecular events and parameters regulating cytochrome oxidase expression and activity. Cytochrome oxidase is a holoenzyme composed of 13 proteins, 10 of which are encoded in the nuclear genome and three of which are encoded in the mitochondrial genome [54,55,146,152]. The catalytic subunits seem to be encoded in the mitochondrial genome because transcription of mitochondria-encoded cytochrome oxidase genes correlates better with cytochrome oxidase activity than nuclear-encoded cytochrome oxidase genes (Refs. [55,89]; but see Ref.[73]). Cytochrome oxidase activity is determined primarily by the abundance of the holoenzyme in the mitochondria [52,55]. Therefore, cytochrome oxidase activity is governed by a complex interaction between intracellular factors that affect both nuclear and mitochondrial gene expressions. For example, GA-binding protein and nuclear respiratory factors 1 and 2 are important in the transcription of cytochrome oxidase genes, and levels of expression of these transcription factors correlate with cytochrome oxidase [91,149,153].

The abundance and activity of cytochrome oxidase are tightly linked to the energy demand involved in neuronal activity and to the ratio of excitatory/inhibitory inputs. Changes in cytochrome oxidase are not limited to particular neurotransmitters or cell signaling systems. Instead, changes in cytochrome oxidase activity closely follow those of the Na^+/K^+ pump, which restores the resting membrane potential in excitable cells such as neurons because this pump demands the highest amount of ATP in neurons [56,60,61,146–148]. For example, experimentally induced decreases in afferent excitatory input (e.g., via tetrodotoxin) lead to significant decrements in cytochrome oxidase activity [28,53,55,56,62,84,89,91,140–145,147,148,151,152].

In general, increased excitatory input and decreased inhibitory input are correlated with increased cytochrome oxidase activity [72,83,88,90,151]. For example, in the supragranular layers of the macaque extrastriate cortex, cytochrome oxidase-rich zones have more glutamate-immunoreactive synapses relative to cytochrome oxidase-poor zones [90], and NMDAR1 expression is positively correlated with cytochrome oxidase activity in cortical neuronal cultures [151].

Because cytochrome oxidase is intimately linked to neuronal activity, cytochrome oxidase histochemistry has traditionally been used to assess the metabolic history of an area (e.g., Refs. [9,53,140]). In this respect, cytochrome oxidase has been used to trace functional pathways activated during a series of experiences. Information on cytochrome oxidase activity is very different from information based on other metabolic markers such as 2-deoxyglucose and immediate early genes such as c-*fos*; the latter markers provide information on evoked or immediate activity, whereas cytochrome oxidase activity reflects long-term changes in brain activity [41]. For example, 2-deoxyglucose consumption during training or learning tasks reflects ongoing metabolic changes that occur during learning, while changes in cytochrome oxidase activity after learning reflect long-term changes in neural metabolic capacity as a consequence of learning [98]. The activity of cytochrome oxidase is more stable over time relative to 2-deoxyglucose uptake or c-*fos* expression and reflects