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How doth the little busy bee: unexpected metabolism

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Brain energy metabolism powers information processing and behavior, much as electricity powers a computer. However, a recent study in insects suggests that this relationship is more interesting, causally linking aggressive behavior to energetics. These findings may also shed new light on aerobic glycolysis, a long-standing riddle of human brain physiology.

Neuronal signaling demands a high rate of energy consumption. On the whole, the brain is highly energy-efficient, oxidizing glucose to CO_2 via mitochondrial oxidative phosphorylation (OXPHOS). But, intriguingly, 10% of the glucose that enters glycolysis is transiently converted to lactate despite adequate oxygen availability, hence the term aerobic glycolysis [1]. The existence of aerobic glycolysis in the brain is puzzling, as less ATP is generated from glucose precisely when ATP is most needed. Aerobic glycolysis is also of clinical interest, for in Alzheimer's disease amyloid-beta deposits preferentially in areas rich in lactate [2].

The aggressive African honey bee (*Apis mellifera scutellata*) was first introduced into Brazil in 1956 to improve honey production. A few swarms were accidently released and cross-bred with local colonies of the docile European honey bee (*Apis mellifera ligustica*). The resulting hybrid, the Africanized honey bee, quickly spread through the Americas, reaching the United States in 1990. It was one of the most successful biological invasions of recent times [3]. In search of the biological basis of aggressive behavior, a study from Gene Robinson's laboratory found that the brain of the Africanized bee has lower expression and activity of several OXPHOS enzymes. Moreover, increasing age and alarm pheromone treatment, conditions that make European bees more aggressive, were found to reduce brain OXPHOS activity [4]. Having established this correlation, this group recently went on to test for causality, examining the effect on behavior of directly manipulating OXPHOS activity [5]. In brief, acute pharmacological OXPHOS inhibition was found to increase aggressive behavior in European bees, an effect that was sensitive to social modulation. Parallel experiments in the fruit fly *Drosophila melanogaster* showed that genetic reduction of a neuronal OXPHOS complex, but not of its glial counterpart, also increased aggressive behavior in this species. Together with their previous report of a correlation between OXPHOS activity and aggression, these new findings support the counterintuitive notion that a basic biochemical pathway of energy metabolism also serves as a node for the modulation of behavior.

As tends to happen with original science, these studies throw open more doors than they close. Although significant cellular mortality in the brain was duly discarded, skeptics may have difficulty comprehending the behavioral effects of mitochondrial OXPHOS inhibition in the whole insect. However the effects of specific targeting of neuronal OXPHOS with GAL4-driven RNAi in *Drosophila* are more compelling. Thus, inducible RNAi expression in the adult fly, using the GAL4/GAL80/UAS system may help to rule out a developmental explanation for the aggressive phenotype. But what is the link between energy and behavior? In apparent contradiction to the data discussed here, flies have been shown to increase their aggressive behavior in proportion to the amount of food available, a phenomenon mediated by the sugar receptor Gr5a in gustatory neurons. [6]. Conceivably, mitochondrial enzyme inhibition might target behavior by altering the evaluation of the food resource. The existence of neuronal populations that sense the general metabolic state of the organism is of particular interest. In mammals, circuits between the hypothalamus (a region involved in hunger sensation) and other areas of the brain are responsible for evoking complex behavior. Recent studies have identified a fairly direct neuronal link between hunger and aggressive behavior [7].

While the mechanisms that link Africanization, aging and pheromone receptors to behavior remain to be identified [5], we focus here on the extraordinary changes in brain metabolism reported in these studies. Most striking is the acute reduction of OXPHOS activity in honey bees exposed to alarm pheromone. Why does the brain of an aroused aggressive bee, getting ready for fight or flight, turn down its own power supply? Without information about brain activity, fuel consumption and oxygen consumption, we may only speculate. In theory, it is possible that insects, unlike mammals [1,8,9], reduce their neural activity during arousal, diverting fuel and oxygen to muscle. Another trade-off scenario may be that only oxygen consumption is reduced and that normal or even increased neural activity in the aroused insect is covered by glycolytic ATP production, however inefficiently. Alternatively, oxygen consumption and mitochondrial ATP production may not be impaired. For example, partial inhibition of the

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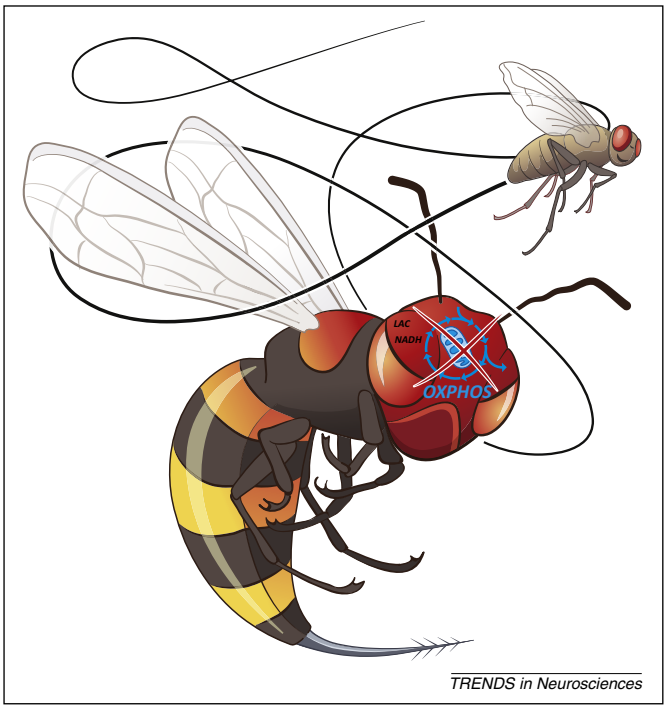

Figure 1. Brain energy metabolism in aggressive bees. Inhibition of mitochondrial oxidative phosphorylation (OXPHOS) in the brain results in increased aggressive behavior in honey bee and fruit fly. Could this effect be partly explained by accumulation of upstream metabolites like NADH and lactate?

OXPHOS complex IV during mild hypoxia may not affect mitochondrial flux and ATP production, as the affinity of complex IV for oxygen increases at low oxygen levels. The thermodynamic price for this is paid via sequential accumulation of upstream electron carriers, firstly NADH and FADH2, then by TCA cycle intermediates and lactate. Functional data would clarify these issues, but it seems reasonable to assume that the various paradigms of OXPHOS inhibition in honey bee and fly should have led to the accumulation of metabolic intermediates, which bring us back to aerobic glycolysis and lactate.

Aerobic glycolysis or the 'Warburg Effect' was first described by Otto Warburg in cancer cells, which profit from accumulated intermediate metabolites for the generation of biomass. Aerobic glycolysis in the human brain reaches levels of 40% during early childhood, consistent with rapid brain growth [9,10]. But what about the 10% levels present in adults? Aerobic glycolysis in the adult brain correlates with the persistence of a gene expression that is typical of infancy, a phenomenon dubbed transcriptional neoteny. Brain regions with the highest aerobic glycolysis, like the medial prefrontal gyrus, express genes related to synapse formation and growth, whereas more oxidative regions such as the cerebellum express genes related to mitochondria and synaptic transmission [10]. As well as providing the building blocks for synaptic growth and remodeling, aerobic glycolysis releases lactate, a highly diffusible metabolite that plays a dual role as a neuronal fuel and an intercellular signal [8,9,11–13]. Worthy of mention is that there is a known link between lactate and arousal, exemplified by the triggering of panic attacks by intravenous lactate infusion and the finding of a substantially larger activity-dependent lactate increase in patients suffering from panic disorder syndrome [14]. In this context, the predicted increase in aerobic glycolysis and lactate levels in response to OXPHOS inhibition may contribute to the behavioral changes observed in bees and flies (Figure 1).

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