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RESEARCH HIGHLIGHT

# Metabolic enzymes link morphine withdrawal with metabolic disorder

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Energy metabolism is a fundamental biological process that is vital for the survival of all species. Disorders in the metabolic system result in deficiency or redundancy of certain nutrients, including carbohydrates, lipids, amino acids, etc. Abnormality of the energy metabolism system leads to a number of metabolic diseases, such as the metabolic syndrome. Broadly speaking, the term "metabolic diseases" now tends to be widened to the category that refers to all diseases with metabolism disorder. It is shown that many diseases associate with metabolic disorders. For example, most malignant tumors progress with mal-nutrition and high consumption, that is, cachexia. Many components of the energy metabolism system, such as lactate dehydrogenase (LDH), are now widely applied in clinical examinations as special markers for tumors and some other diseases. Opioid dependence and addiction are neurobiological diseases associated with malregulation of the metabolic system. However, how chronic drug administration induces metabolic abnormality is not understood. In a recent issue of *Cell Research*, research group of Jing-Gen Liu [1] reports an interesting discovery that three metabolic enzymes are changed in mice after chronic morphine treatment, suggesting new roles of metabolic enzymes as a potential link that associates metabolic disorder with opioid dependence.

The process of energy metabolism is very complex, a major part of which is the tricarboxylic acid cycle. The tricarboxylic acid cycle contains a variety of different enzymes and substrates, such as the pyruvate dehydrogenase (PDH). Functioning as a complex, PDH oxidizes pyruvate, by converting it into acetyl-CoA, and produces the bulk of ATP. Both the pyruvate cycle and PDH itself are under stringent regulation. PDH activity is regulated by its phosphorylation state, being most active in the deposphorylated state. PDH dysregulation may lead to metabolic diseases. Lack of PDH activity has long been recognized as the most common cause of primary lactic acidosis in infancy. PDH deficiency occurs in rats after exposure to high glucose or free fatty acid, indicating its close relationship with diabetes. It has been proposed recently that PDH kinase inhibitors might be an effective therapy for Type II diabetes [2]. On the other hand, PDH increment has been reported in hypertrophic cardiomyocytes induced by hypoxia-reoxygenation. Kobayashi *et al*. reported that high level of cardiac work increases PDH activity, which associates closely with reduced mitochondrial NADH/$NAD^+$ ratios and acetyl CoA/CoA ratios [3].

Accumulating evidence stresses that dysregulation of energy metabolism system relates with cerebral diseases or psychiatric disorders. It has been demonstrated that ischemic brain injury results in the reduction of energy metabolism. Loss of PDH activity and reduced expression level were found in vulnerable neurons after cerebral ischemia and reperfusion, which may result in the reduced cerebral glucose and oxygen consumption [4-5]. Studies also link metabolic abnormality to chronic cerebral diseases and dementia, such as Alzheimer disease (AD). Metabolic syndrome has been recently reported to associate with increased risk for AD. Cognitive abnormalities of AD to a large extent result from decreasing brain metabolism. Mitochondrial dehydrogenases affecting energy transfer are frequently altered in AD. One of the AD associating protein, the amyloid precursor protein (APP) can target mitochondria, and reduce cytochrome oxidase activity and ATP level [6]. It has been reported that mitochondrial movement is impaired in neurons of AD patients [7], which correlates with altered expression of APP.

Drug dependence and addiction are chronic, relapsing brain disorders, manifesting as brain changes resulted from chronic drug exposure. Addiction to drugs, such as alcohol, has been well shown to be related with abnormality of the energy metabolic system. Development of opioid dependence involves a variety of different signaling pathways and neurotransmitters, among which glutamate and GABA play crucial roles. It has been shown that ATP could inhibit glutamate synaptic release in the hippocampus, suggesting its importance in modulating neurotransmitters and glutamate signal transduction [8]. In the brain of opioid addicts and opiate dependent animals, metabolic processes such as glycolysis and the tricarboxylic acid cycle are reduced [9-10]. Moreover, glucose has been shown to suppress acute morphine withdrawal signs, attenuating acute morphine-induced memory impairment and increment of locomotor activity [11]. These studies suggest that the energy metabolic system plays an important part in opioid dependence. Therefore should we treat opioid dependence as one new type of energy metabolism disorder? If so, what is the molecular mechanism for such kind of dysregulation?

The paper by Chen *et al.* [1] shows for the first time, through 2-dimensional gel electrophoresis and mass spectrometry, that three key components of the energy metabolism system are regulated by opioid. In hippocampus of chronic morphine-treated mouse, the expression levels of E2 component of the pyruvate dehydrogenase complex (PDHC-E2), lactate dehydrogenase 2 (LDH2), and Fe-S protein 1 of NADH dehydrogenase are decreased, accompanied with reduced ATP production and impaired glucose metabolism. Their finding directly links chronic morphine treatment to energy metabolism disorder. Furthermore, they observe that both intrahippocampal and intraperitoneal injection of D-glucose could suppress naloxone-precipitated morphine withdrawal jumping and memory impairment in acute morphine-treated mice, indicating a potential metabolic treatment for morphine withdrawal symptoms.

The results of Chen *et al*. disclose a possible mechanism of morphine dependence and morphine treatment-induced memory impairment. Their study suggests that chronic morphine treatment may down-regulate certain components of the energy metabolism system, inhibit glucose metabolism and ATP production, and thus disturb the releasing of neurotransmitters, such as glutamate, to intrigue withdrawal syndrome and memory impairment (Figure 1).

This work raises an important question: why are there differences in acute and chronic morphine-treatment? As proposed by the authors, metabolic enzymes do not change in acute morphine-treated mouse hippocampus, and glucose can only relieve withdrawal syndrome and memory impairment in acute treated animals. Does this mean that hypoglycemia is one of the causes of acute morphine-treatment induced withdrawal syndrome? Acute morphine treatment may result in reversible glucose-ATP transition abnormality and chronic treatment may lead to irreversible reduction of enzymes, but why? More experiments are required to address these questions.

Moreover, the way through which morphine treatment alters energy metabolism and how energy metabolism affects withdrawal are still enigmatic. It has been reported by Li *et al.* that cholinergic system is involved in reversal of morphine withdrawal-induced memory impairment in

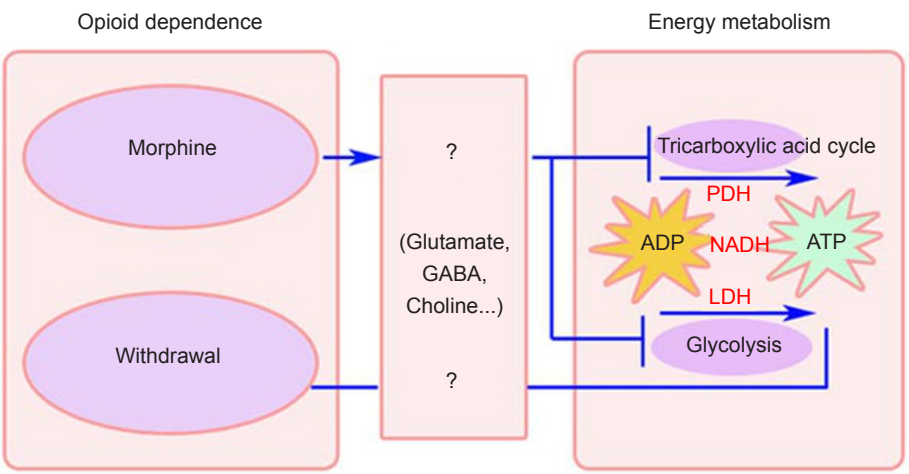


**Figure 1** Model for the role of energy metabolism enzymes in morphine dependence. Morphine treatment can down-regulate the expression level of certain metabolic enzymes, including PDH, LDH, and NADH, and thus impairs the energy metabolism. The reduction of ATP is associated with morphine withdrawal symptoms and impairment in memory.

mice [12]. Then what signal transduction results in the change of the glucose level and ATP production? How can we explain the alterations in metabolic enzymes following chronic morphine treatment? These questions need to be further investigated.

The work by Chen *et al.* proposes a new model linking opioid dependence and metabolic system. In such a model, opioid treatment plays a role in regulating energy metabolism and the latter in turn influences withdrawal symptoms. More studies should be done to confirm the regulations of the metabolic enzymes in morphine dependence, learning and memory. This would help elucidate the precise molecular mechanisms for the physical and psychiatric disorders caused by morphine treatment. If we can find out the way the metabolic enzymes are regulated and the way they regulate morphine withdrawal symptoms, we may explain morphine dependence in a new way.

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