Materials and methods

Animals

Male Wistar rats weighing 200–280g were used in all experiments. Homogla-bolin-free, non-recrurilating perfusia was performed.

Samples of the eiluent perfusion fluid were collected. The following compounds were assayed by means of standard enzymatic procedures: glucose, lactate, pyruvate, ammonia and ura. The oxygen concentration in the outihng perfusate was monitored continuously, employing platinum electrode. AMP, ADP, and ATP were assayed by means of high-per-formance liquid chromatography (HPLC). Respiratory activity was measured polarographically using a teflon-shielded platinum electrode.

Membrane-bound enzymatic activities were assayed in freeze-thawing-disrupted mitochondria. All activities were measured polarographically. Statistical analysis was done by means of the GraphPad Prism software.

Conclusion

This work presents a comprehensive investigation of the direct effects of berberine on metabolic pathways in the liver that are linked to energy metabolism. At low portal concentrations (starting at 5 µM) berberine can significantly modify several pathways in the liver. As one important contribution, our study systematically elucidates the concentration range in which berberine inhibits hepatic gluconeogenesis and increases glycosis. Furthermore, it also reveals the concentration range by which berberine detoxification is affected, an important aspect of its toxicity. Although gluconeogenesis inhibition and glycolysis stimulation were already suggested for berberine in different experimental conditions, this work demonstrates that the direct acute effects of berberine on the liver may give a great contribution in clinical topics. Another contribution concerns safety of berberine since the observed effects can affect the hepatic healthy tissue and led to metabolic disorders as well as to cell damage due to a deficient maintenance of its homeostasis.

Acknowledgements

This work was carried out with the support of the Coordination for the Improvement of Higher Education Personnel – Brazil (CAPES).

THE SHORT-TERMS EFFECTS OF BERBERINE IN THE PERFUSED LIVER

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Abstract

A systematic study on the effects of berberine on hepatic metabolism was conducted with emphasis on parameters linked to energy metabolism. The experimental system was the isolated perfused rat liver. The results demonstrate that at low portal concentrations (up to 5 µM) berberine can significantly modify several pathways in the liver. Berberine inhibited hepatic gluconeogenesis from different substrates and increased the glycolysis, two important mechanisms underlying its anti-diabetic action. Ammonia detoxification was also inhibited. Furthermore, berberine diminished liver ATP content and the ATP/ADP and ATP/AMP ratios. Respiration of intact mitochondria was inhibited, especially when pyruvate was given as substrate. However, no inhibition was found in disrupted mitochondria, with different results. These results are strong evidence that the short-term effects of berberine in the liver represent a great contribution to its clinical efficacy as an antihypertensive drug. Safety concerns also arise, and toxic symptoms can include lack of circulating glucose due to gluconeogenesis inhibition, metabolic acidosis due to excessive lactate production, impairment of ammonia detoxification and cell damage due to a deficient maintenance of its homeostasis.

Introduction

Berberine is a benzyl tetra isoquinoline plant alkaloid, a traditional herbal medicine used in China. Several studies have shown that berberine has antioxidant, anti-inflammatory, anti-mutagenic, antidote, anti-diabetic and lipid-lowering effects [1]. Altered mitochondrial physiology has been associated with some of the pharmacological properties of berberine [2]. The liver is the main organ responsible for its metabolism, and also the organ where berberine accumulates [3]. Therefore, interference with important hepatic metabolic pathways can be expected, although no specific studies have focused on this subject. Although berberine is considered relatively safe in humans [2], toxicity symptoms are observed in animals [4]. The fact that berberine is commercially available without the need for medical recommendation, and the fact that it is a natural product, favor its indiscriminate use, greatly increasing the possibility of harmful effects on health. Taking into account what was exposed above and, knowing that substances that impair mitochondrial functioning also interfere with hepatic energetic metabolism [5], it is relevant to study the short-term effects of berberine on liver metabolism. This is a technique that has some advantages over the use of isolated cells, including the fact that microcirculation and intercellular relationships are maintained, which has been rendered as physiological as possible. Therefore, the purpose of the present work was to conduct a systematic study on the effects of berberine on hepatic metabolism. The results should bring additional information about the interactions of berberine with the liver.

Results

Glycolysis catabolism, glycolysis and oxygen uptake: there was a concentration-dependent decrease in oxygen consumption. Glycolysis was also increased by berberine, also in a concentration-dependent manner, beginning at 25 µM. Glucose output was not significantly changed by berberine.

Adenosine nucleotide levels: the ATP levels were reduced by 32% at the concentration of 25 µM and by 53% at the concentration of 50 µM. The ADP levels were increased by 56% only at the concentration of 25 µM. The ATP/ADP and ATP/AMP ratios were substantially.

Conclusion

This work presents a comprehensive investigation of the direct effects of berberine on metabolic pathways in the liver that are linked to energy metabolism. At low portal concentrations (starting at 5 µM) berberine can significantly modify several pathways in the liver. As one important contribution, our study systematically elucidates the concentration range in which berberine inhibits hepatic gluconeogenesis and increases glycosis. Furthermore, it also reveals the concentration range by which berberine detoxification is affected, an important aspect of its toxicity. Although gluconeogenesis inhibition and glycolysis stimulation were already suggested for berberine in different experimental conditions, this work demonstrates that the direct acute effects of berberine on the liver may give a great contribution in clinical topics. Another contribution concerns safety of berberine since the observed effects can affect the hepatic healthy tissue and led to metabolic disorders as well as to cell damage due to a deficient maintenance of its homeostasis.

Recommendations


Acknowledgements

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