Berberine inhibits intracellular Ca2+ signals in mouse pancreatic acinar cells through M3 muscarinic receptors: New target, mechanism, and implication

Kunkun Xia¹, Zhijun Hei¹, Shuangtao Li², Huimin Song², Rongni Huang², Xiaoyu Ji², Fenni Zhang³, Jian-Xin Shen², Shuijun Zhang¹, Shuang Peng⁴, and JIE WU²

¹The First Affiliated Hospital of Zhengzhou University
²Shantou University Medical College
³Arizona State University
⁴Guangzhou Sport University

Abstract

Background and Purpose: Berberine, a natural isoquinoline alkaloid, exhibits a variety of pharmacological effects but the pharmacological targets and mechanisms are remained elusive. Here, we report a novel finding that berberine inhibits acetylcholine (ACh)-induced Ca2+ oscillations which may underlie the pathogenesis of the L-arginine-induced mouse model of acute pancreatitis (AP). Experimental approach: Patch-clamp recordings and confocal Ca2+ imaging were applied in acute dissociated pancreatic acinar cells prepared from CD1 mice to examine the effects of berberine on ACh-induced Ca2+ oscillations. The L-arginine-induced acute pancreatitis mouse model was used to evaluate the protective effects of berberine against pathological changes. Key Results: Whole-cell patch-clamp recordings showed that berberine (from 0.1 to 10 μM) reduced ACh-induced Ca2+ oscillations in a concentration-dependent manner, and this inhibition was also depended on ACh concentrations. The inhibitory effect of berberine neither occurred in intracellular targets nor extracellular cholecystokinin (CCK) receptors, chloride (Cl-) channels, and store-operated Ca2+ channels. Together, the results demonstrate that berberine directly inhibits M3 muscarinic receptors, which is further confirmed by the evidence of the interaction between berberine and M3 receptors in acinar cells. In a L-arginine AP model, berberine eliminates the ACh-induced Ca2+ oscillations, the elevation of pancreatic amylase and pulmonary myeloperoxidase, and improves acinar cell pathological injury. Conclusions and Implications: We provide novel evidence that berberine inhibits M3 receptors, in turn eliminates ACh-induced Ca2+ oscillations and L-arginine-enhanced Ca2+ signaling, which underlie the protective effects of berberine on pancreatic acinar cells against pathological changes in an acute pancreatitis model.

Hosted file

A) Binding kinetics of cell-1 (10 μM BBR)

K_{on} = 6.4e+03
K_{off} = 8.2e-04
K_{D} = 1.3e-07

B) Experimental Fitted

C) a (K_{on})

b (K_{off})

c (K_{D})

A) ACh 10 nM +L-A 10 mM +BBR 1 μM V_{m} = -30 mV

B) P=0.0003 P=0.0001

C) Normalized net charge

P=0.0003 P=0.0001

(10) (10) (10) (10)