Diclofenac inhibits Kv1.3 and Kir2.1 expressions in human macrophages and affects the membrane potential and foam cell formation(点击查看pdf全文)

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Title: 双氯芬酸对人巨噬细胞钾通道Kv1.3、Kir2.1表达的抑制作用及其对膜电位和泡沫细胞形成的影响

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摘要: 目的分研究双氯芬酸对人巨噬细胞电压依赖性钾通道Kv1.3、内向整流钾通道Kir2.1表达的影响及意义。方法以健康人外周血单核细胞源性巨噬细胞为对象，采用Real-time RT-PCR及Western blot技术研究双氯芬酸对Kv1.3和Kir2.1表达的影响；电压敏感染料膜电位标测技术分析膜电位的变化，并用酶荧光化学法检测摄取氧化修饰低密度脂蛋白（OxLDL）的巨噬细胞内胆固醇酯（CE）的构成比率。结果双氯芬酸（1.5和15 μmol/L）抑制巨噬细胞Kv1.3和Kir2.1的表达。同对照组相比，Kv1.3 mRNA下降分别超过80%和90%（P<0.05），Kir2.1 mRNA下降分别超过20%和30%（P>0.05）；两种钾通道蛋白水平的下降均分别超过10%和60%，且存在明显的剂量依赖性（P<0.05）。同时，双氯芬酸可剂量依赖性减弱巨噬细胞表面的荧光强度，使膜电位分别下降约28%和54%（P<0.05）。巨噬细胞同30 mg/L OxLDL 孵育60 h 后，细胞体积明显增大，且有许多红色的脂质颗粒沉积于细胞质内，CE/TC 的百分比超过50%。1.5和15 μmol/L双氯芬酸分别使摄取OxLDL的巨噬细胞内CE的百分比显著减少到（23.624±3.34）%和（13.601±2.916）%，但缺乏明显的量效关系（P>0.05）。结论双氯芬酸显著下调人巨噬细胞Kv1.3 和Kir2.1的表达，降低细胞膜电位，并抑制泡沫细胞形成。

Abstract: Objective To investigate the effect of diclofenac on the expression of Kv1.3 and Kir2.1 channels in human macrophages and the membrane potential and foaming process of the macrophages. Methods The effect of diclofenac on the expression of Kv1.3 and Kir2.1 channels in cultured human monocyte-derived macrophages was investigated using real-time RT-PCR and Western blotting, and its effect on the membrane potential was analyzed with optical mapping of the membrane

导航/NAVIGATE
本期目录/Table of Contents
下一篇/Next Article
上一篇/Previous Article

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potential with voltage-sensitive dyes. The ratio of cholesterol ester (CE) in the macrophages following intake of oxidized
low-density lipoprotein (OxLDL) was analyzed by an enzymatic fluorometric method. Results The expression of Kv1.3 and
Kir2.1 channels in the macrophages were down-regulated by diclofenac (1.5 μmol/L and 15 μmol/L). Compared with those in
the control group, Kv1.3 mRNA expression was reduced by over 80% and 90% ($P<0.05$), and Kir2.1 mRNA by over 20% and
30% ($P>0.05$), respectively; both their protein expression was reduced by over 10% and 60% with a dose- dependent effect ($P<0.05$). Diclofenac at the two doses dose-dependently reduced the surface fluorescence intensity of the macrophage, and the
membrane potential was decreased by 28% and 54%, respectively ($P<0.05$). Incubation of the macrophages with 30 mg/L
OxLDL for 60 h caused an obvious enlargement of the cell volume and deposition of numerous lipid granules in cytoplasm,
resulting also in a CE/TC ratio over 50% ($P<0.05$). Diclofenac at 1.5 and 15 μmol/L both significantly decreased the CE/TC ratio
to (23.624±3.34)% and (13.601±2.916)% ($P<0.05$), respectively, but this effect did not show a dose-response relationship ($P>0.05$).
Conclusion Diclofenac can significant down-regulate the expression of Kv1.3 and Kir2.1 channels in human macrophages,
lower their membrane potential and inhibit the process of foam cell formation.

参考文献/REFERENCES

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