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磷脂酶 A_2 抑制剂对家兔内毒素休克血中血小板活化因子活性的调节作用观察

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提 要 通过家兔内毒素休克模型重点观察了磷脂酶 A_2(PLA_2)抑制剂磷酸氯喹和地塞米松对血中 PLA_2 及其相关脂介质的影响。实验分成4组:(1)假手术组(SO);(2)内毒素休克组(ES);(3)磷酸氯喹预处理组(CQ);(4)地塞米松预处理组(DXM)。分别于给药前、内毒素或生理盐水注射后5、30 min,1、3、5、8 h取血测 PLA_2、血小板活化因子(PAF)、TXB_2/6-keto-$PGF_{1\alpha}$,同时连续监测平均动脉压(MAP)、心率和呼吸,观察动物8 h存活率。TXB_2/6-keto-$PGF_{1\alpha}$浓度均明显升高,PLA_2 抑制剂能显著抑制 PLA_2 及PAF活性,其中磷酸氯喹对 TXB_2/6-keto-$PGF^{1\alpha}$的抑制最为显著。此外,PLA_2 抑制剂可使家兔8 h存活率由48%提高到75%(CQ组)和70%(DXM组)。提示,用 PLA_2 的抑制剂磷酸氯喹和地塞米松均能显著抑制内毒素休克时 PLA_2 的活性及相关脂介质如PAF、TXB_2/6-keto-$PGF_{1\alpha}$的升高,提高动物存活率,有效地改善休克动物的预后。

关键词 磷脂酶 A_2;内毒素休克;血小板活化因子
中图法分类号 R631.4

感染性休克是临床最常见的严重并发症之一。传统的治疗方法难以有效地降低死亡率[1,2]。探讨感染性休克的发病机制和寻找有效的防治方法已成为当前国内外休克研究的中心问题。磷脂酶 A_2(Phospholipase A_2,PLA_2)与血小板活化因子(Platelet activating factor,PAF)在感染性或内毒素性休克发病机制中均具有重要的作用。内毒素可以活化 PLA_2 继而作用在细胞膜磷脂产生PAF、TXB_2 及6-keto-$PGF_{1\alpha}$。但有关内毒素休克时 PLA_2 与其相关脂介质如PAF、TXB_2 和6-keto-$PGF_{1\alpha}$的改变与调节,尤其是探讨使用 PLA_2 抑制剂治疗休克的研究尚不多见,本文对此进行了重点探讨。

1 材料和方法

家兔69只,雌雄不拘,体重2.4±0.5 kg,实验前禁食过夜,自由饮水。3%戊巴比妥钠耳缘静脉麻醉,右侧股动脉插管,连续监测平均动脉压(Mean arterialpressure,MAP)及采样。动物随机分成4组:(1)假手术组(SO,$n=12$);(2))内毒素休克组(ES,$n=31$);(3)磷酸氯喹预处理组(CQ,$n=16$);(4)地塞米松预处理组(DXM,$n=10$)。磷酸氯喹(Chloroquine,CQ,购自西南制药三厂)和生理盐水配成浓度3%,剂量3 mg/kg;地塞米松(Dexamethasone,DXM,重庆制药六厂产品)5 mg/kg静脉一次性注射。ES组与SO组与CQ、DXM组对应,给动物注射生理盐水1 ml/kg,30 min后除假手术组给等量生理盐水外,其余三组分别从静脉给予大肠杆菌内毒素(E.coli 055B5,购自上海第二军医大学微生物教研室)300 μg/kg,1~2 min内注射完毕。各组分别于给药前、内毒素或生理盐水注射后5、30 min,1、3、5、8 h取动脉血标本以微量滴定法测 PLA_2 活性[3],以5-HT释放法测PAF活性[4]。同位素液闪法测血浆 TXB_2 和6-keto-$PGF_{1\alpha}$(由中国医学科学院基础医学研究所提供试剂盒)。以二道生理记录仪(LMS-2B,成都仪器厂产品)连续监测血压、心电图、心率和呼吸,观察动物8 h存活率)。

实验结果以 $\bar{x}\pm s$ 表示,作单因素方差分析,存活率作 χ^2 检验。

2 结果

2.1 一般情况

内毒注射后动物出现呼吸急促、流涎和稀便等症状,心率加快,死亡前呼吸、心率明显减慢。磷酸氯喹和地塞米松对内毒素诱导的MAP下降有明显的抑制作用(见表1)。

表1 PLA_2 抑制剂对内毒素休克家兔平均动脉压的影响(kPa)

Tab 1 Effects of PLA_2 inhibitors on MAP of the endotoxic shock rabbits (kPa)

Group	n	Before LPS Infusion	After LPS Infusion					
			5 min	30 min	1 h	3 h	5 h	8 h
SD	12	13.47±1.31	12.97±1.71	12.07±1.08	11.71±1.37	12.03±1.33	12.67±1.33	12.49±1.32
ES	31	12.84±1.27	7.72±3.57**	7.68±3.32**	6.72±4.23**	6.44±4.13**	5.32±4.06**	4.33±4.19**
CQ	16	12.49±1.84	9.27±3.68**	8.12±4.55**	7.12±4.55**	7.65±4.53**	7.72±4.27**+	7.40±4.16**+
DXM	10	13.44±1.19	13.44±1.19	11.44±2.35*++	9.89±3.37+	9.89±3.59*+	9.04±4.43*+	9.01±4.32*++

*:$P<0.05$, **:$P<0.01$, *vs* SO; +:$P<0.05$, ++:$P<0.01$, *vs* ES

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Effects of phospholipase A_2 inhibitors on the activity of platelet-activa ting factor in rabbits with endotoxic shock

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Abstract　The effects of chloroquine and dexamethasone，inhibitors to phospholipase A_2(PLA_2)，on the activity of blood PLA_2 and its related lipid mediators were observed in rabbits with endotoxic shock. The rabbits were randomized into control group with sham operation (SO，$n=12$)，endotoxic shock group (ES，$n=31$)，chloroquine (3 mg/kg)-pretreated group (CQ，$n=16$) and dexamethasone (5 mg/kg)-pretreated group (DXM，$n=10$). Blood samples were obtained before and 5 min，30 min，1 h，3 h，5 h and 8 h after the initiation of endotoxic shock and PLA_2，platelet-activating factor (PAF)，TXB_2/6-keto-$PGF_{1\alpha}$ were determined and changes of mean arterial pressure (MAP) and respiratory rate (RR) were recorded. It was found that the activity of PLA_2，PAF and TXB_2/6-keto-$PGF_{1\alpha}$ were markedly increased after the inusion of endotoxin and CQ and DXM markedly inhibited the activities of PLA_2 and PAF. The inhibitory effects of CQ on TXB_2/6-keto-$PGF_{1\alpha}$ seemed to be more efficient. In addition，the survival time was increased to 75% in CQ group and to 70% in DXM group. The findings suggest that CQ and DXM，inhibitors to PLA_2，can significantly suppress the activity of PLA_2 and decrease the elevation of the related lipid mediators such as PAF and TXB_2/6-keto-$PGF_{1\alpha}$. Consequentl the prognosis of the animals with endotoxic shock is improved and the survival rate increased.

Key words　phospholipase A_2；endotoxic shock；platelet-activating actor

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