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PAPEL DA CICLOOXIGENASE-1 NO CHOQUE ENDOTÓXICO

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RESUMO

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As ciclooxigenases têm um papel fundamental na patogênese da sepse, em especial a isoforma COX-2. No entanto, apesar de o papel da isoforma "constitutiva" COX-1 ter sido negligenciado, evidências recentes indicam que esta isoforma participa em respostas induzidas por altas doses de lipopolissacarídeo bacterano. Este trabalho visou elucidar os mecanismos pelos quais a COX-1 participa da inflamação sistêmica mais grave. Propomos que a fonte principal da COX-1 nesta condição é o baço e testaremos se os prostanoides derivados dessa isoforma medeiam alterações termometabólicas e cardiovasculares de modo dependente de citocinas. Essa hipótese foi testada em ratos empregando o modelo de choque endotóxico. Para avaliar os efeitos da COX-1 durante a inflamação sistêmica, utilizamos seu inibidor seletivo (SC-560). O SC-560 atenuou a hipotermia, o hipometabolismo, acidose metabólica e hipotensão induzidos por LPS (1000 µg/kg i.v.). Este efeito atenuante teve duas fases: 30-60 min e 60-100 min. Em animais esplenectomizados, a resposta atenuante do SC-560 na hipotermia, hipotensão e acidose metabólica foi observada somente na primeira fase da resposta. Associado a esses resultados, o SC-560 não alterou o nível plasmático das citocinas TNF-α, IL-1β e IL-10 nas duas fases da resposta. No entanto, diminuiu a expressão tecidual de IL-10 no baço e observou-se uma tendência a aumento de IL-1β, mas não alterou o nível das citocinas no fígado, diencéfalo e pulmão. Detectamos LTB_4 no plasma, enquanto PGE_2, PGD_2, PGF_2, TXB_2 e LTC_4 foram detectados no baço. Nossos resultados indicam que o mecanismo de ação da COX-1 no choque endotóxico tem duas fases distintas: (i) na fase inicial da resposta a COX-1 envolvida não é proveniente do baço e age de forma independente de citocinas; na fase tardia da resposta a COX-1 parece agir de forma dependente do baço e através da produção de prostanoides, tais como PGE_2 e PGD_2 ou de leucotrienos, como LTC_4, e esta ação pode depender de efeitos locais de citocinas IL-10 e IL-1β.

Palavras-chave: COX-1. Inflamação Sistêmica. Hipotermia. Eicosanoides.

ABSTRACT

Brito CFC. The role of cyclooxygenase-1 during endotoxic shock. [Masters thesis (Immunology)]. São Paulo: Instituto de Ciências Biomédicas, Universidade de São Paulo, 2016.

Cyclooxygenases play a key role in the pathogenesis of sepsis, especially the COX-2 isoform. However, although the role of the "constitutive" COX-1 isoform has been neglected, recent evidence indicates that this isoform participates in responses induced by high doses of bacterial lipopolysaccharide. This work aimed to elucidate the mechanisms by which COX-1 participates in the most severe systemic inflammation. We propose that the main source of COX-1 in this condition is the spleen and we will test whether prostanoids derived from this isoform mediate thermometabolic and cardiovascular changes in a cytokine-dependent manner. This hypothesis was tested in rats employing the endotoxic shock model. To evaluate the effects of COX-1 during systemic inflammation, we used its selective inhibitor (SC-560). SC-560 attenuated hypothermia, hypometabolism, metabolic acidosis and hypotension induced by LPS (1000 μg/kg i.v.). This attenuating effect had two phases: 30-60 min and 60-100 min. In splenectomized animals, the attenuating response of SC-560 to hypothermia, hypotension and metabolic acidosis was observed only in the first phase of the response. Associated with these results, SC-560 did not alter the plasma levels of cytokines TNF-α, IL-1β and IL-10 in the two phases of the response. However, tissue expression of IL-10 in the spleen decreased and IL-1β increased, but did not alter the level of cytokines in the liver, diencephalon and lung. We detected LTB_4 in plasma, while PGE_2, PGD_2, $PGF_{2\alpha}$, TXB_2 and LTC_4 were detected in the spleen. Our results indicate that the mechanism of action of COX-1 in endotoxic shock has two distinct phases: (i) in the initial phase of the COX-1 response involved it does not originate from the spleen and acts independently of cytokines; (ii) in the late phase of the COX-1 response appears to act in a spleen dependent manner and through the production of prostanoids, such as PGE_2 and PGD_2 or of leukotrienes, such as LTC_4, and this action may depend on local effects of IL-10 and IL-1β cytokines.

Keywords: COX-1. Systemic Inflammation. Hypothermia. Eicosanoid

1. INTRODUÇÃO E JUSTIFICATIVA

A inflamação sistêmica decorrente de infecção (sepse) é uma das principais causas de morte em pacientes hospitalizados (1-3). Apesar dos avanços científicos e tecnológicos da medicina atualmente, como o desenvolvimento de terapias anti-inflamatórias e antibacteriana, a incidência de sepse continua aumentando (4), tornando evidente que a luta contra a sepse possa ser altamente dependente dos próprios mecanismos de defesa do organismo.

A patogênese desta síndrome envolve uma ativação aguda de células do sistema imune, tais como neutrófilos e macrófagos. Os macrófagos, particularmente, secretam mediadores solúveis tais como o fator de necrose tumoral alfa (TNF-α), interleucina 1β (IL-1β) e interleucina 6 (IL-6) que, por sua vez, agem no sistema nervoso central (SNC) e perifericamente culminando em alterações na fisiologia da temperatura corporal (Tc), taxa metabólica, pressão arterial (PA) e frequência cardíaca. A febre é a manifestação mais comum da sepse (90% dos pacientes) (5) e é entendida como uma estratégia de defesa do organismo em resposta a infecção, entretanto, a queda da pressão arterial e a virada de febre para hipotermia caracterizam os casos mais graves de sepse (6).

Na patogênese da sepse, além das citocinas, os mediadores lipídicos derivados do ácido araquidônico por ação das enzimas ciclooxigenases (COXs), dentre eles as prostaglandinas (PGs), têm recebido atenção significativa ao longo dos anos por seus papéis na mediação das respostas inflamatórias (7). O foco das investigações tem estado nas prostaglandinas derivadas da isoforma induzível da ciclooxigenase, a COX-2, por ser caracteristicamente expressa por células envolvidas em processos inflamatórios (8). Até pouco tempo atrás, acreditava-se que a COX-1, isoforma constitutiva, não estivesse envolvida na inflamação (9). No entanto, dados recentes apontam que a COX-1 pode ser tão ou mais importante que a COX-2 nos casos mais graves de inflamação sistêmica (10).

O foco deste trabalho é avançar mecanísticamente preenchendo as lacunas do conhecimento acerca da participação da COX-1 na inflamação sistêmica grave empregando o modelo de choque endotóxico, o qual a administração intravenosa de preparações de lipopolissacarídeo bacteriano em animais de laboratório é

comumente utilizada para induzir respostas termometabólicas e cardiovasculares associadas com inflamação sistêmica.

2. CONCLUSÃO

Nossos resultados identificaram um papel essencial da COX-1 na fase mais inicial da inflamação sistêmica grave, uma vez que é a isoforma requerida para o desenvolvimento da hipotermia, além de também participar da indução de hipometabolismo, hipotensão e acidose metabólica durante o choque endotóxico.

Nossos resultados ainda indicam que o mecanismo de ação da COX-1 no choque endotóxico apresenta duas fases distintas:

(i) na fase inicial da resposta a COX-1 envolvida não é proveniente do baço e age de forma independente de citocinas;

(ii) na fase avançada da resposta a COX-1 parece agir de forma dependente do baço e através da produção de prostanoides, tais como PGE_2 e PGD_2 (consistentemente produzidas no baço), ou redução de leucotrienos, como LTC_4 (produzido no baço), e esta ação pode depender de efeitos locais de citocinas IL-10 e IL-1β, mas sem que haja alterações sistêmicas nos níveis dessas citocinas.

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