Samuel Penna Wanner

PARTICIPAÇÃO DO HIPOTÁLAMO DORSOMEDIAL NAS RESPOSTAS TERMORREGULATÓRIAS INDUZIDAS PELA INFLAMAÇÃO SISTÊMICA E PELO EXERCÍCIO FÍSICO

Orientador: Prof. Dr. Cândido Celso Coimbra

Co-orientador: Dr. Andrej A. Romanovsky

Belo Horizonte, Março de 2010

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Tese de doutorado apresentada ao Programa de Pós-Graduação em Ciências Biológicas (Fisiologia e Farmacologia) do Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais, como requisito parcial para a obtenção do grau de Doutor em Ciências Biológicas.

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“Pedras no caminho? Guardo todas, um dia vou construir um castelo...”

(Fernando Pessoa)

“The difficult takes time, the impossible takes a little longer.”

(Ditado japonês)

Lista de abreviações

3V – terceiro ventrículo

ACTH – hormônio adrenocorticotrófico

Arc – núcleo arqueado hipotalâmico

DH – corno dorsal da medula espinhal

DMH – hipotálamo dorsomedial

DMN – núcleo dorsomedial hipotalâmico

DRG – gânglio da raiz dorsal

f – fórnice

GABA – ácido gama aminobutírico

IML – coluna intermédio-lateral da medula espinhal

IV – infravermelho

LPB – núcleo parabraquial lateral

LPS – lipopolissacarídeo bacteriano

MnPO – núcleo pré-ótico mediano

MPO – área pré-ótica medial

mt – trato mamilo-talâmico

NTS – núcleo do trato solitário

PGE_2 – prostaglandina E_2

PVN – núcleo paraventricular do hipotálamo

rRPa – rafe pallidus rostral

RVLM – bulbo ventrolateral rostral

SG – gânglio simpático

T_a – temperatura ambiente

TAM – tecido adiposo marrom

TRP – canal catiônico de potencial transiente

VMH – núcleo ventromedial hipotalâmico

RESUMO

A inflamação sistêmica e o exercício físico são duas situações que modificam o controle autonômico e comportamental da temperatura corporal interna. Entretanto as vias neurais envolvidas na termorregulação nessas situações ainda não estão completamente descritas. Considerando que o hipotálamo dorsomedial (DMH) é uma das áreas cerebrais envolvidas na ativação de efetores autonômicos e comportamentais, o objetivo do presente estudo foi avaliar a sua participação nas respostas termorregulatórias induzidas pela inflamação sistêmica e exercício físico. Ratos Wistar, pesando entre 250 e 350 g, foram submetidos às lesões bilaterais (eletrolíticas ou térmicas) no DMH. Após a recuperação das lesões, os animais foram expostos a ambientes frios ou quentes. Observou-se que os ratos com lesões bilaterais no DMH, assim como os animais controles, conseguiram defender a temperatura interna em resposta ao aquecimento do ambiente; no entanto, os animais lesionados não foram capazes de defender a temperatura interna frente ao frio.

Nós também investigamos as respostas autonômicas e comportamentais dos animais lesionados quando tratados sistemicamente com lipopolissacarídeo bacteriano (LPS). Durante a inflamação sistêmica moderada induzida por 10 µg/kg de LPS, as lesões no DMH inibiram a ativação das respostas autonômicas, sem afetar o comportamento de busca pelo ambiente quente. Por outro lado, durante a inflamação sistêmica severa (LPS 500 ou 5000 µg/kg), as lesões no DMH inibiram a busca pelo ambiente frio, contudo não modificaram respostas autonômicas, tais como a diminuição do consumo de oxigênio e a vasodilatação cutânea.

Foi também estudada a relação de diferentes substratos anatômicos do DMH com a ativação da resposta autonômica induzida pela exposição ao frio e a ativação do comportamento de busca pelo ambiente frio. Os resultados mostraram que a

resposta autonômica estava mais associada à área hipotalâmica dorsal, enquanto a busca pelo ambiente frio estava mais relacionada às porções ventrais e caudais dos núcleos dorsomediais hipotalâmicos.

O último objetivo do presente estudo foi investigar se o DMH participa das respostas termorregulatórias induzidas pelo exercício físico realizado em esteira rolante até a fadiga. O desempenho dos animais foi reduzido pelas lesões bilaterais no DMH nos dois protocolos utilizados (exercício de intensidade constante ou progressiva), sem que houvesse alterações no aumento da temperatura interna induzido pelo exercício físico.

Em conjunto, os resultados apresentados ampliam o entendimento da participação do DMH na termorregulação durante a inflamação sistêmica e o exercício físico. Diferentes grupos neuronais do DMH são importantes para: 1- a defesa da temperatura interna contra o frio; 2- a busca pelo ambiente frio que leva à hipotermia durante a inflamação sistêmica severa. Por outro lado, o DMH não está relacionado com o aumento da temperatura interna induzido pelo exercício físico, embora seja fundamental em outros ajustes fisiológicos que possibilitam a manutenção da corrida na esteira rolante.

ABSTRACT

Systemic inflammation and physical exercise are two experimental models that change the autonomic and behavioral control of core body temperature. However, the neural pathways controlling thermoregulation under these conditions are not completely described. Considering that the dorsomedial hypothalamus (DMH) is one of the brain areas involved in the activation of both autonomic and behavioral thermoeffectors, the present study was aimed at investigating the participation of this area on thermoregulatory responses induced by systemic inflammation and physical exercise. Male Wistar rats weighing 250 – 350 g were submitted to bilateral lesions (electrolytic or thermal) within the DMH. After recovering from this surgical procedure, the animals were exposed to cold or warm environments. It was observed that rats with bilateral lesions within the DMH were able to defend core temperature against heat when compared with control animals; however, the DMH-lesioned rats were not able to defend core temperature against cold.

The autonomic and behavioral responses of the DMH-lesioned rats systemically treated with bacterial lipopolysaccharide (LPS) were also investigated. During mild systemic inflammation induced by LPS 10 μg/kg, DMH lesions inhibited the activation of autonomic responses, without affecting warmth-seeking behavior. On the other hand, during severe systemic inflammation (LPS 500 or 5,000 μg/kg), bilateral lesions of the DMH prevented cold-seeking behavior, although the autonomic responses were not changed; cutaneous vasodilation and the decrease of oxygen consumption were preserved in lesioned-animals.

The association of different anatomic substrates within the DMH with the activation of the autonomic response induced by cold exposure and the activation of cold-seeking behavior was also studied. The results showed that autonomic response was more associated to the dorsal hypothalamic area, whereas cold-

seeking behavior was more associated to the ventral and caudal portions of the dorsomedial hypothalamic nuclei.

The last aim of the present study was to investigate whether the DMH participates on thermoregulatory responses induced by running on a treadmill until the point of fatigue. Bilateral lesions within the DMH greatly reduced physical performance in both protocols (constant- or graded-intensity exercise), without changing the exercise-evoked increase of core temperature.

Taking together, our data extend the understanding of the role of DMH in thermoregulatory responses during systemic inflammation and physical exercise. Different neuronal populations of the DMH are essential for: 1- the defense of core temperature against cold; 2- cold-seeking behavior that produces hypothermia during severe systemic inflammation. On the other hand, DMH is not implicated in the increase of core temperature evoked by physical exercise, although it is critical for other physiological adjustments that allow the maintenance of running exercise on the treadmill.

SUMÁRIO

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