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ESTIMULAÇÃO DO CÓRTEX MOTOR E ANTINOCICEPÇÃO: ENVOLVIMENTO DA VIA DE ANALGESIA SEROTONÉRGICA DESCENDENTE

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RESUMO

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A estimulação epidural do córtex motor (ECM) tem sido eficaz no tratamento de dor crônica refratária, porém os mecanismos envolvidos neste efeito ainda são incertos. Demonstrados previamente que a ECM aumenta o limiar nociceptivo mecânico de ratos, via opióides endógenos, sendo esse efeito decorrente, em parte, da inibição de núcleos talâmicos e da ativação da substância cinzenta periaquedutal mesencefálica (PAG). Sabendo que a ativação da PAG induz a ativação da via de analgesia serotonérgica descendente, fomos investigar o efeito da ECM sobre os principais núcleos dessa via, o núcleo dorsal da rafe (NDR) e o núcleo magno da rafe (NMR), assim como sobre os neurônios da coluna posterior da medula espinhal (CPME), para melhor elucidar os mecanismos envolvidos na analgesia induzida pela ECM. Ratos Wistar foram implantados com eletrodos transdurais sobre o córtex motor primário na área correspondente à pata posterior direita. Após uma semana foram estimulados (1 V, 60 Hz, 210 μs) por 15 min e ainda sob estimulação foram avaliados no teste de pressão da pata. Ratos *naive* ou falso-estimulados foram usados como controle. Imediatamente ou 1 h após a ECM, a imunomarcação para Egr-1 (marcador de ativação neuronal) ou serotonina (5HT) foi avaliada no NDR, no NMR e na CPME. Em adição, foi também avaliada a marcação para substância P (SP) na CPME. A ECM aumentou o limiar nociceptivo em 62% na pata contralateral a estimulação, quando comparado com os controles. A estimulação cortical não alterou a ativação do NDR, entretanto induziu a ativação do NMR (67%), quando comparado aos controles. Com relação à 5HT, a ECM induziu um aumento na imunomarcação para 5HT em 75% no NDR e em 92% no NMR. Na medula espinhal, a ECM inibiu os neurônios da CPME (48%), porém não interferiu com a marcação de fibras SP-positivas. Estes resultados sugerem que a antinocicepção induzida pela ECM é proveniente da ativação do sistema serotonérgico descendente, com consequente inibição dos neurônios nociceptivos espinhais levando ao aumento do limiar nociceptivo. Esses dados reforçam o papel do córtex motor no controle da resposta dolorosa.

Palavras-chave: Estimulação do Córtex Motor. Via de Analgesia Descendente. Serotonina. Núcleo Dorsal da Rafe. Núcleo Magno da Rafe. Coluna Posterior da Medula Espinhal.

ABSTRACT

LOPES, P. S. S. **Motor cortex stimulation and antinociception**: involvement of descending serotonergic pain pathway. 2013. 48 p. Masters thesis (Human Physiology) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2013.

Motor cortex stimulation (MCS) has been effective in the treatment of refractory chronic pain; however, the mechanisms involved in this effect remain unclear. We previously demonstrate that MCS increases the mechanical nociceptive threshold in rats, via endogenous opioids, being this effect due to thalamic nuclei inhibition and periqueductal gray matter (PAG) activation. Knowing that the PAG activation induces the activation of descending serotonergic pathway, we investigated the MCS effect on the main nuclei of this pathway, the dorsal raphe nucleus (DRN) and the magnus raphe nucleus (MRN), and also on the neurons of the dorsal horn of the spinal cord (DHSC), to better understand the mechanisms involved in MCS-induced analgesia. Male Wistar rats were implanted with transdural electrodes on the motor cortex in the area corresponding to the right hind paw. After one week, the animals were stimulated (1 V, 60 Hz, 210 μs) for 15 min and still under stimulation they were evaluated by paw pressure test. *Naive* or sham rats were used as controls. Immediately or 1 h after MCS, the immunostaining to Egr-1 (neuronal activation marker) or serotonin (5HT) were evaluated in the DRN, MRN and DHSC. Furthermore, it was evaluated the substance P (SP) staining in the DHSC. MCS increased 62% of nociceptive threshold in the contralateral hindpaw to the stimulation, when compared to control groups. MCS did not modify the NDR activation; however, induced MRN activation (67%), when compared to controls. Regarding to 5HT, MCS increased 75% the immunostaining for 5HT in the NDR and 92% in the MRN. In the spinal cord, MCS inhibited the DHSC neurons (48%), however did not change the staining for SP-positive fibers.These results suggest that MCS-induced antinociception is arising to the activation of the descending serotonergic pathway, with subsequent inhibition of the spinal nociceptive neurons, leading to increasing of the nociceptive threshold. These data reinforce the role of the motor cortex in the control of the painful response.

Keywords: Motor Cortex Stimulation. Descending Pain Pathway. Serotonin. Dorsal Raphe Nucleus. Magnus Raphe Nucleus. Dorsal Horn of the Spinal Cord.

1 INTRODUÇÃO E OBJETIVO

Aproximadamente um terço da população mundial sofre de dor crônica ou persistente, tornando-se esta uma das mais frequentes razões para a procura de atendimento médico, trazendo altos gastos em saúde pública, quanto agravos e comorbidades físicas e emocionais aos pacientes (STUCKY et al., 2001). Uma variedade de tratamentos farmacológicos tem sido proposta para controle da dor neuropática, porém, até o momento, nenhum deles responde de maneira satisfatória. Desta maneira, o aprimoramento terapêutico em tais condições dolorosas se faz necessário. Nesse sentido, a estimulação do córtex motor (ECM), uma técnica terapêutica não destrutiva, ajustável e reversível, tem sido aplicada no tratamento de dores centrais complexas ou síndromes periféricas neuropáticas, resistentes à outros tratamentos (FAGUNDES-PEREYRA et al., 2010). Entretanto, a ECM falha em reverter a dor neuropática em aproximadamente um terço dos pacientes (NGUYEN et al., 2000), apontando para uma necessidade de prosseguir com a pesquisa nesse campo. Anteriormente, nosso grupo demonstrou que a ECM ativa a substância cinzenta periaquedutal mesencefália (PAG) (PAGANO et al., 2012). Considerando que a PAG está intimamente ligada a neurônios do núcleo dorsal da rafe (NDR), que junto com o núcleo magno da rafe (NMR) modulam a resposta dolorosa pela via serotonérgica descendente (BAJIC; COMMONS, 2010; BASBAUM; FIELDS, 1984), agindo sobre neurônios nociceptivos espinhais com a finalidade de inibir a transmissão do estimulo nociceptivo (VIISANEN; PERTOVAARA, 2010b), decidimos investigar o efeito da estimulação cortical sobre a ativação dos núcleos serotonérgicos NDR e NMR, envolvidos na via de analgesia descendente, e sobre os neurônios da coluna posterior da medula espinhal (CPME).

1.1 Objetivos específicos

1. Avaliar o padrão de ativação neuronal no NDR, NMR e CPME, visto por imunomarcaçao para Egr-1;
2. Avaliar o padrão de imunomarcação para serotonina (5HT) no NDR e NMR;
3. Avaliar o padrão de imunomarcação para substância P (SP) na CPME.

6 CONCLUSÃO

Os resultados sugerem que a ECM ativa neurônios serotonérgicos no NDR e no NMR, levando a inibição de neurônios nociceptivos presentes na CPME, via 5HT, consequentemente aumentando o limiar nociceptivo. Esses dados reforçam o envolvimento do córtex motor na via de analgesia descendente e enfatizam a participação do sistema serotonérgico no efeito antinociceptivo induzido pela estimulação cortical.

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