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Effects of Salbutamol on non-NMDA glutamate-induced motor neuron loss

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Recent data suggests that catecholamine systems might have a trophic role in the spinal cord. These data are based on the clinical evidence that beta-2 agonists produce a relief in spinal motor neuron disorders.

Therefore, in the present study we isolated ventral spinal cord cell cultures and we administered either the beta-2 agonist salbutamol alone or in combination with the beta-2 antagonist butoxamine. These experiments were carried out both in baseline conditions and in the presence of a non-NMDA glutamate shock. In fact, increased extracellular glutamate concentration can be toxic for neuronal cells. Glutamate-mediated excitotoxicity relies on the stimulation of both NMDA and non-NMDA receptors although naturally occurring motor neuron loss is thought to depend on an excess of stimulation of non-NMDA receptors. Therefore, primary cell cultures obtained from the ventral spinal cord of 14-days-old mice embryos were pre-administered MK-801, a non-competitive antagonist of NMDA receptors, immediately before the non-NMDA (both kainate and AMPA) receptor agonist kainic acid (KA, 50 and 100 μM for 15 min) either in baseline conditions or in combination with salbutamol (10 μM) and butoxamine (50 μM) administered 30 min before KA. We found that the beta-2 antagonist butoxamine did not produce any effect either alone or in combination with kainate. Although butoxamine prevented the effects induced by the beta-2 agonist salbutamol. In particular, salbutamol prevented non-NMDA-induced motor neuron loss and this effect was abolished by the concomitant administration of butoxamine. When salbutamol was administered alone we detected morphological changes at motor neuron level. We also analysed whether salbutamol administration increased the expression of survival motor neuron protein (SMN, an endogenous molecule which provides protective effect for motor neurons) as a possible mechanism of neuroprotection. Unexpectedly, the protective effects induced by salbutamol were accompanied by a reduction of the SMN, while KA induced an increase in SMN levels. These results lend substance that catecholamine receptors subtype beta-2 protect motor neurons in the short term following glutamate excitotoxicity. It is likely that the paradoxical effects observed for SMN level might be due to the need of a compensatory mechanism (following NMDA) or the reduced level of neuronal stress (following salbutamol). Further studies are in progress to unravel the mechanisms responsible for neuroprotection induced at motor neuron level by catecholamine and beta-2 receptors.

Keywords: Salbutamol, SMN protein, beta-2 adrenoceptors, glutamate excitotoxicity.