THE COMBINATION OF SR141716A AND ACTH-(1-24) IMPROVES THE THERAPEUTIC EFFICACY IN THE MANAGEMENT OF HEMORRHAGIC SHOCK

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Endocannabinoids produced by macrophages and platelets may be mediators of hemorrhagic hypotension. Functional links exist in the mechanisms of action of cannabinoids and opioid peptides; and opioids, too, play a role in the pathophysiology of circulatory shock. Melanocortin peptides - main endogenous functional antagonists of opioids - have an anti-shock effect in animals and humans. So, we investigated whether an interaction exists between endocannabinoids and the endogenous opioid/antiopioid system also in a condition of hemorrhagic shock, and particularly whether the blockade of cannabinoid CB1 receptors potentiates the anti-shock effect of melanocortins. Anesthetized rats were bled until mean arterial pressure (MAP) decreased to, and stabilized at, 22-25 mmHg. In such condition, which caused the death of all control rats (n=10) within 30 min after vehicle (tween 80, 5% in saline) injection, the i.v. bolus injection of the cannabinoid CB1 receptor antagonist N-piperidino-5-[4-chlorophenyl]-1-2,4-dichloro-phenyl]-4-methyl-3-pyrazolecarboxamide (SR141716A) increased, within 10-15 min, MAP, pulse pressure (PP), respiratory rate (RR) and survival rate in a dose-related manner (0.1-3 mg/kg; n=7-10 per dose level), an almost complete recovery of MAP, PP and RR, and 100% survival at the end of the observation period (2 h), occurring with the dose of 3 mg/kg. The melanocortin ACTH-(1-24) also produced in a dose-related manner (0.02-0.16 mg/kg i.v.; n=7-8 per dose level), and within 10-15 min, a restoration of cardiovascular and respiratory functions, and increased survival rate; an almost complete recovery and 100% survival at the end of the observation period (2 h) occurring with the dose of 0.16 mg/kg. When a subactive dose of SR141716A (0.2 mg/kg: MAP=32±2, PP=18±1, RR=61±4, survival=30%; n=10) was associated with a subactive dose of ACTH-(1-24) (0.02 mg/kg: MAP=27±2, PP=13±1, RR=51±4, survival=12%; n=8), a complete reversal of the shock condition was obtained (MAP=79±5, PP=37±2, RR=95±6, survival=100%; n=10, P<0.05 at least). The present results suggest that the concurrent inhibition of both endogenous opioid and cannabinoid systems may be more effective in the reversal of hemorrhagic shock.

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