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THE INFLUENCE OF MANGIFERIN, A POLYPHENOLIC ANTIOXIDANT, ON THE HYPOXIC VENTILATORY RESPONSE IN THE RAT

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Reactive oxygen species (ROS) have a role in the initiation of the hypoxic ventilatory response, which is generated by carotid body chemoreceptor cells. The exact nature of this role is unsettled. Nor is it full well clear whether ROS formation is decreased or increased by hypoxia in chemoreceptor cells, although the current prevailing opinion is that ROS increase in the mitochondrial electron transport chain during hypoxia. Furthermore, ROS interact with the very mechanisms of hypoxia-sensing, as they are required for hypoxia inducible factor-1α stabilization by hypoxia; a step being essential for activation of the expression of hypoxia-responsive genes. If it is so, then antioxidant pretreatment could reasonably well be expected to downregulate the hypoxic ventilatory response. We investigated this hypothesis in the present study by comparing the hypoxic ventilatory responses before and after application of mangiferin (Sigma, St. Luis, USA), a polyphenolic antioxidant, belonging to a class of xanthones that commonly occur in plants and having extensive free radical scavenging and iron chelating activities. The study consisted of biochemical and functional parts. In the former, we found that mangiferin did not cross the blood-brain barrier after intraperitoneal injection, as it could not be recovered from brain extracts, using thin-layered chromatography. That finding made us to reason that an interaction of mangiferin with the hypoxic ventilatory response would be centered at the peripheral, carotid body mechanisms. In the functional study, the acute ventilatory responses to two levels of the hypoxic stimulus, 12% O_2 and 8% O_2 in N_2, were carried out in conscious rats before and 40 min after intraperitoneal injection of mangiferin in a dose of 300 mg/kg. Minute ventilation and its constituent components, frequency of breathing and tidal volume, were studied in an unrestrained plethysmographic rodent chamber (Buxco, UK). We found that mangiferin significantly depressed the profile of the hypoxic ventilatory response over the 3-min test time. The peak hypoxic ventilation decreased from 1226.7 ±34.8SE to 924.0 ±75.7 ml/min/kg and from 2349.2 ±217.6 to 1616.4 ±91.8 ml/min/kg at 12% and 8% hypoxia, respectively ($P<0.01$). An enhanced decline in peak ventilation with increasing strength of the hypoxic stimulus shows that mangiferin depressed hypoxic sensitivity. Both components of respiratory pattern contributed to the ventilatory changes observed, but mangiferin exerted a greater influence on the respiratory rate. In conclusion, the study supports the notion that ROS are key modifiers of the hypoxic ventilatory response. ROS may be essential for a full development of the hypoxic hyperventilation, but do not seem the underlying determinants of the response, as antioxidant treatment does not abolish the ventilatory hypoxic reactivity.