MANGIFERIN AND RESPIRATION

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Previously, we found that mangiferin, a polyphenolic antioxidant and a free radical scavenger that does not permeate into the brain, has a depressant effect on hypoxic reactivity in the rat. We also found that mangiferin does not penetrate into the brain after systemic injection, which points to its prevailing peripheral action, likely in the carotid body, a sensory paired organ generating the hypoxic ventilatory response. The present study addresses two possible mechanisms of mangiferin's action: free radical scavenging power and the compound's influence on metabolism, either capable of modifying hypoxic ventilation. We compared the effect of mangiferin (300 mg/kg, in a single i.p. shot 40 min before hypoxia) on the ventilatory response to two levels of hypoxia (12 and 8% O2 in N2) before and after chronic Fe2+ chelation induced by ciclopirox olamine (CPX) (20 mg/kg, i.p., daily for 7 days) in conscious rats. The rationale for iron chelation was that it complexes ferrous iron required for proteosomal HIF-1? degradation and also for free radical generation through Fenton chemistry. The premise, therefore, was that the antecedent stabilization of HIF-1? and less circulating free radicals could dampen the subsequent response to mangiferin, if it were mediated by these mechanisms. Ventilation was studied breath-by-breath in a rodent plethysmograph. In another 5 rats O2 consumption and CO2 production were measured during hypoxic exposures in an open-circuit system (Buxco Electronics, Wilmington, NC). We found that mangiferin significantly depressed the peak hypoxic ventilation by 302.7 +/- 87.7 and 732.8 +/-145.2 ml/min/kg at 12% and 8% hypoxia, respectively ($P<0.006$) and that similar decreases were also present after iron chelation. That result contradicts the presumption that the complexing of ferrous iron and slowing the Fenton reaction could underlie, through prior HIF-1alpha stabilization, the mangiferin's effects on hypoxic ventilation. The metabolic part of the study showed, however, that mangiferin significantly lowered O2 consumption and CO2 production, which may be key for its inhibiting the ventilatory response to hypoxia. Recently, there seems to be a rising consensus that oxidant-dependent signaling pathway is involved in post-transitional phosphorylation of prolyl hydroxylases, which turns off their catalytic activity and stabilzes HIF-1? in hypoxia. Mangiferin, by virtue of its antioxidant activity, ought to inhibit the phosphorylation which, on the one hand, sustains HIF-1alpha degradation and, on the other, decreases mitochondrial ATP production, both of which would act to lower hypoxic ventilatory responsiveness. Alternative study designs are required to resolve the proposed mechanisms.