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THE ROLE OF IRON IN CAROTID BODY FUNCTION IN THE ANESTHETIZED RAT

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Ferrous iron is a cofactor in the continuous deactivation of hypoxia inducible factor-1alpha (HIF-1alpha) in normoxia and thus should play a mitigating role in the generation of the hypoxic ventilatory response by the carotid body. In a previous study we found that resting ventilation in conscious rats was 1092,8 ±97,2 ml/min/kg and chronic iron chelation indeed reduced the ventilatory response to acute hypoxia. The reduction in peak hypoxic ventilation was significant, amounting on average to 43% and 20% at 14 and 9% hypoxia, respectively. Since iron is essential for the HIF-1alpha metabolism, the question arises whether inhibition of the hypoxic ventilatory response (HVR) due to iron chelation was not mitigated by a compensatory cortical counteraction in response to a noxious hypoxic stimulus in the state of wakefulness. In the present study we addressed this issue by carring out iron chelation experiments in anesthetized Wistar rats. Minute ventilation and its tidal and frequency components were measured with a whole body plethysmography at all experimental stages. The animals were given low-dose α-chloralose and urethane (60 mg and 600 mg/kg, i.p.) anesthesia effective for 1h. The ventilatory responses to 14 and 9% hypoxia, separated by a 10 min normoxic interval, as a basic control and the animals were allowed to recover from anesthesia. Then, a seven days' period of iron chelation started with a lipophilic intracellular iron chelator - ciclopirox olamine (CPX; 20 mg/kg, ip, daily). We found that anesthesia heavily dampened resting ventilation which at baseline amounted to 799,0 ±47,3 ml/min/kg hypoxic, but the effect on the HVR of chronic iron chelation remained little affected. The peak HVR was reduced on average by 17% and 20% at 14 and 9% hypoxia, respectively. We conclude that the mitigating effect of the lack of iron on hypoxic ventilatory reactivity is not exaggerated under anesthesia. The findings lend support for the notion that iron chelation may have a specific inhibitory effect on the HVR in that it induces a 'pseudohypoxic' state in normoxia, in terms of HIF-1alpha stabilization, which dampens the subsequent response to true hypoxia.