PHARMACOLOGICAL IMPACT ON LOOP-GAIN PROPERTIES TO PREVENT IRREGULAR BREATHING

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Considerations from the control theory reveal that an elevated loop-gain may lead to instability of the feedback system. The steady state loop-gain (G) for respiratory control can be assessed as a ratio of the slope of the ventilatory CO_2 response (S) and $S_L=863\cdot(VCO_2)_{STPD}/(PaCO_2)^2$, the slope of the metabolic hyperbola. Therefore, an optimal medication to lower G should attenuate respiratory chemosensitivity, improve blood-gases, e.g., in case of chronic hypercapnia, and counteract the down-regulation of metabolic CO_2-production that occurs, e.g., during sleep and anesthesia. Here we determined effects on loop-gain either of carbonic anhydrase inhibitors (acetazolamide, methazolamide) or of sodium/proton exchanger type 3 (NHE3) inhibitors (S8218, S11654 and AVE0657A, Sanofi-Aventis). Ventilatory CO_2-responses, arterial blood gases and metabolic CO_2-production were measured in anesthetized spontaneously breathing rabbits.
Both acetazolamide (N=7) and methazolamide (N=7) significantly ($P<0.01$) reduced G by 42.0 ±9.3% and 35.0 ±9.5%, respectively. The effects of NHE3-inhibition on loop-gain properties depended on the initial base-line $PaCO_2$. In a range of ~35 mmHg, NHE3-inhibition by either substance reduced G by an average of 36.0 ±8.2% (N=9, $P<0.01$), whereas in 3 rabbits at lower levels of $PaCO_2$ no significant effect on G could be discerned. These data provide theoretical support for the clinical experience that acetazolamide is able to reduce the incidence of apneas in sleep disordered breathing. With respect to the tentative role of NHE3 in the control of breathing, it has recently been shown that elevated expression of brainstem NHE3 mRNA is accompanied by lower base-line ventilation and higher $PaCO_2$ in conscious rabbits, bearing a higher risk for irregular breathing. In humans, NHE3 abundance appears to be associated with sudden infant death syndrome (SIDS). Thus, therapeutic means to treat the risk of breathing disorders and apneas should aim to reduce the overall chemosensitivity of the respiratory control system under the closed-loop conditions.