THE NHE3 INHIBITOR AVE1599 STIMULATES PHRENIC NERVE ACTIVITY OF THE WORKING HEART-BRAINSTEM PREPARATION OF THE RAT

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Inhibitors of the sodium-proton exchanger subtype 3 (NHE3) reduced the intracellular pH in chemosensitive neurons and augmented respiratory drive in anaesthetized, vagotomized and mechanically ventilated rabbits. Here we tested the NHE3 inhibitor AVE1599 for its ability to stimulate phrenic nerve (PN) discharge and compared its effect to that of hypercapnia. Experiments were carried out in the absence of anaesthetics using an *in situ* preparation derived from young adult rats. Bioelectric signals from the right PN were recorded *via* a suction electrode and analysed off-line. Hypercapnia increased PN burst frequency (f) by ~66% from 6.2 ±0.9 (mean ±SD) to 10.3 ±1.2 min^{-1} (n=20; P<0.01), and typically reduced duration of each single burst. AVE1599 (0.3 µM) added to the perfusate reversibly increased f by ~75 ±13.2% and 176 ±36.7% after 10 and 30 min, respectively (n=10, P<0.01 for both values). We also tested the hypercapnic response of the preparation in the absence and presence of AVE1599. Although hypercapnia-mediated increases of f persisted in some animals, the group mean data were no longer significant in the presence of AVE1599. Surprisingly, the stimulatory effect of AVE1599 on PN discharges was absent at 0.9 µM. As AVE1599 accumulates about 10-fold in the brain, we hypothesized that this concentration may inhibit other NHE isoforms such as NHE1. In fact, the NHE1 inhibitor HOE642 (0.9 µM), which was used for comparison, reduced f in 6 preparations. HOE642 also failed to stimulate respiration in the anaesthetized rabbit. These data confirm the view that a selective inhibition of NHE3, but not NHE1, stimulates central respiratory drive.