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Influences of Neurokinin receptor activation on respiratory rhythm generation in the Lamprey

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Neural mechanisms underlying respiratory rhythmogenesis in the lamprey are far from being defined. Recently, we have demonstrated that a specific opioid-sensitive region, located rostrolateral to the trigeminal motor nucleus and termed the paratrigeminal respiratory group (pTRG), contains respiration-related neurons and plays a pivotal role in respiratory rhythm generation. Although the excitatory effects of substance P (SP) on respiration in mammals are well known, no information is available on the role of neurokinins (NKs) in the lamprey respiratory network. The present study was performed on in vitro lamprey brainstem preparations to investigate whether 1) NKs affect respiratory activity possibly through an action on the pTRG, and 2) the inspiratory burst-promoting currents described in mammals, i.e. the persistent Na^+ current (I_{NaP}) and the Ca^{2+}-activated non-specific cation current (I_{CAN}), contribute to the respiratory rhythm generation. Respiratory activity was monitored as vagal motor output. SP as well as NK1, NK2 and NK3 receptor agonists (GR 73632, NKA and senktide, respectively) and antagonists (CP-99,994, MEN 10376 and SB 222200, respectively) were applied to the bath. SP was also microinjected (0.5-1 nl) at sites of the pTRG, where extra- and intracellular neuronal activity was recorded. I_{NaP} and I_{CAN} were blocked by bath application of riluzole (RIL) and flufenamic acid (FFA), respectively. SP as well as the specific NK receptor agonists (0.4-0.8 μM) induced marked increases in both the frequency and amplitude of respiratory bursts. Bath application of NK receptor antagonists (10 μM) did not affect vagal motor output, but prevented agonist-induced effects. Excitatory effects on respiration were also produced by SP (1 μM) microinjections into the pTRG. Bath application of either RIL or FFA (20-50 μM) depressed, but not suppressed respiratory activity. Coapplication of RIL and FFA at 50 μM abolished the respiratory rhythm that was restarted by SP microinjected into the pTRG. The results show that NKs may have a modulatory role in the lamprey respiratory network through an action on the pTRG. They also indicate that endogenous NKs are not required for the generation of baseline respiratory activity. Furthermore, we provide evidence that I_{NaP} and I_{CAN} are expressed within the lamprey respiratory network and contribute to vagal burst generation. We also suggest that the "group-pacemaker" hypothesis is tenable for the lamprey respiratory rhythm generation since respiratory activity is abolished by blocking both I_{NaP} and I_{CAN}, but is restored by enhancing network excitability.

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