INVESTIGATION OF INOS-DERIVED NO IN THE IMPAIRMENT OF MOUSE VAGAL AFFECTIVE SENSITIVITY IN DIET-INDUCED OBESITY

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Background: Our previous studies have demonstrated impaired vagal afferent sensitivity to satiety mediators and distention of the gut in high fat fed (HFF) obese mouse iNOS (inducible nitric oxide synthase) knockout mice are protected against high fat diet-induced metabolic dysfunction. In addition, NO has an inhibitory effect on the sensitivity of a select population of vagal afferents.

Aims: The aim of this study was to examine the involvement of iNOS-derived NO in obesity-induced impairment of vagal nerve sensitivity.

Methods: All experiments were performed in accordance with the guideline of Canadian Council for Animal Care. Nodose ganglion and jejunum were obtained from high (60% calories from fat) and low (10%) fat fed male C57/BL6 mice. NO was measured using a Nitrate/Nitrite fluorometric assay kit. Membrane excitability of nodose neurons was assessed by whole cell patch clamp. Afferent discharge was recorded from jejunal mesenteric nerves.

Results: In comparison with low fat fed (LFF) mice, NO concentration in the jejunum from high fat fed (HFF) mice was significantly increased (P<0.05, N≥7, unpaired t-test) and pre-treatment with L-NIL (10 mg/kg, IP injection) reversed this change (P<0.001, N≥7, unpaired t-test). Excitability of nodose neurons was significantly increased by pre-incubation with L-NIL (10 mM), as evidenced by decreased rheobase (P<0.05, N≥10, unpaired t-test) and increased action potentials at twice rheobase (P<0.05, N≥10, unpaired t-test). In addition, IP injection of L-NIL in HFF mice significantly augmented afferent response to 5-HT (10 mM, P<0.001, N=10, unpaired t-test) and ramp distention (P<0.05, N≥12, two-way ANOVA), while cholecystokinin (CCK, 100 nM) response was partially increased (P=0.09, N≥8, unpaired t-test). In line with this observation, NO donor, sodium nitroprusside (10 mM) inhibited afferent response to 5-HT (P<0.05, N=7, paired t-test) and distention (P<0.001, N=13, two-way ANOVA) instead of CCK in LFF mice. Single unit analysis revealed that NO had diverse effects on the sensitivity of different afferent units.

Conclusions: These data suggest that iNOS may be a key molecule in obesity-induced impairment of vagal nerve sensitivity and thus a potential therapeutic target for obesity-related dysfunction.
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