CO_2 Decreases the Activity of Locus Coeruleus Neurons in the Streptozotocin-Induced model for Alzheimer's Disease

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Introduction: Locus Coeruleus (LC) is an important chemosensitive nucleus and affected by neurodegenerative diseases like Alzheimer's disease (AD). LC dysfunction in AD may account for the respiratory problems observed in patients.

Objective: To test the electrophysiological properties of LC neurons in a model for sporadic AD.

Material and Methods: AD was induced in rats (6-7 weeks) by intracerebroventricular injection of streptozotocin (STZ; 2 mg/kg). 14 days following injection, LC neurons were recorded using the patch clamp technique and tested for CO_2 chemosensitivity (10% CO_2, pH = 7.0).

Results: When exposure hypercapnic condition, most LC neurons (~60%) exhibited a blunted spike discharge to current injections in comparison to baseline responses. The minority of cells either increased spiking (~20%) or did not respond (~20%) to CO_2. Within cells that were inhibited by CO_2, current-evoked spike discharge at baseline condition had the same magnitude in control and STZ rats. Responses in both groups decreased significantly when exposed to 10% CO_2 (bsl vs. 10% CO_2: CTL, p=0.003, n=8 and STZ, p=0.001, n=9). In the STZ group, this CO_2-induced decrease in spike discharge was more pronounced when compared to control (CTL vs. STZ, p=0.038), suggesting greater sensitivity to hypercapnia. There was no difference in resting membrane potential and input resistance (R_i, cell membrane resistance) between groups at baseline and CO_2. However, although there was no difference between groups values, we found a significant decrease of R_i within the STZ group when exposed to hypercapnia (bsl, 126.5 ± 14.9 MΩ vs. 10% CO_2, 98.4 ± 8.2 MΩ; p=0.01), indicating opening of ion channels. The current-voltage relationship of the cell membrane showed a significant CO_2-induced decrease of the steady state current (bsl vs. 10% CO_2: CTL, p=0.002, and STZ, p=0.001).

The magnitude was similar in both groups. This result would paradoxically favor increased excitability in neurons. Analysis of action potential (AP) parameters (AP threshold, AP peak, upstroke slope, peak to anti-peak) also showed no difference between groups. However, within the STZ group spike threshold was significantly shifted to more positive potentials under increased CO_2 (-39.6 ± 1.9 mV vs -34.8 ± 2.2 mV, p=0.01). This shift in spike threshold would explain the blunted spike discharge of LC neurons in the STZ group during hypercapnic conditions.

Conclusions: In summary, our data suggest that the majority of LC neurons in adult rats are inhibited under CO_2 exposure. Further, the STZ-treated group exhibits a greater sensitivity to CO_2, likely due to an increased spike threshold and opening of additional, yet unidentified membrane channels. Decreased excitability of LC neurons may be an underlying mechanism for the breathing disturbances observed in patients with AD.

Keywords: CO2,neurons,adult rats, locus coeruleus Neurons, streptozotocin-Induced model, Alzheimer's Disease

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