

Acute Nicotine Stimulates GABA Synthesis in Human Brain

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Background

Animal studies with nicotine have revealed enhanced release of glutamate and GABA in the brain (1). In humans, it is much more difficult to make those measurements, but ¹³C magnetic resonance spectroscopy allows the measurement. We hypothesized that nicotine would increase the rate of synthesis of brain GABA.

Methods

9 healthy smokers were abstinent 10-18 hours, as verified with a measurement of expired CO below 15 ppm. ¹³C magnetic resonance spectroscopic detection of the GABA C2 position was carried out in a 5 x 4 x 4.5 cm³ volume with polarization transfer (2) at a magnetic field strength of 4T while [1-¹³C]glucose was infused, in 5-minute blocks of acquisitions. The measurements were first without nicotine administration to obtain a baseline measurement. After waiting at least a week after the first study, nicotine was administered to seven of the subjects with a Nicorette® nicotine inhaler (1-2 mg systemically available), and the ¹³C MRS was repeated. Spectra were processed in running averages of 3 scans using LCModel, with labeled resonances treated as independent signals. For example, glutamate C4 was fitted independently of glutamate C3. Metabolic modeling (3) was performed using CWave (4).

Results

The ¹³C time course averaged over all subjects (Fig. 1) shows more rapid labeling of GABA with nicotine than without. The individual data sets, with lines linking individuals' own scans without and with nicotine, show that GABA synthesis increases 4-fold with nicotine.

Conclusion

These data show that nicotine-induced GABA and glutamate release are accompanied by increased GABA synthesis in the human brain.

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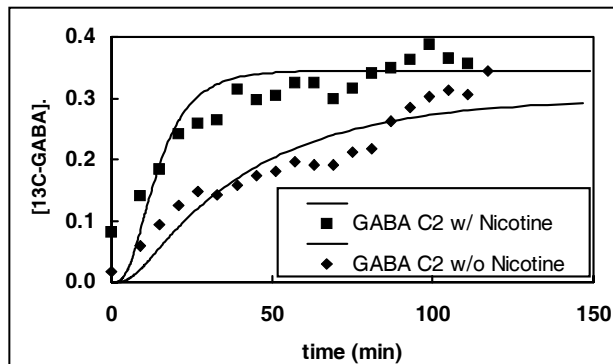


Fig. 1. Time courses of GABA C2 ¹³C concentrations averaged over 9 smokers who consumed no nicotine (lower curve) and 5 of them after a nicotine inhaler, during 2-hour infusions of [1-¹³C]glucose. Two of the subjects with the inhaler had data whose GABA signal-to-noise ratio was too low to use. Fitting the averaged time courses yielded $V_{\text{gad}} = 0.04$ and 0.16 mmol/kg/min without and with nicotine, respectively.

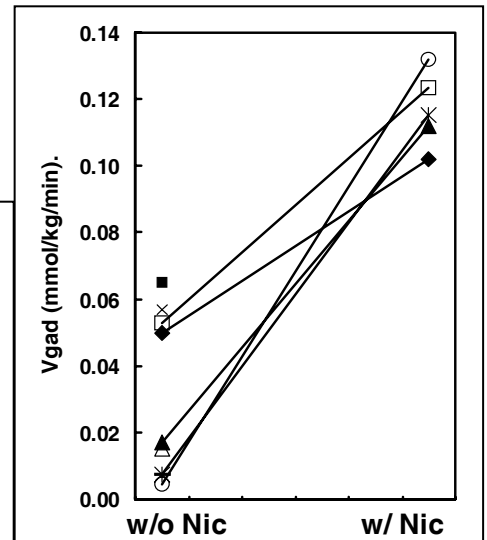


Fig. 2. Fitting individual time courses showed that GABA synthesis was 0.03 and 0.12 mmol/kg/min without and with nicotine, respectively. The lines connect the five subjects that yielded useful data with and without nicotine. Another four subjects were studied only once due to compliance or hardware problems with the scanner. A paired, two-tailed t-test on the five repeaters yielded $p = 0.0025$. An unpaired, two-tailed t-test of the means for both complete groups yielded a $p = 0.0000013$.