Effects of antidepressant phenelzine on glutamate transmission and GABAergic system in rat neocortex

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Introduction

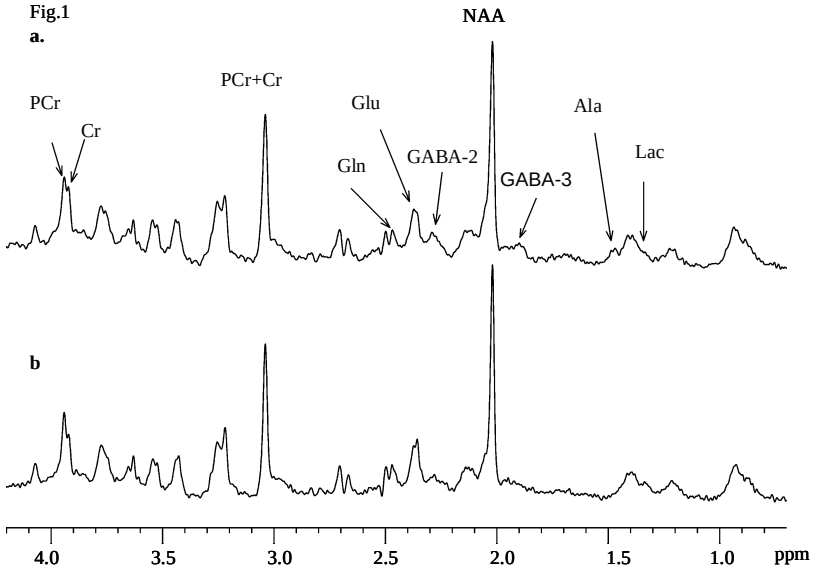
Phenelzine is a non-selective monoamine oxidase inhibitor which is efficacious in the treatment of depression and panic disorders. Administration of phenelzine increases levels of the amine neurotransmitters noradrenaline, dopamine, and serotonin in brain, which has been the focus of many previous studies of the mechanisms of the therapeutic action of phenelzine. There are also ex vivo evidences of augmented GABAergic function and reduced glutamate release in rats following acute and chronic phenelzine treatment (1). In vivo magnetic resonance spectroscopy allows non-invasive assessment of glutamate neurotransmission and GABAergic function. In this study, the effects of acute phenelzine administration on the turnover kinetics of [4-^{13}C]glutamate, [4-^{13}C]glutamine and [2-^{13}C]GABA from intravenously infused [1,6-$^{13}C_2$]glucose was measured in the rat neocortex in vivo.

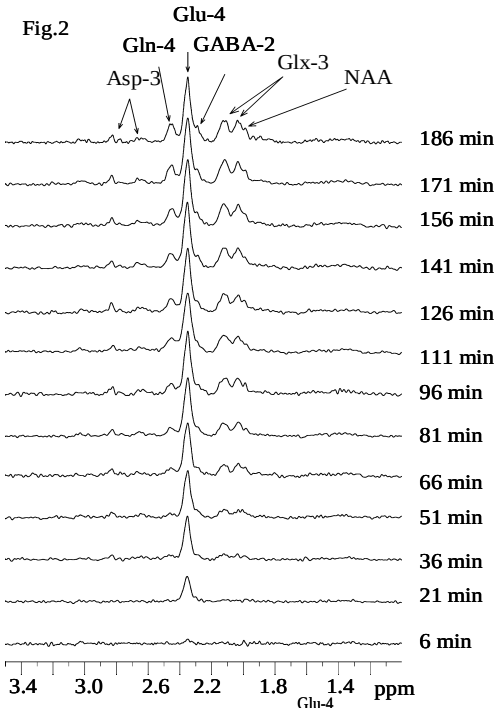
Materials and Methods

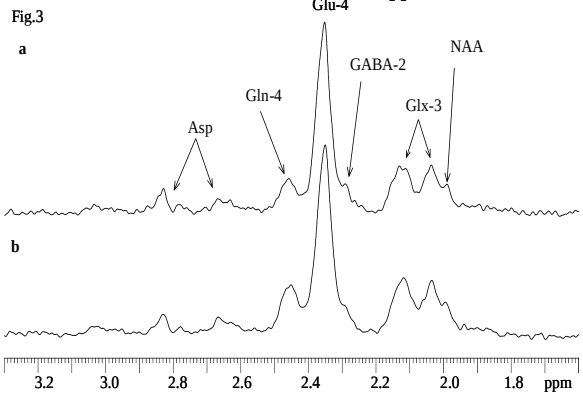
All experiments were performed on a microimager interfaced to an 11.7 Tesla 89-mm bore vertical magnet. Male Sprague-Dawley rats (160-200 g, n = 17) fasted for 24 hours were studied. All rats were orally intubated and mechanically ventilated with a mixture of 70% N_2O, and 30% O_2. Anesthesia was maintained by continuous intravenous infusion of α-chloralose. The dose of phenelzine used was 10 mg/kg (i.p.). [1,6-$^{13}C_2$]Glucose infusion was performed on both controls and phenelzine-treated rats (i.v.). All spectroscopy voxels (4.5 x 2.5 x 4.5 mm^3) were located in the neocortex 0-1 mm rostral to the bregma. Localized ^{1}H MRS was used to measure the total concentrations of metabolites in controls and in the treated group four hours after phenelzine administration. ^{1}H[^{13}C] POCE MRS was performed with single-shot adiabatic three-dimensional localization and WALTZ-4 decoupling (γB_2=625 Hz, AQ=196 ms). The POCE data acquisition was restarted every 15 minutes for an interleaved acquisition of 256 scans over 11.5 min. The 3.5 min interval of dead time was used to periodically re-shim the spectroscopy voxel to maintain optimal B_0 homogeneity throughout the data acquisition process.

Results

Fig. 1 shows typical localized in vivo ^{1}H short-TE spectra from the controls (b) and treated rats (a, 4 hr after phenelzine treatment). The spectrally resolved GABA-2 peak at 2.30 ppm and GABA-3 peak at 1.91 ppm are markedly elevated following administration of phenelzine. Fig. 2 shows an in vivo time course of edited POCE spectra with [1,6-$^{13}C_2$]glucose infusion started four hours after phenelzine treatment. [2-^{13}C]GABA signal at 2.30 ppm is spectrally resolved from the overlapping [4-^{13}C]Glu signal at 2.35 ppm. Fig. 3 shows the edited POCE spectra acquired over the 2nd hour period after the start of [1,6-$^{13}C_2$]glucose infusion from (b) controls (a) the







phenelzine-treated group. The intensity of [4-^{13}C]Gln in the phenelzine-treated group is markedly lower than that in non-treated group, indicating slower incorporation of ^{13}C labels into glutamine primarily located in glia from glutamate primarily located in glutamatergic neurons.

Discussion

The slower ^{13}C-label incorporation into [4-^{13}C]Gln in the treated rats indicates slower glutamate-glutamine cycling, by inference, slower glutamate release, which is consistent with ex vivo studies which have shown significantly reduced depolarization-induced outflow of glutamate with either acute or chronic phenelzine treatment. Fig. 3 provides the first in vivo evidence that phenelzine attenuates glutamate transmission. The observed modulatory effect of phenelzine on glutamate could be attributed to elevated serotonin, dopamine and norepinephrine levels since they have been shown to inhibit glutamate release. The concentration of GABA and its release are also markedly increased by acute phenelzine treatment (1). We have shown recently that increased GABA level by GABA-elevating anticonvulsants is correlated with decreased BOLD response to focal activation in the rat somatosensory cortex (2). The anticonvulsant gabaculine also causes significant attenuation in the release of glutamate. The GABAergic mechanism therefore could also explain the dampening effect of phenelzine on synaptic glutamatergic neurotransmission. The alterations of glutamatergic and GABAergic functions by phenelzine may contribute to its efficacy in the treatment of depression.

References 1.Parent et al, Biochem Pharmacol. 2000; 59:1253. 2. Chen et al, J Neurosci Res, in press.