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Short Communication

Topiramate Selectively Attenuates Nicotine-Induced Increases in Monoamine Release

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It is widely held that the reinforcing and dependence-producing properties of nicotine rely on activation of the mesocorticolimbic dopamine (DA) system. This notion is primarily derived from demonstrations that lesions of ventral tegmental area (VTA) DA neurons projecting to the nucleus accumbens (NAcc) can reduce both locomotor activation and the reinforcing effects of nicotine (Clarke et al., 1988; Corrigall et al., 1992). However, it appears that pharmacologically targeting isolated DA receptors is not sufficient to reduce symptoms associated with nicotine dependence (Di Chiara, 2000; Kameda et al., 2000). Recent studies suggest that N-methyl-D-aspartate (NMDA) glutamate receptor activation within the VTA may be required for nicotine to stimulate DA release in the NAcc (Leikola-Pelho and Jackson, 1992; Nisell et al., 1994; Shim et al., 2001), consistent with demonstrations that microinfusion of ionotropic glutamate receptor antagonists reduces nicotine-induced increases in neurochemical and locomotor activity (Schilstrom et al., 1998; Svensson et al., 1998). It has been proposed that this effect is mimicked by noradrenergic neurons, such that nicotine-induced increases in norepinephrine (NE) activity, associated with its cognition-enhancing effects, is mediated by glutamatergic transmission (Chen and Engberg, 1989; Erhardt et al., 2000). Alternatively, it has been proposed that augmented NAcc DA activity is the result of a disinhibited system, where increasing the activity of GABAergic interneurons modulates reward-related neurochemical and behavioral changes induced by nicotine (Corrigall et al., 2000; Dewey et al., 1999; Kawahara et al., 1999). Consistent with this, studies in our laboratory (Dewey et al., 1999; Schiffer et al., 2000) and others (Bevins et al., 2001) have demonstrated that pretreatment with γ-vinyl GABA (GVG), which blocks GABA degredation, modulates nicotine-induced increases in DA and craving for nicotine in animal models.

It follows that if both decreasing excitatory activity with glutamatergic antagonists and increasing inhibitory activity with GABA agonists can reduce nicotine-induced increases in DA, a drug which possesses both mechanisms might also suppress nicotine-induced increases in neurotransmitter activity. Topiramate (Topomax®) was developed as an anticonvulsant and is well tolerated in humans, with some evidence of relieving symptoms associated with bipolar disorder and obesity (Gordon and Price, 1999; Teter et al., 2000). Topiramate reduces EAA activity by antagonizing ionotropic alpha-amino-3-hydroxy-5-metyloisoxazolo-4-propionate (AMPA)/kainate glutamate receptors (Gibbs et al., 2000; Skradski and White, 2000). Further, considerable evidence indicates topiramate increases brain GABA levels (Petroff et al., 1999, 2001; White et al., 1997), possibly by activating a novel site on the $GABA_A$ receptor complex (Czuczwar and Patsalos, 2001). In the present study, we used in vivo microdialysis to explore the effects of acute pretreatment with topiramate (25 mg/kg or 50 mg/kg) on increases in mesolimbic extracellular DA, NE, and serotonin (5-HT) activity following a subcutaneous dose of nicotine (0.4 mg/kg). Further, we present the effects of topiramate (75 mg/kg) on nicotine-induced DA release in animals pretreated with nicotine for 14 days.

Details of microdialysis methods can be found in Dewey et al. (1999). Briefly, 2 days prior to the microdialysis experiments, siliconized guide cannulae were implanted targeting the NAcc ($A = +1.5$ mm, $L = -1.0$ mm, $V = -5.6$ mm). Pretreated animals received their last dose of nicotine on the day before the surgery, 2 days prior to the microdialysis study. Dialysate samples were assayed for monoamine content by

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microbore high-pressure liquid chromatography (HPLC) coupled with electrochemical detection. Probe recovery was calculated as 13.8% from 2-mm probes with correction for tissue recovery over time and appropriate standards indicated NE, DA, and 5-HT eluted at 2.5, 6, and 12 min, respectively. Peak effects were analyzed with a one-way ANOVA and post-hoc Bonferroni t-test of topiramate pretreated groups compared to saline-pretreated controls provided ANOVA significance at a critical value of 0.05.

Basal monoamine concentrations of DA, NE, and 5-HT were 40 ± 23 pg/10 μl, 1.12 ± 0.17 pg/10 μl and 8 ± 4.7 pg/10 μl (mean and standard error), respectively. Administration of topiramate alone did not produce any significant changes in extracellular basal DA or NE concentrations, but produced a nonsignificant, 20% increase in basal 5-HT activity ($t = 1.218$, $P = 0.258$). In animals pretreated with saline, nicotine produced significant increases in all three neurotransmitters, with DA increasing 70 ± 10.5%, NE increasing 176 ± 26%, and 5-HT increasing 116 ± 11.2% (Fig. 1a,b,c). Pretreatment with topiramate inhibited nicotine-induced increases in DA and NE, but not 5-HT activity (Fig. 1). Specifically, 25 and 50 mg/kg topiramate reduced the NAcc DA response to acute nicotine by 67 and 83%, respectively (significant treatment effect compared to saline pretreated controls; $F = 7.785$, $P = 0.004$, no significant dose–response relationship; $t = 0.753$, $P = 1.0$). Topiramate inhibited nicotine-induced increases in NE activity by 53 and 60%, respectively (50 mg/kg significance at $t = 3.015$, $P = 0.044$). It is evident from Figure 1c that topiramate increases 5-HT activity, which might account for the lack of attenuation observed following a nicotine challenge. Similarly, drugs believed to increase 5-HT activity appear to diminish the incidence of smoking in clinical trials (Ascher et al., 1995; Hughes, 2000). Thus, the observed sparing of nicotine-induced increases in 5-HT demonstrated here may prove beneficial for the specific treatment of nicotine dependence.

In the present study, acute nicotine produced larger increases in NAcc DA in animals previously exposed to nicotine compared with an acute injection in saline-pretreated animals (Fig. 2), consistent with progressively larger increases in locomotor and neurochemical activity demonstrated by other groups (Benwell and Balfour, 1992; Shim et al., 2001). This apparent neurochemical sensitization was dramatically reduced by treatment with 75 mg/kg topiramate ($F = 9.627$, $P = 0.0005$), demonstrating that the effects of topiramate on nicotine-induced DA release are sustained even in sensitized animals.

Here we present the first evidence in support of an original pharmacotherapeutic strategy, where a drug that both diminishes EAA activity and increases inhibitory GABAergic activity reduces hyperactive neurochemical activity believed to underlie the dependence-

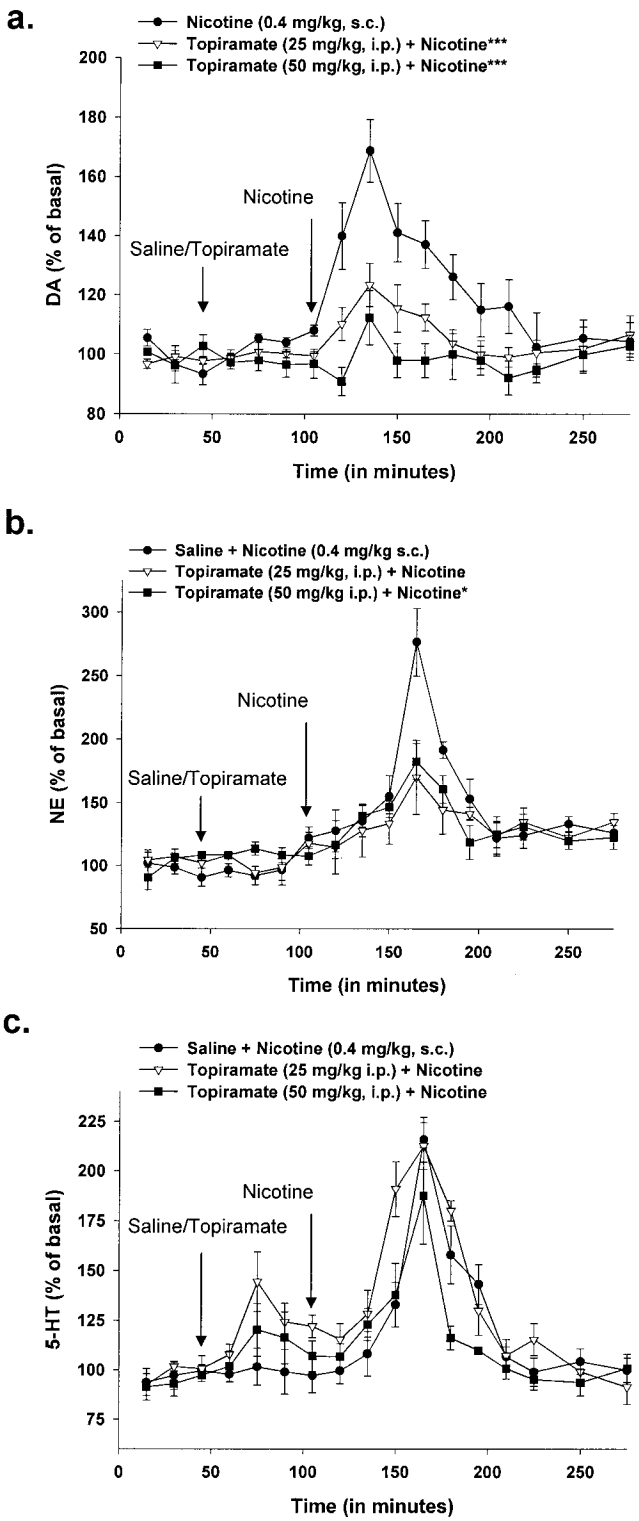

Fig. 1. Time activity of topiramate or saline pretreatment on nicotine-induced NAcc dopamine, DA (**a**), norepinephrine, NE (**b**), and serotonin, 5-HT (**c**) release in freely moving animals. Measures of statistical significance compared each topiramate-treated group to saline pretreated controls, where $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ assessed by one-way ANOVA and post hoc Bonferroni t-test.

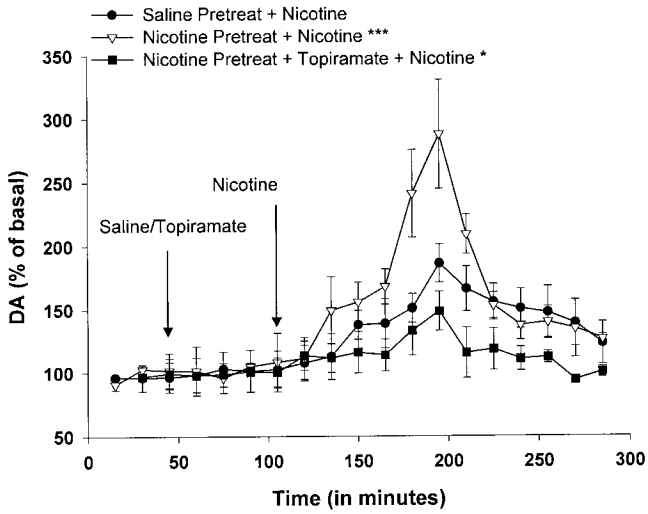

Fig. 2. Time activity of topiramate or saline pretreatment on nicotine-induced NAcc DA release after 14-day pretreatment with nicotine and a 2-day washout period. One-way ANOVA indicated a significant treatment effect across all groups ($F = 9.627, P = 0.0005$; $^{*}P < 0.05$ or $^{***}P < 0.001$, significantly different from saline-treated control animals).

producing effects of nicotine. Although oversimplified, this mechanistic understanding points to the GABAergic and glutamatergic neurotransmitter systems as potential pharmacologic targets for drugs to suppress psychostimulant-induced activations of DA systems. Finally, because nicotine is typically abused chronically and often in escalating doses by humans, the efficacy of topiramate as a modulator of nicotine-induced DA release in previously exposed animals promotes its utility as a potential pharmacotherapy for nicotine dependence.

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