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Neural response to lidocaine in healthy subjects

Bryon Adinoff[a,b,*], Michael D. Devous Sr.[c], Donald C. Cooper[a], Susan E. Best[a,b], Thomas S. Harris[c], Mark J. Williams[a]

[a]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, United States
[b]VA North Texas Health Care System, Dallas, TX, United States
[c]Nuclear Medicine Center and Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, United States

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ABSTRACT

Recent studies suggest that some of cocaine's central nervous system (CNS) effects may be mediated through its sodium channel inhibiting local anesthetic properties. Local anesthetics that lack cocaine's strong affinity for the dopamine transporter (DAT) also produce sensory and mood effects, further suggesting a role for this neural pathway. Due to an absence of affinity at the DAT, the local anesthetic lidocaine may offer the potential to assess sodium channel activity *in vivo* in humans. To assess the utility of lidocaine as a CNS probe, we determined regional cerebral blood flow (rCBF) with single photon emission computed tomography (SPECT) following the intravenous administration of lidocaine (0.5 mg/kg) and compared this response to procaine (0.5 mg/kg and 1.0 mg/kg), a local anesthetic with partial affinity for the DAT, and saline. Infusions were administered in nine healthy female controls over a 10-day period with at least 2 days between each scan. Increased rCBF was observed following lidocaine, relative to saline, in the insula, caudate, thalamus, and posterior cingulate. Decreased rCBF was detected in a different region of the posterior cingulate. In general, increases in rCBF were more marked following lidocaine relative to procaine. Mood and sensory changes following lidocaine were limited and significantly less than those induced by either dose of procaine. There were no significant changes in blood pressure or heart rate following either medication. These findings suggest that lidocaine can be safely used to assess sodium channel function in persons with addictive and other psychiatric disorders.

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1. Introduction

Cocaine is reinforcing through its ability to increase mesolimbic dopamine levels through blockade of the dopamine transporter (DAT) [reviewed by Adinoff, 2004; Lile, 2006]. The effect of cocaine upon monoamine transporters is complemented by its local anesthetic actions blocking voltage-gated sodium channels (Butterworth and Strichartz, 1990). Other local anesthetics share cocaine's ability to block sodium channels, yet for the most part they lack cocaine's potent affinity for the DAT (Ritz et al., 1987; Ritz and George, 1993). This relative lack of DAT affinity presumably explains the absence of powerful reinforcing effects in local anesthetics other than cocaine. However, our group has recently reported that low, physiologically relevant concentrations (10 μM) of cocaine, lidocaine, and tetrodotoxin (20 nM) alter the action potential bursting output of hippocampal subicular neurons (Cooper et al., 2006). This effect of cocaine, as well as lidocaine and tetrodotoxin, is related to its inhibition of sodium channels and is independent of cocaine's effect on monoamine uptake. As others have shown that electrical stimulation of the subiculum induces drug-seeking behavior in animal models of stimulant addiction (Vorel et al., 2001; Taepavarapruk and Phillips, 2003) while complete inhibition of subicular activity decreases cocaine-primed drug-seeking (Sun and Rebec, 2003), cocaine's direct effect upon the subicular sodium channels may be relevant to its addictive properties. These findings reveal the need to develop methods that allow exploration of sodium channels in the human central nervous system (CNS). In this study, we assessed the utility of lidocaine, a local anesthetic with minimal activity at monoamine reuptake receptors, as a relatively specific probe of sodium channel activity in humans at rest. To our knowledge, the neural response to lidocaine has not been systematically assessed in humans using functional neuroimaging techniques.

We have previously used the local anesthetic procaine to assess limbic activation in cocaine-dependent subjects (Adinoff et al., 1998, 2001, 2003b). While procaine shares cocaine's effect on sodium channel conductance, procaine has relatively low affinity for monoamine reuptake activity. Relative to cocaine, the affinity of procaine for the dopaminergic, serotonergic, and noradrenergic reuptake receptor is 1%, 0.05%, and 0.4%, respectively (Ritz et al., 1987). Nevertheless, procaine administration has been shown to potently activate anterior limbic activity and subjective anxiety in healthy subjects (Ketter et al., 1996; Servan-Schreiber et al., 1998; Adinoff et al., 2001, 2003a).

* Corresponding author. 5323 Harry Hines Blvd., Dallas, TX 75390-8564, United States. Tel.: +1 214 645 6975; fax: +1 214 645 6976.
E-mail address: bryon.adinoff@utsouthwestern.edu (B. Adinoff).

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Interestingly, abstinent cocaine-dependent subjects, particularly men, administered procaine demonstrate a relative absence of regional cerebral blood flow (rCBF) limbic activation (Adinoff et al., 2001, 2003b). We have previously hypothesized that the attenuated rCBF response to procaine in cocaine-addicted subjects reflects a non-dopaminergic mechanism. However, while procaine's affinity for the DAT is low compared to cocaine, both preclinical and clinical studies suggest an overlap between the rewarding and stimulus effects of cocaine and procaine (Woolverton and Balster, 1979, 1982; Fischman et al., 1983b; Garza and Johanson, 1983; Jarbe, 1984; Silverman and Schultz, 1989; Adinoff et al., 1998; Wilcox et al., 2000; Tella and Goldberg, 2001). Studies demonstrating a direct effect of procaine upon dopamine efflux (Woodward et al., 1995) and a relationship between procaine's reinforcing effects and DAT occupancy (Wilcox et al., 2005) suggest that these cocaine-like effects of procaine may be mediated through the DAT. Therefore, it remains uncertain if the CNS effects of procaine are a result of its interaction with the DAT, the sodium channel, or other physiological processes.

The putative importance of non-dopaminergic interactions in the acute- and long-term effects of cocaine, discussed above, necessitates a more thorough understanding of the precise mechanisms of local anesthetic probes. To help tease apart these disparate processes, we explored the central effects of lidocaine. Lidocaine shares the sodium channel blocking effects of procaine and cocaine, but is essentially devoid of any activity at the monoamine reuptake receptors. For example, relative to cocaine, the affinity of lidocaine for the dopaminergic, serotonergic, and noradrenergic reuptake receptor is 0.02% (1/50th of procaine's affinity), 0.04%, and 0.7%, respectively (Ritz et al., 1987). Preclinical studies have consistently observed that lidocaine does not have reinforcing properties (Woolverton and Balster, 1979, 1982; Wilcox et al., 2000) and fails to generalize to a cocaine stimulus (Colpaert et al., 1979; Middaugh et al., 1998; Tella and Goldberg, 2001). Lidocaine, like procaine, does not produce the dopamine-mediated rotational behavior observed with cocaine (Silverman and Schultz, 1989) and Fischman et al. (1983a) reported that the autonomic and subjective effects of lidocaine were indistinguishable from those of placebo. Finally, *in vivo* microdialysis shows that lidocaine, unlike procaine, actually reduces dopamine in dialysate (Woodward et al., 1995).

In this study, we assessed the effects of lidocaine, compared to procaine and saline, upon rCBF and subjective responses in healthy control subjects at rest. We utilized single photon emission computed tomography (SPECT) to provide a net measure of lidocaine's effect upon CNS perfusion. We hypothesized that the shared sodium channel effects of lidocaine and procaine would result in similar neural and subjective responses in both compounds. Although others have used procaine doses up to 2.3 mg/kg (Kellner et al., 1987), safety concerns led us to use only a 0.5 mg/kg dose of lidocaine. A similar dose of procaine (0.5 mg/kg) was therefore used to allow a direct comparison of equal doses of procaine and lidocaine. As the minimal nerve blocking property of lidocaine (0.010 mM) is approximately two-fold greater than procaine's (0.021 mM)(Agin et al., 1965), a procaine dose of 1.0 mg/kg was also included.

2. Methods

The study design has previously been described (Adinoff et al., 2002). Ten female volunteers were recruited for the study. Subjects were between 25 and 45 years old, and underwent a thorough medical history and physical examination, Structured Clinical Interview for DSM-IV (SCID), clinical laboratory tests, urine drug screen, electrocardiogram, electroencephalogram, and magnetic resonance imaging (MRI) of the brain. Informed consent was obtained from all subjects, and subjects were financially compensated for their participation. Exclusion criteria included any Axis I or Axis II disorder or a first-degree relative with an Axis I disorder or two or more second-degree relatives with an Axis I disorder. Subjects had no significant past or present medical disorders that would interfere with the central nervous system (CNS) functioning, and were not on medications known to alter CNS activity. Urine drug screens were negative. One subject was removed from the data analysis when a cerebral cyst was noted on MRI, leaving a total of nine subjects. Subjects were age 32.8 ± 6.8 years old (mean ± S.D.)

Subjects underwent four separate study sessions over a 10-day period. Scans were at least 48 h apart and all sessions were at the same time of day. Subjects received the following infusions: saline (placebo), 0.5 mg/kg lidocaine, 0.5 mg/kg procaine, and 1.0 mg/kg procaine. [Results from the latter two scans have previously been reported (Adinoff et al., 2002), but are included here as comparisons with the lidocaine infusion.] The infusion order was randomized. Both the study coordinator and the subject were blinded to medication order, but the physician (B.A. or S.B.) administering the drug was not blinded. The physician administered the saline/procaine/lidocaine out of the subject's and the study coordinator's view. For the first five subjects in this group, the 1.0 mg/kg procaine dose was not administered before the saline session. An electrocardiogram was monitored by a physician throughout the infusion.

2.1. Study sessions

Study sessions took place at the Nuclear Medicine Center at the University of Texas Southwestern Medical Center at Dallas. All subjects were requested to abstain from caffeine and nicotine for at least 2 h prior to the study. Upon arrival at the study site, a Quik-Cath needle was inserted into the left forearm vein for administration of procaine, lidocaine, or saline and the rCBF radiotracer (^{99m}Tc HMPAO, GE Healthcare, Princeton, New Jersey). Subjects were seated in a recliner in a dimly lit room, with eyes and ears open. Following 30 min of rest after i.v. insertion, blood pressure, pulse, and the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983) were measured. The BSI uses 53 questions to assess cognitive, sensory, and affective changes. Subjects were instructed on the use of a joystick, which allowed the subject to endorse her present affective state in real-time. (These data will not be presented here). Subjects were then advised that the study medication would be administered in the next few minutes. Two minutes later, either procaine, lidocaine, or saline was administered over 60 s by slow push, followed by 3 ml saline flush over 45 s, 20 mCi of ^{99m}Tc HMPAO over 30 s, and 10 ml saline flush over 30 s. Four minutes following the final infusion, blood pressure and pulse were measured and the Drug Effect Questionnaire (DEQ) and BSI were administered. The DEQ consisted of five questions, rated on a scale of 0 (no effect) to 6 (strongest effect). The five questions concerned whether the subject 1) felt any drug effect, 2) felt a good effect, 3) felt a bad effect, 4) liked the effect, and 5) disliked the effect. (For statistical analysis, items 2 and 4 were combined to "good effect" and 3 and 5 combined to "bad effect") (Adinoff et al., 2001). The intravenous line was removed following assessment of mood states. Ninety minutes after infusion of the study medication, the subject was moved to the SPECT scanner where the brain image was obtained. Note that although the image acquisition was 90 min following lidocaine/procaine/saline infusion, the rCBF pattern reflected brain activity immediately following tracer infusion, which immediately followed the lidocaine, procaine, or saline. This perfusion image thus represents rCBF at the time of radiotracer administration and not at the time of the scan.

2.2. SPECT imaging

SPECT images were acquired on a PRISM 3000S three-headed SPECT camera (Picker International, Cleveland, OH) using ultra high-resolution fan-beam collimators (reconstructed resolution of 6.5 mm) in a 128 × 128 matrix in three-degree increments. 20 mCi of ^{99m}Tc HMPAO was administered for each scan, and total scan duration was 23 min. Image reconstruction was performed in the transverse domain using back-projection with a ramp filter. For our system voxels in reconstructed images were 1.9 mm^3. Reconstructed images were smoothed with a 4th-order Butterworth three-dimensional filter and attenuation corrected using a Chang first-order method with ellipse size adjusted for each slice.