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Neural Response to Lidocaine in Healthy Subjects

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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 ten-day period with at least two days between each scan. Increased rCBF was observed following lidocaine, relative to saline, in the insula, caudate, thalamus, 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.

Keywords

Tomography; Emission-Computed; Single-Photon; Lidocaine; Humans; Anesthetics; Local; Procaine; Limbic system; Basal ganglia

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

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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 μ M) of cocaine, lidocaine, and tetrodotoxin (20nM) 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; Adinoff et al., 2001; Adinoff et al., 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; Adinoff et al., 2003a). Interestingly, abstinent cocaine-dependent subjects, particularly men, administered procaine demonstrate a relative absence of rCBF limbic activation (Adinoff et al., 2001; Adinoff et al., 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) suggests 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, DSM-IV Structured Clinical Interview (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 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 $\pm$ SD).

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, the Drug Effects Questionnaire (DEQ), and the 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 3-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. 20mCi of ^{99m}Tc HMPAO was administered for each scan, and total scan duration was 23 minutes. Image reconstruction was performed in the transverse domain using back-projection with a ramp filter. For our system voxels in reconstructed images were 1.9mm³. 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.

2.3. Statistical Analysis

2.3.1. Image Analysis—Image analyses consisted of three different activities: normalization, coregistration, and subtraction. SPECT images were resliced to 2mm³ voxels, co-registered to Talairach space (Talairach and Tournoux, 1988) using the MNI template and normalized to whole brain counts. Analyses of change in rCBF were measured relative to global cerebral blood flow. Images were smoothed from their original resolution of 6.5 mm to a final resolution of 10mm. Areas differing between lidocaine/procaine and saline were overlaid on an MRI model in Talairach space. Voxel-wise analyses of lidocaine- or procaine-induced effects on rCBF were analyzed using Statistical Parametric Mapping (SPM2) (Wellcome Department of Cognitive Neurology, University College, London, England) with a statistical threshold of $p < 0.005$ for voxel z scores and a cluster size no smaller than 100 voxels. Significant changes relative to each active drug were computed by comparison to the saline infusion. This, in effect, identifies voxels that were active relative to saline but differed between the pharmacologic challenges. Since comparisons between the 0.5 mg/kg and 1.0 mg/kg procaine scans have been previously published (Adinoff et al., 2002), only comparisons between lidocaine with either dose of procaine are reported in this manuscript.

2.3.2. Subjective and cardiovascular responses to lidocaine and procaine compared to saline—Because the assumptions of parametric statistics were not met in the BSI and DEQ data, the Wilcoxon signed ranks tests was used for within-group comparisons and the Mann-Whitney U Test was used for between-group comparisons. Raw BSI scores were utilized. Comparisons for BSI were first conducted for all four infusions between pre- and post-infusion measures, followed by comparisons between lidocaine [(post-lidocaine minus pre-lidocaine) – (post-saline minus pre-saline)] and both doses of procaine. Similar analyses were

conducted on DEQ, although only post-infusion measures were collected. Repeated measures ANOVA were used to assess differences in systolic/diastolic blood pressure and heart rate.

3. RESULTS

3.1. rCBF Within-Group Comparisons

3.1.1. rCBF following lidocaine 0.5 mg/kg infusion (Figure 1, top panel; MNI coordinates on Table 1)—Increases in rCBF ($p < 0.005$) were observed in the right anterior insula, the right caudate and putamen and a somewhat similar region on the left that includes the caudate, putamen and globus pallidus [extending inferiorly into Brodman Area (BA) 25], anterior nucleus of the right thalamus, posterior cingulate, right pons, and cerebellum following lidocaine relative to saline. rCBF decreases were found only in a region extending superiorly from the left posterior cingulate to the precuneus.

3.1.2. rCBF following procaine 0.5 mg/kg infusion (Figure 1, middle panel; MNI coordinates on Table 1)—Procaine 0.5 mg/kg infusion, relative to saline, induced increased rCBF in the left anterior insula, right thalamus (similar to that observed following lidocaine), and right parietal cortex (not shown). There were no areas of decreased rCBF.

3.1.3. rCBF following procaine 1.0 mg/kg infusion (Figure 1, bottom panel; MNI coordinates on Table 1)—Increases in rCBF following procaine 1.0 mg/kg were evident only in a small area of the right parahippocampus (not shown) relative to saline. More prominent regions of decreased rCBF were observed in a region overlapping the left posterior insula and superior temporal gyrus (STG), the left posterior cingulate (similar to that observed following lidocaine), right inferior temporal gyrus (not shown), right parietal cortex (not shown) and right precuneus (not shown).

3.2. Comparisons Between Lidocaine and Procaine

Direct comparisons, using SPM2, were also obtained between the lidocaine and procaine scans. Since the saline session was the same for all of the other scans, the saline scan was not included in this comparison. Lidocaine was entered into the comparison first, such that red regions (Fig. 2) may reflect either an increased rCBF response to lidocaine relative to procaine (0.5 mg/kg in the top panel, 1.0 mg/kg in the lower panel), a decreased rCBF response to procaine relative to lidocaine, or a combination of both. Conversely, blue areas may reflect either an increased rCBF response to procaine relative to lidocaine, a decreased rCBF response to lidocaine relative to procaine, or a combination of both. The driving force (i.e. lidocaine or procaine) could usually be determined by visual inspection of the saline comparisons presented above. In general, these comparisons revealed lidocaine induced a greater rCBF response, particularly in limbic and basal ganglia regions, relative to either low or high dose procaine.

3.2.1. rCBF following lidocaine 0.5 mg/kg vs. procaine 0.5 mg/kg (Figure 2, top panel; MNI coordinates in Table 1)—Lidocaine 0.5 mg/kg induced a relative increase in rCBF (yellow/red regions on Fig. 2), compared to procaine 0.5 mg/kg, in the right OFC extending superiorly to right anterior insula and a relative decrease (blue regions on Fig. 2) in the left posterior cingulate and right precentral gyrus (not shown). Large areas of increased rCBF were also noted in the cerebellum following lidocaine relative to low dose procaine, presumably due to more modest rCBF increases following lidocaine relative to procaine. Based upon lidocaine vs. saline and procaine vs. saline comparisons at $p < 0.01$, the driving force behind the difference observed in the lingual gyrus was an increase in rCBF following lidocaine and a decrease following procaine, whereas the decrease in left hippocampus was a result of decreased rCBF following lidocaine. The etiology of the relative rCBF difference in the right posterior insula / putamen was uncertain.

3.2.2. rCBF following lidocaine 0.5 mg/kg vs. procaine 1.0 mg/kg (Figure 2, bottom panel)—In the lidocaine vs. procaine 1.0 mg/kg comparison, lidocaine 0.5 mg/kg induced a relative rCBF increase (yellow/red regions on Fig. 2) in the right pons, left putamen, left posterior cingulate, right superior frontal gyrus (the latter observed in procaine vs. saline at $p < 0.01$) and large areas of the bilateral cerebellum. The right and left lingual gyrus / cuneus also showed an rCBF increase due to lidocaine vs. saline increases (observed at $p < 0.01$). Procaine-induced decreases in rCBF (also yellow/red regions on Fig. 2), relative to lidocaine, included the left posterior insula/STG. The pharmacologic challenge driving the relative change in the right OFC / superior frontal gyrus, right superior temporal gyrus and left middle frontal gyrus could not be determined.

3.3. Subjective Measures

Repeated measures ANOVA revealed significant differences on all BSI measures between lidocaine and both procaine doses (Table 2). The high dose of procaine significantly increased both BSI dimensions of anxiety (i.e. Anxiety, Somatization) and all global measures post-drug relative to pre-drug scores ($p < 0.05$ uncorrected). The lower dose of procaine also showed significant increases in BSI measures, although all scores were less than those observed with procaine 1.0 mg/kg. In contrast, only Somatization and GSI increased after lidocaine. The two anxiety and three global BSI measures were significantly higher following 1.0 mg/kg procaine relative to lidocaine, and Anxiety, PST, and GSI were higher following 0.5 mg/kg procaine compared to lidocaine.

On the DEQ, lidocaine and both doses of procaine significantly increased Any Effect scores whereas Bad Effect significant increased for only procaine; Good Effect was not increased following any infusion relative to saline ($p < 0.05$ uncorrected) (Table 3). Any and Bad Effect progressively increased, and Good Effect decreased, from lidocaine, procaine 0.5 mg/kg, to procaine 1.0 mg/kg. Within group comparison between Δ lidocaine (post-infusion - saline) and Δ procaine (post-infusion - saline) revealed significant ($p < .05$ uncorrected) differences between Δ lidocaine and Δ procaine 1.0 mg/kg for Any Effect and Bad Effect but not between Δ lidocaine and Δ procaine 0.5 mg/kg.

3.4. Blood Pressure and Heart Rate

Measures of systolic and diastolic blood pressure and heart rate were obtained prior and following drug infusion (Table 4). Neither lidocaine nor procaine induced significant increases in either measure, and there were no blood pressure or heart rate differences following lidocaine compared with either procaine dose.

4. DISCUSSION

These findings reveal a marked increase in insular, midbrain, thalamic, cingulate, and striatal rCBF following the administration of lidocaine. Generally, lidocaine infusion increased rCBF more than either the same dose or a higher dose of procaine. In contrast, the mood and sensory effects of lidocaine were minimal and significantly less than those experienced following the procaine administration. These findings suggest that sodium channel inactivation by lidocaine has profound and regionally specific effects upon CNS rCBF despite minimal sensory effects. These findings were unexpected and difficult to interpret. Differences between lidocaine and procaine that may explain these findings are discussed below.

As procaine has relatively greater effects on the DAT relative to lidocaine (Ritz et al., 1987), it is presumed that the greater neural alterations induced by lidocaine are due to its effects on the sodium channel. However, there are several other factors that could account for the observed differences in rCBF. Both procaine and lidocaine exhibit affinity for the 5HT₃ receptor,

procaine more so than lidocaine (Barann et al., 1993). Interestingly, procaine (and cocaine) have equal affinity at both the sodium channel and 5HT₃ receptor, whereas lidocaine has 4-fold the affinity for the sodium channel relative to the 5HT₃ receptor (Barann et al., 1993). Procaine also has affinity for nicotinic (Swanson and Albuquerque, 1987; Niu et al., 1995) and muscarinic (Karpen and Hess, 1986; Sharkey et al., 1988; Flynn et al., 1992) acetylcholine receptors at pharmacologically relevant concentrations; the affinity of lidocaine at these receptors is not known.

There are also both pharmacokinetic and other pharmacodynamic differences in procaine and lidocaine that may account for the differences observed, including assumptions regarding the relative doses administered and their potency at the voltage-dependent sodium channel. Usubiaga et al. (Usubiaga et al., 1967) observed higher mean cerebrospinal fluid concentrations (CSF) concentrations of lidocaine relative to procaine following intravenous infusion, suggesting either increased CSF penetration or less metabolism of lidocaine. Reports of the relative potencies of lidocaine and procaine at the sodium channel also differ (Agin et al., 1965; Barann et al., 1993). In our laboratory, we have found lidocaine has approximately 1.5 times the potency of procaine in activating prefrontal cortical field excitatory post-synaptic potential (EPSP) in rodents (unpublished).

There are few studies assessing the CNS effects of both lidocaine and procaine in humans. To our knowledge, only Foldes et al. (1960) and Usubiaga et al. (1966) also directly compared these two medications. Foldes et al. (1960) utilized dramatically higher doses than those given in the present study, administering lidocaine (0.5 mg/kg/min) and procaine (1.0 mg/kg/min) for up to 25 minutes or until severe CNS symptoms became evident (i.e. seizures, loss of consciousness). Clinical symptoms of CNS toxicity showed a similar time onset following both drugs, although the infusion was tolerated significantly less time following lidocaine relative to procaine. These findings were similar to those of Usubiaga et al. (1966), which compared even higher doses of lidocaine (1.5 to 3.0 mg/kg/min) and procaine (3.0 to 9.0 mg/kg/min) and used only seizures as their clinical endpoint. The increased therapeutic index of procaine over lidocaine may be a result of procaine's more rapid clearance through hydroxylation or its effect on sodium channels. Detsch et al. (1997) measured spectral EEG in eleven healthy volunteers following lidocaine (2 minute bolus of 100mg followed by 40 ug/kg-min for 15 minutes) or placebo. Both frontotemporal and occipital EEG changes were observed in both delta and beta spectral power during lidocaine relative to placebo. Other investigators have described significant sensory disturbances following lidocaine (Attal et al., 2000), although concurrent neural measures have not been obtained. Plewnia et al. (2007) recently reported an association between the transient suppression of verbal auditory hallucinations in a 74-year-old woman following intravenous lidocaine administration (100mg) and rCBF reductions (as measured by PET) in the right angular and supramarginal gyrus, right inferior frontal gyrus, orbitofrontal cortex and cingulate cortex. It is likely that the relatively low dose of lidocaine administered in the present study (0.5 mg/kg) accounted for the near absence of sensory effect of lidocaine. The lidocaine in our study was also administered as bolus over one minute as opposed to the more extended dosing (5-90 minutes) used in other studies (Usubiaga et al., 1967; Galer et al., 1993; Detsch et al., 1997; Attal et al., 2000) and clinical practice (Roden, 2001).

Procaine induces activation of the anterior limbic region, including the anterior cingulate, anteromesial temporal cortex, and anterior/middle insula (Ketter et al., 1996; Servan-Schreiber et al., 1998; Adinoff et al., 2001; Adinoff et al., 2003a) and significant sensory and anxiogenic effects (Stark-Adamec et al., 1982; Kellner et al., 1987; Ketter et al., 1996; Servan-Schreiber et al., 1998; Adinoff et al., 2001; Adinoff et al., 2003a). Although sensory disturbances were observed following procaine in the present study, particularly at the higher dose (1.0 mg/kg), limbic rCBF was limited compared to increases in rCBF observed at the somewhat higher procaine dose of 1.38 mg/kg (Adinoff et al., 2001; Adinoff et al., 2003b). It should be noted

that the findings in the present study differed from our previous report of these data (Adinoff et al., 2002) following a more detailed analysis using a smaller smoothing kernel (10 mm vs. 14 mm), a more rigorous statistical threshold ($p < 0.005$ vs $p < 0.01$), and a larger cluster extent threshold (100 vs. 50 voxels).

Methodologic strengths of our study include a carefully selected population of healthy volunteers and the inclusion of one gender (females). Although our study design (4 scans over 10 days) did not allow menstrual phase to be controlled, the within-subject design and randomized order of medication administration make menstrual phase an unlikely confound. Limits of spatial resolution and the ability to only determine relative measures of limbic rCBF are inherent in our SPECT methodology and camera. It should also be noted that the SPECT utilized assessed relative (to whole brain), not absolute, rCBF differences between groups. However, Ketter et al. (1996) found that procaine induced significant regional changes in limbic regions using both absolute and normalized measures of cerebral blood flow. Thus, direct vascular effects, typically removed by normalization, appear not to play a major role in procaine regional responses. Dormehl et al. (1993) has reported that baboons administered lidocaine (6 mg/kg) intravenously exhibited an increased in rCBF (with SPECT) that was associated with changes in PaCO_2 , suggesting that changes in cerebrovascular autoregulation may have contributed to lidocaine-induced neural activation. In addition, Usubiaga et al. (Usubiaga et al., 1967) observed a marked fall in systolic and diastolic blood pressure following lidocaine infusion (5-10mg) but not following procaine (10-20mg). However, our findings demonstrate that neither drug induced a significant change in blood pressure or heart rate at the doses administered. Although this does not rule-out a cerebrovascular effect of lidocaine, the specific regional distribution of rCBF findings argues against this explanation of our findings.

These findings reveal that lidocaine, a medication essentially devoid of activity at monoamine transporters, induces marked increases in striatal, thalamic, insular, cingulate, and brainstem rCBF with minimal changes in mood, sensory, or autonomic activity. Lidocaine may serve as a useful tool for neuroimaging studies to probe the specific neural circuits most sensitive to sodium channel blockade.

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Figure 1.

Increases (red) and decreases (blue) in regional cerebral blood flow (rCBF) in response to lidocaine or procaine infusion, relative to the response to saline infusion ($p < 0.01$), in healthy subjects. Talairach coordinators (z-axis) noted at the bottom left of each image. L = left. R = PFC = prefrontal cortex. ant = anterior. post = posterior. STG = superior temporal gyrus.

Complete transverse, sagittal, and coronal images can be viewed for lidocaine (<http://www4.utsouthwestern.edu/psychiatry/Addictions/lidocaine.htm>), procaine 0.5 mg/kg (<http://www4.utsouthwestern.edu/psychiatry/Addictions/procaine0.5.htm>), and procaine 1.0 mg/kg (<http://www4.utsouthwestern.edu/psychiatry/Addictions/procaine1.0.htm>).

Fig. 2.

Relative rCBF differences between lidocaine and procaine scans. Top panel: Red/yellow display voxels greater following lidocaine relative to procaine 0.5 mg. Blue indicates voxels less following lidocaine relative to procaine 0.5 mg. Bottom panel: Red/yellow display voxels greater following lidocaine relative to procaine 0.5 mg. Talairach coordinators (z-axis) are noted at the bottom left of each image. Blue indicates voxels less following lidocaine relative to procaine 0.5 mg. L = left. R = right. Complete transverse, sagittal, and coronal images can be viewed for lidocaine vs. procaine 0.5 mg/kg (<http://www4.utsouthwestern.edu/psychiatry/Addictions/lidocainevsprocaine0.5.htm>) and lidocaine vs. procaine 1.0 mg/kg (<http://www4.utsouthwestern.edu/psychiatry/Addictions/LidocaineVsProcaine1.0.htm>).

Table 1

Brain regions demonstrating increased and decreased ($p < 0.005$) regional cerebral blood flow (rCBF) following lidocaine, procaine 0.5 mg/kg and procaine 1.0 mg/kg compared with saline in healthy controls.

Identified region	MNI coordinates			k_E Cluster-level $P_{corrected}$
	X	y	z	
<i>Lidocaine 0.5 mg/kg</i>				
Increased rCBF relative to saline				
L caudate	-16	18	-2	4250.004
R thalamus (ant nucleus)	10	-6	12	1160.663
R ant insula	32	26	-6	2460.072
R putamen/caudate	18	14	0	1050.758
L post cing	-8	-30	46	1310.537
R pons	8	-36	-16	2910.033
L cerebellum	-34	-50	-36	2400.081
Decreased rCBF relative to saline				
L post cing	-16	-44	48	3720.009
<i>Procaine 0.5 mg/kg</i>				
Increased rCBF relative to saline				
R thalamus	-30	16	16	1350.469
L anterior insula	10	-12	8	1080.703
R parietal cortex	12	-42	72	3030.022
<i>Procaine 1.0 mg/kg</i>				
Increased rCBF relative to saline				
R parahippocampus	36	-20	-10	1200.588
Decreased rCBF relative to saline				
L posterior insula/STG	-52	-20	10	1590.303
L posterior cingulate	-10	-48	44	1020.751
L superior frontal gyrus	-8	24	56	1100.679
R inferior temp gyrus	36	-12	-38	1480.369
R parietal cortex	24	-52	54	1550.325
R precuneus	16	-56	24	1170.615
<i>Lidocaine 0.5 mg/kg vs. procaine 0.5 mg/kg</i>				
Δ lidocaine increased relative to Δ procaine				
R anterior insula/OFC	34	24	-10	3840.082
Lingual gyrus	-6	-92	0	3870.079
Δ procaine increased relative to Δ lidocaine				
R precentral gyrus	42	-2	32	1010.954
R posterior insula	-32	-42	4	1360.831
<i>Lidocaine 0.5 mg/kg vs. procaine 1.0 mg/kg</i>				
Δ lidocaine increased relative to Δ procaine				
R pons	8	-24	-30	1130.921
L putamen	-26	6	-2	1710.659
L post insula/STG	-54	-18	8	310.005
R OFC/sup frontal gyrus	16	66	-6	1820.604
L posterior cingulate	-14	-26	44	1060.941
R lingual gyrus	6	-98	16	2490.324
L lingual gyrus	-22	-96	-8	1290.861
R superior frontal gyrus	4	42	48	2530.311
Δ procaine decreased relative to Δ lidocaine				
R superior temporal gyrus	50	14	-24	1220.183
L middle frontal gyrus	-18	-16	56	1210.893

Table 2

BSI scales by pharmacologic challenge.

BSI subscales	Lidocaine		Procaine 0.5 mg/kg		Procaine 1.0 mg/kg		Lidocaine vs. procaine 0.5 ²		Lidocaine vs. procaine 1.0 ²	
	Mean (S.D.) ¹	Median	Mean (S.D.) ¹	Median	Mean (S.D.) ¹	Median	z-value ¹	P-value	z-value ¹	P-value ²
Somatization	0.27±0.33*	0.15	0.81±1.08**	0.43	1.03±0.71**	1.00	-1.600.11		-2.100.033*	
Obsessive-compulsive	0.00±0.00	0.00	0.04±0.07*	0.00	0.17±0.33	0.00	-1.400.16		-1.600.11	
Interpersonal sensitivity	0.00±0.00	0.00	0.00±0.00	0.00	0.00±0.00	0.00	0.001.00		0.001.00	
Depression	0.00±0.00	0.00	0.00±0.00	0.00	0.00±0.00	0.00	0.001.00		0.001.00	
Anxiety	0.15±0.29	0.17	0.37±0.31*	0.50	0.48±0.43*	0.50	-2.100.039*		-2.000.05	
Hostility	0.00±0.10	0.00	0.04±0.09	0.00	0.04±0.13	0.00	-1.000.32		-0.400.66	
Phobic anxiety	0.00±0.00	0.00	0.00±0.00	0.00	0.00±0.00	0.00	0.001.00		0.001.00	
Paranoid ideation	0.00±0.00	0.00	0.00±0.00	0.00	0.00±0.00	0.00	0.001.00		0.001.00	
Psychoticism	0.00±0.00	0.00	0.00±0.00	0.00	0.00±0.00	0.00	0.001.00		0.001.00	
GSI	0.05±0.06	0.04	0.16±0.17**	0.11	0.22±0.14**	0.23	-2.500.012*		-2.500.012*	
PST	1.33±2.00	1.00	4.55±2.88**	4.00	5.00±2.69**	5.00	-2.700.007**		-2.500.011*	
PSDI	0.55±0.94	0.50	1.32±0.51*	1.33	2.01±0.94**	1.86	-1.700.09		-2.400.017*	

¹Mean±S.D. change in BSI domain post-drug infusion relative to pre-drug infusion. Δlidocaine (post-infusion minus pre-infusion) and Δprocaine (post-infusion minus pre-infusion) were compared to Δsaline (post-infusion minus pre-infusion) using Wilcoxon Signed rank test. * $P<0.05$, ** $P<0.01$.

²Mean±S.D. change in BSI domain between Δlidocaine (post-infusion minus pre-infusion) vs. Δprocaine (post-infusion minus pre-infusion). * $P<0.05$, ** $P<0.01$.

Table 3

Drug Effect Questionnaire (DEQ) by pharmacologic challenge.

DEQ item	Lidocaine		Procaine 0.5 mg/kg		Procaine 1.0 mg/kg		Lidocaine vs. procaine 0.5 ^d		Lidocaine vs. procaine 1.0 ^d	
	Mean (S.D.) ^b	Median	Mean (S.D.) ^b	Median	Mean (S.D.) ^b	Median	z-value ^b	P-value	z-value ^b	P-value ^d
Any Effect	3.1±2.6*	4.0	3.7±1.9**	4.0	4.9±1.8**	6.0		.85.39	2.24	.03*
Good Effect	2.9±3.7	0.0	2.3±4.3	0.0	1.3±4.0	0.0		.54.59	1.46	.14
Bad Effect	3.1±4.8	0.0	6.7±5.1*	0.0	7.9±4.8*	10.0		1.78.07	2.36	.02*

^a Change in DEQ domain between Δlidocaine (lidocaine–saline) vs. Δprocaine (procaine–saline). **P*<0.05.

^b Mean±S.D. change in DEQ domain post-drug infusion less saline. Lidocaine and procaine were compared to saline using Wilcoxon signed rank test. **P*<0.05, ***P*<0.01.

Table 4

Blood pressure and heart rate by pharmacologic challenge.

Measure	Saline ^a	Lidocaine ^a	Procaine 0.5 ^a	Procaine 1.0 ^a	Lidocaine vs. procaine 0.5 mg/kg ^{a,b}		Lidocaine vs. procaine 1.0 mg/kg ^b	
					t (7)	P	t (8)	P
Systolic BP	1.3±6.5	2.7±6.8	-0.8±5.0	2.9±8.0	1.5	0.19	0.1	0.94
Diastolic BP	0.7±6.2	0.0±7.7	-2.0±5.0	0.9±6.9	0.9	0.40	0.3	0.80
Heart rate	2.4±5.8	2.2±4.9	-1.5±5.2	1.3±4.9	1.1	0.32	0.3	0.74

^a Mean±S.D. change in blood pressure and heart rate measures post-drug infusion relative to pre-drug infusion. Δlidocaine (post-infusion minus pre-infusion) and Δprocaine (post-infusion minus pre-infusion). None of the comparisons were significant.

^b Mean±S.D. change in Δlidocaine (post-infusion minus pre-infusion) vs. Δprocaine (post-infusion minus pre-infusion) using within-subject t-test. None of the comparisons were significant.