Published in final edited form as:

Drug Alcohol Depend. 2011 September 1; 117(2-3): 176–183. doi:10.1016/j.drugalcdep.2011.01.015.

Modulation of resting brain cerebral blood flow by the GABA B agonist, baclofen: A longitudinal perfusion fMRI study

Teresa R. Franklin^{a,*}, Ze Wang^a, Nathan Sciortino^a, Derek Harper^a, Yin Li^a, Jonathan Hakun^a, Susan Kildea^a, Kyle Kampman^{a,d}, Ron Ehrman^{a,d}, John A. Detre^{b,c}, Charles P. O'Brien^{a,d}, and Anna Rose Childress^{a,d}

^aDepartment of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

^bDepartment of Radiology, University of Pennsylvania, Philadelphia, PA, USA

^cDepartment of Neurology, University of Pennsylvania, Philadelphia, PA, USA

^dPhiladelphia VA Medical Center, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Background—Preclinical studies confirm that the GABA B agonist, baclofen blocks dopamine release in the reward-responsive ventral striatum (VS) and medial prefrontal cortex, and consequently, blocks drug motivated behavior. Its mechanism in humans is unknown. Here, we used continuous arterial spin labeled (CASL) perfusion fMRI to examine baclofen's effects on blood flow in the human brain.

Methods—Twenty-one subjects (all smokers, 12 females) were randomized to receive either baclofen (80 mg/day; $N = 10$) or placebo ($N = 11$). A five minute quantitative perfusion fMRI resting baseline (RB) scan was acquired at two time points; prior to the dosing regimen (Time 1) and on the last day of 21 days of drug administration (Time 2). SPM2 was employed to compare changes in RB from Time 1 to 2.

Results—Baclofen diminished cerebral blood flow (CBF) in the VS and mOFC and increased it in the lateral OFC, a region involved in suppressing previously rewarded behavior. CBF in bilateral insula was also blunted by baclofen (T values ranged from -11.29 to 15.3 at $p = 0.001$, 20 contiguous voxels). CBF at Time 2 was unchanged in placebo subjects. There were no differences between groups in side effects or cigarettes smoked per day (at either time point).

Conclusions—Baclofen's modulatory actions on regions involved in motivated behavior in humans are reflected in the resting state and provide insight into the underlying mechanism behind

© 2011 Elsevier Ireland Ltd. All rights reserved.

*Corresponding author at: Department of Psychiatry, University of Pennsylvania, Center for Studies of Addiction and VA Medical Center, 3900 Chestnut Street, Philadelphia, PA, USA. Tel.: +1 215 222 3200x119; fax: +1 215 386 6770. franklin.t@mail.trc.upenn.edu (T.R. Franklin).

Contributors

TF wrote the protocol. TF, ARC and RE were responsible for study concept, design and interpretation of findings. TF and SK managed the literature searches and summaries of previous related work. NS, DH, JH, SK contributed to acquisition of imaging and behavioral data, and data entry. ZW and JD optimized and monitored perfusion fMRI data acquisition. ZW, YL, NS, JH and TF analysed imaging data. TF wrote the first draft of the manuscript. All authors critically reviewed content and approved final version for publication.

Conflict of interest

Dr. J.A. Detre has received royalties for the commercial licensure of ASL perfusion fMRI. The following authors served as consultants within the past 2 years: TF (Pfizer, Abbott), CO (Abbott, Embera), AR (Abbott). None of the other authors have reported any potential conflicts of interest.

its potential to block drug-motivated behavior, in preclinical studies, and its putative effectiveness as an anti-craving/anti-relapse agent in humans.

Keywords

Baclofen; GABA B agonist; Resting baseline perfusion fMRI; Addiction; Limbic circuitry; Cerebral blood flow

1. Introduction

Numerous preclinical studies have examined the effects of the gamma-amino-butyric acid-B (GABA B) agonist, baclofen, on drug-seeking motivated behavior. Baclofen dose-dependently prevented self administration of several drugs of abuse (Roberts and Andrews, 1997; Shoaib et al., 1998; Spano et al., 2007), including nicotine (Corrigall et al., 2000; Fattore et al., 2002; Markou et al., 2004; Paterson et al., 2004), and inhibited dopamine (DA) release in rats trained to self administer nicotine, cocaine and morphine (Fadda et al., 2003).

Clinically, baclofen has shown potential for reducing drug-motivated behaviors, including craving and relapse in opiate (Assadi et al., 2003), cocaine (Gudeman et al., 1997; Ling et al., 1998; Shoptaw et al., 2003) amphetamine (Heinzerling et al., 2006), alcohol (Addolorato et al., 2000; Agabio et al., 2007; Colombo et al., 2000; Johnson et al., 2005; Malcolm, 2003), and most recently, marijuana addictions (Haney et al., 2010). In nicotine-dependent smokers, we observed reductions in the number of cigarettes smoked per day in a *Baclofen for Smoking Reduction* clinical trial (Franklin et al., 2009a).

Only one published neuroimaging study has examined the effects of baclofen on drug-motivated behavior. Using positron emission tomography and $O^{15}H_2O$, our laboratory demonstrated that baclofen reduced cocaine cue-induced craving, cocaine use, and brain activity (compared to nondrug cues) in the amygdala and orbitofrontal and anterior cingulate cortices (Brebner et al., 2002). This study prompted our further investigation into the effects of baclofen on the addicted brain – both in cocaine and nicotine addiction. Preliminary data acquired towards this goal suggested that baclofen reduced brain activity, in the nicotine-addicted brain in the resting state in the ventral striatum, medial orbitofrontal cortex, amygdala and the anterior ventral insula.

Based on the animal studies demonstrating that the effects of baclofen on drug-motivated behaviors are mediated through its property to reduce dopamine release in the VS and mPFC, the clinical studies showing that it is helpful in reducing craving and relapse, and the preliminary neuroimaging results, we hypothesized that chronic baclofen administration would reduce cerebral blood flow (CBF) in the brain at rest in the VS and its afferents including the medial orbitofrontal cortex (mOFC), amygdala and insula. Such knowledge might provide insight into its mechanism of action to reduce craving and decrease relapse rates in humans.

To test the hypothesis that baclofen would modulate RB blood flow, we acquired 5 min of resting baseline (RB) neural activity using continuous arterial spin labeled (CASL) perfusion fMRI in smokers before and following three weeks of chronic baclofen (or placebo) administration. Similar to positron emission tomography (PET), perfusion is quantitative, providing a measure of blood flow in ml of blood/100 g of tissue/min (Alsop and Detre, 1996), which facilitates the measurement of medication-induced neural modifications in the brain in the resting condition (without provocation) (Wang et al., 2007) at successive time points. A pharmacological manipulation can have profound effects on the brain that, with current technology, cannot be observed using a relative measure such as blood oxygen level

dependent (BOLD) fMRI, which can only accurately examine changes that occur within a scanning session during a task or other provocation. Perfusion is reliable and reproducible following intervals as great as seven weeks and is therefore ideal for longitudinal studies examining brain modifications induced by pharmacological agents (Hermes et al., 2007).

2. Methods

2.1. Subjects

The study was conducted at the Center for the Studies of Addictions, a University of Pennsylvania School of Medicine-affiliated outpatient treatment center. The RB data presented here were acquired in the context of an ongoing study examining the effects of baclofen on several brain/behavioral endpoints. All procedures were approved and monitored by the University Of Pennsylvania School of Medicine Institutional Review Board, and adhered to the Declaration of Helsinki. Smokers were compensated \$60.00 for the first scanning session (pre-administration) and \$90.00 for the second (following three weeks administration). Subjects were also compensated for weekly monitoring visits (\$6.00 for each appointment and \$5.00 for each returned medication card). Subjects were recruited by word of mouth and from a radio advertisement that specifically stated the study was for smokers contemplating quitting but not quite ready. Smokers were encouraged to set a Quit Date after the second scan and were invited to continue on medication for an additional 8 weeks. If uninterested, they were given other treatment options. Approximately 60% opted to continue treatment.

Subjects were screened, tested on study knowledge, and consented prior to psychological and physical evaluations. The Minnesota International Neuropsychiatric Interview [MINI (Sheehan et al., 1998)] was used to determine current DSM-IV diagnosis of psychoactive substance dependence other than nicotine and to diagnose current severe psychiatric symptoms. Individuals with other current psychoactive substance dependence or current DSM-IV psychiatric diagnoses were excluded. Severity of nicotine dependence was determined from a laboratory-developed Smoking History Questionnaire that included the Fagerstrom Test for Nicotine Dependence [FTND (Fagerstrom and Schneider, 1989)].

Individuals with an abnormal structural MRI, a history of head trauma or other injury resulting in loss of consciousness lasting greater than 3 min or associated with skull fracture or inter-cranial bleeding, or who had magnetically active objects on or within their body were excluded.

The sample consisted of twenty-one ($N=12$ females) smokers who were 62% African American (13) 33% European American (7) and 5% Multiple Ethnicity (1). Subjects were between the ages of 18 and 60 (38.6 ± 2.15) who met DSM-IV criteria for nicotine dependence [FTND: 5.3 ± 0.25 ; indicating moderate to high dependence]. Subjects smoked from 12 to 35 cigarettes per day (21.4 ± 1.33) at study start and averaged 13.6 ± 0.46 years of education.

2.2. Medication

Study medication was manufactured and donated by Murty Pharmaceuticals Inc., Lexington, KY. Study medication was prepared and maintained by the Institutional Drug Service (IDS) located at the Hospital of the University of Pennsylvania in capsules containing 10 mg baclofen or matching placebo that consisted of a dextrose matrix. The study physician dispensed the medication.

About 15% of individuals who take baclofen experience drowsiness, which may interfere with CNS or subjective responses (http://www.rxlist.com/cgi/generic/baclofen_ad.htm). To

minimize this effect the dose was titrated upwards to a dose of 20 mg of baclofen four times a day (80 mg total) over 12 days. This dose is the same as that used in Franklin et al. (2009a) demonstrating a reduction in cigarettes smoked per day in a smoking reduction trial, and is 20 mg higher than that used in earlier studies examining baclofen's effects on drug craving and relapse (Addolorato et al., 2007; Agabio et al., 2007; Ling et al., 1998). After the second scanning session at 3 weeks, the dose was tapered to discontinuation in reverse order of the induction schedule.

Adverse events, adherence to the dosing schedule and cigarette smoking behaviors were monitored by the subjects using a 'Daily Diary', by study staff during biweekly telephone calls, and by the study physician on days 4, 7, 14, 21 and 28 (follow up visit).

2.3. Design

Baclofen or placebo was prescribed to nonabstinent, nontreatment-seeking smokers as described above. The importance of using nontreatment-seeking smokers is twofold. First, our goal was to determine if and how baclofen affected resting baseline brain activity independent of withdrawal (symptoms of which last up to one month) (Hughes, 2007), as it has been shown that withdrawal itself can affect brain activity (Wang et al., 2007). Second, differences in smoking behavior modulate brain activity (Stein et al., 1998), so it is important that baclofen- and placebo-treated groups had similar smoking characteristics. Thus, issues related to withdrawal and quitting smoking, which might obviate accurate interpretation of the findings were minimized in this design.

2.3.1. Scanning procedures—Two scanning sessions were administered: One at randomization prior to medication administration, at Time 1 and the second on the 21st day of medication administration, at Time 2. Both scanning sessions were preceded by *ad lib* smoking, to minimize interference in signal related to craving and/or withdrawal and to standardize physiological and pharmacological states. For each session, a five-minute CASL perfusion scan was acquired approximately 15–20 min after smoking to ensure dissipation of the acute cardiovascular effects of smoking (Benowitz and Gourlay, 1997).

2.3.2. Imaging parameters—Data were acquired on a 3.0T Trio whole-body scanner (Siemens AG, Erlangen, Germany), using a standard Bruker volume coil (volume coils are designed to provide a homogenous receiving sensitivity and are 1 channel; Bruker Biospin, Billerica, MA). A T1-weighted 3D MPRAGE scan was acquired (FOV = 250 mm, TR/TE = 1620/3 ms, 192 × 256 matrix, slice thickness = 1 mm for anatomical co-registration and spatial normalization. CASL perfusion fMRI was used to acquire 5 min of resting baseline brain CBF (100 acquisitions). Interleaved images with and without labeling were obtained using a gradient echo echo-planar imaging sequence with a delay of 700 ms inserted between the end of the labeling pulse and image acquisition (FOV = 220 mm, matrix = 64 × 64, TR/TE = 3000/17 ms, flip angle = 90°, 14 sequential slices with thickness = 8 mm with a 2 mm inter-slice gap).

2.3.3. Data processing—An SPM-based (Wellcome Department of Cognitive Neurology, London, UK) ASL data processing toolbox (Wang et al., 2008) was used for data analyses as described previously (Franklin et al., 2007). Briefly, ASL image pairs were realigned to the mean of all control images and spatially smoothed with a 3D isotropic Gaussian kernel with full-width-half-magnitude of 10 mm. Fifty CBF image series were generated from the 50 label/control ASL image pairs using a simplified two-compartment model with the sinc interpolation method for CBF calculations (Aguirre et al., 2005). The mean control image of each subject's data was co-registered to the structural image using the mutual information based co-registration algorithm provided by SPM2. The same co-

registration parameters were also used to co-register the CBF maps to the structural image. The structural image was then spatially normalized to the Montreal Neurological Institute (MNI) standard brain. The same parameters were used to normalize the CBF images to the MNI standard space. Each subject's normalized mean control images were segmented using SPM2. The segmented gray matter masks were averaged and the overlap of subject's gray matter was extracted. This final mask was used for calculating global CBF for each session. The whole brain CBF value was also calculated from each CBF map, resulting in a global CBF value time series with 50 time points.

2.4. Statistical analyses

2.4.1. Brain analyses—Voxel-wise analyses of the CBF data were conducted on each subject, using a general linear model (GLM). Global CBF time course was included in the model at the individual level, at each time point as a nuisance covariate to examine the effects of baclofen on absolute regional blood flow independent of its global CBF effects. No temporal smoothing was applied. Contrasts between conditions (Time 1 vs. Time 2) were defined in the GLM model to assess the voxel by voxel CBF difference. Using the corresponding parametric maps of this contrast, random effects analysis was employed to test for a significant main effect of condition with a statistical parametric map of the T statistic at each voxel for population inference for each session for the placebo and baclofen groups (second-level analysis). A 2×2 factorial design matrix was used to assess the effects of the pharmacological manipulation by including the group (placebo or baclofen) and condition (Time 1 or Time 2) as the two factors. This two-stage analysis is theoretically equivalent to a two-way ANOVA (Penny and Friston, 2003).

For comparisons between conditions and/or groups only clusters with voxels having a height threshold exceeding $p < 0.0001$ (uncorrected), and an extent threshold of 20 contiguous voxels are reported. Coordinates are in MNI as provided by SPM and are those chosen from the suprathreshold voxel of each cluster using the Duvernoy Brain Atlas and the Atlas of the Human Brain as references (Duvernoy, 1999; Mai et al., 2008).

2.4.2. Demographics analyses—Continuous demographic variables were summarized, by calculating means and standard error measurements ($\bar{X} \pm \text{SEMs}$). Nominal demographic variables were summarized by calculating proportions and compared across groups using chi-square analyses.

3. Results

3.1. Demographics

Demographic characteristics of the sample and the separate groups are listed in Table 1. Differences between baclofen/placebo groups in ethnicity, sex, cigarettes smoked per day, pack years (a measure to quantify intensity of chronic cigarette exposure since smoking initiation) or other general demographic items were insignificant, with the exception of age.

3.2. Adverse events

T -tests for two-tailed distribution/unequal variance were used to determine if CNS results were related to adverse events associated with taking baclofen. There were no differences between baclofen/placebo groups in overall side effects not related to medication ($p = 0.73$), possibly related to medication ($p = 0.33$), or unlikely related to medication ($p = 0.11$). As sedation or drowsiness is the side effect most often associated with taking baclofen, sedation was analysed separately. There were no differences between groups in mild ($p = 0.20$) moderate ($p = 0.82$), or severe sedation (no severe sedation was reported).

3.3. Baclofen effects on resting brain CBF

Table 2 lists the brain regions, coordinates, *T* values and quantitative differences in CBF modulated by baclofen administration in the brain at rest independent of its global effects. Baclofen-induced decreases in CBF were observed selectively in the mOFC, insula and VS. Increases in CBF were observed in the cerebellum and several regions of the frontal cortex including the lateral OFC and the inferior, superior and ventral medial cortices. Both increases and decreases in blood flow were observed in distinct subregions of the cingulate. Fig. 1 shows representative coronal and sagittal sections depicting a subset of the baclofen-induced brain modifications. An interactive visual display of all brain data in all three planes can be found at <http://franklinbrainimaging.com>. There were no significant differences in RB CBF in the placebo group.

4. Discussion

Here we report that resting brain blood flow to the reward-relevant VS, mOFC and insula was significantly diminished by three weeks chronic administration of 80 mg of the GABA B agonist, baclofen. Baclofen increased CBF in the reward-evaluating lateral OFC and in the inferior, superior and ventral medial cortices. Both increases and decreases in blood flow were observed in distinct subregions of the large heterogeneous multi-functioned cingulate cortex. There were no differences in RB activity in the placebo group. Notably, the VS, mOFC and insula are regions that were consistently activated during smoking cue exposure in three independent perfusion fMRI smoking cue reactivity studies within our laboratory (Franklin et al., 2009b, 2007, 2011b).

This report provides insight into the neurobiological mechanisms underlying an agent that shows promise in reducing relapse, craving and/or withdrawal in opiate (Assadi et al., 2003), cocaine (Gudeman et al., 1997; Ling et al., 1998; Shoptaw et al., 2003) marijuana (Haney et al., 2010), and amphetamine (Heinzerling et al., 2006) addictions however see (Kahn et al., 2009). Baclofen has been studied more extensively in alcohol trials, showing potential for increasing treatment retention, decreasing withdrawal symptoms, and reducing craving and relapse (Addolorato et al., 2000; Agabio et al., 2007; Colombo et al., 2000; Johnson et al., 2005; Malcolm, 2003). To our knowledge we are the only research group who have published on the effects of chronic baclofen on the brain in the resting condition. In the singular study using position emission tomography and O^{15} H_2O it was shown that baclofen reduced cocaine cue-induced craving, cocaine use and brain activity during cue exposure in the amygdala, mOFC and anterior cingulate, consistent with the results reported here of baclofen's effects in the brain at rest (Brebner et al., 2002).

4.1. Potential roles of the brain structures affected by chronic baclofen administration

The VS and mOFC are consistently implicated in over thirty-five years of preclinical research as neurobiological substrates underlying conditioned responses to drugs of abuse (Balfour et al., 2000; Di Chiara, 2000). Numerous preclinical studies have examined the effects of baclofen on the dopaminergic reward system demonstrating its ability to block drug motivation and decrease drug-induced dopamine release in the VS. Importantly, microdialysis studies have confirmed that intra-VTA baclofen decreases extracellular dopamine in the VS and medial PFC (analogous to the mOFC in humans) (Enrico et al., 1998; Westerink et al., 1998; Yoshida et al., 1994), and dose-dependently reduced nicotine self administration (Corrigall et al., 2000; Corrigall et al., 2001). Further, systemic baclofen antagonizes nicotine-induced dopamine release in the VS (Fadda et al., 2003). Baclofen's modulatory actions on the same VS/mOFC dopamine driven reward-related circuitry on the brain at rest, and its confirmed actions on this circuitry in the animal literature provide

insight into the mechanisms underlying its capabilities to reduce drug-related behaviors in humans.

Baclofen also reduced CBF in the anterior ventral insula in the brain at rest. In light of recent findings, the insula is gaining considerable attention in the drug addiction field. Smokers who acquired lesions to the brain that included sizable portions of the insular cortex spontaneously quit smoking, while cigarette addiction was not disrupted in smokers with minimal damage to the insula (Naqvi et al., 2007). Furthermore, the smokers with large insula lesions reported an absence of craving for cigarettes while craving for other naturally rewarding substances, such as food, was left intact. Drug cues trigger craving in drug users that is associated with autonomic arousal (Robbins et al., 1997). Given that one function of the anterior ventral insula is to relay autonomic sensations to higher cortical processing structures (Craig, 2009), hyperactive insulas may potentiate increased autonomic arousal to ubiquitous smoking reminders, and increase vulnerability to higher dependence and increased risk of relapse in the presence of cues. Baclofen's actions to dampen activity in the ventral anterior insula may be helpful in suppressing overactive autonomic responses to cues.

Baclofen's effects extended beyond dampening activity in the VS/mOFC and insula to increasing CBF in frontal cortical cognitive control regions including the lateral OFC and inferior, superior and ventral medial cortices. Modulation of the lateral OFC is of particular interest as there is a substantial literature demonstrating that lateral prefrontal regions are involved in regulating impulses, re-evaluating previously rewarded behavior and modulating downstream limbic regions involved in motivated behavior (Elliott et al., 2000; Rolls, 2004; Small et al., 2001; Franklin et al., 2011a). Baclofen's reciprocal actions in the reward-activated mOFC and reward-evaluating lateral OFC extend hypotheses of two separate motivational systems within the OFC: the medial portion orchestrating approach to reward and reward-related stimuli and the lateral portion evaluating the consequences of past behavior, which may lead to a change in future behavior (Kringelbach and Rolls, 2004). Notably, in other work we found that the smoking cessation medication, varenicline activated lateral orbitofrontal cortex in the brain at rest and its activation predicted blunting of the medial orbitofrontal cortex and ventral striatum during smoking cue exposure.

The superior frontal cortex is another region shown to be reactive to smoking and other drug cues. For example, following overnight abstinence smokers demonstrated higher activation while exposed to smoking reminders in several regions (anterior cingulate, OFC, occipital cortex) including the superior frontal gyrus (McClernon et al., 2005). Franklin et al. (2009b) also demonstrated superior frontal gyrus involvement during smoking cue exposure, however its involvement was dependent on variance in the dopamine transporter. Considering baclofen's blunting effects on other regions (VS/mOFC/insula) activated during cue exposure, one would speculate that it might decrease, rather than increase, activity in this region similarly. However, the superior frontal cortex is multi-functional and has been shown to be activated by intravenous nicotine during fMRI (Stein et al., 1998), and its subcutaneous administration was associated with improved accuracy and response times in the cognitively demanding N-back task in both smokers and nonsmokers (Kumari et al., 2003). Inferior frontal and ventral medial cortices are regions that were also strongly activated by intravenous nicotine at low, medium and high doses in fMRI (Stein et al., 1998) and showed increased CBF to nasal nicotine spray using positron emission tomography (PET) and [0-15]H₂O (Domino et al., 2000). Given the role of these regions in attention, similar hypotheses generated regarding the superior frontal cortex may also apply in this instance.

Baclofen-induced RB increases in CBF were also observed in the cerebellum and may be an important mechanism underlying baclofen's potential effectiveness as a treatment for addiction. Several neuroimaging studies have suggested a role for the cerebellum in craving including cocaine, (Grant et al., 1996; Kilts et al., 2001; Bonson et al., 2002), alcohol (Schneider et al., 2001) and nicotine (Franklin et al., 2009b). Two studies observed lower gray matter densities in the cerebellum of smokers compared to nonsmokers. In both studies cerebellar volume was inversely correlated with smoking history as assessed by pack-years (Brody et al., 2004; Gazdzinski et al., 2005). Others have shown that cerebellar volume is reduced in cocaine abusers and that the reductions correlated with longer duration of cocaine use (Sim et al., 2007). One might speculate that baclofen's enhancing effects on cerebellar activity may produce neurotrophic effects with chronic use, correcting vulnerabilities underlying addictive behavior. This possibility warrants further investigation as both medication and behavioral regimens may alter brain structure (Bearden et al., 2008; Boyke et al., 2008; Driemeyer et al., 2008; Yucel et al., 2008).

Baclofen had a strong suppressing effect on blood flow in a large cluster in the mid-to-posterior region of the anterior cingulate, with equivalent but opposite effects on the visuospatial region of the posterior cingulate. The cingulate is a large cytoarchitecturally heterogeneous structure with varied functions related to emotional, sensory, motor and cognitive processes. A functional dichotomy has emerged such that anterior regions have been demonstrated to be involved in executive functioning whereas posterior regions are involved in evaluative processes. The anterior portion is reciprocally connected with the 'emotive' amygdala and participates in responses to emotional stimuli, such as pain (Vogt and Sikes, 2000) and craving for drugs (Childress et al., 1999; Franklin et al., 2009b; Wilson et al., 2005) and leads to emotionally charged motivated behavior. Elevated anterior cingulate cortex activity is associated with obsessive-compulsive behaviors and aberrant social behavior (Devinsky et al., 1995). The posterior region, which is reciprocally connected with the 'memory-laden' hippocampus is involved in spatial orientation and memory and thus is evaluative in nature. Baclofen's reciprocal effects on the cingulate may act to diminish the effects of emotional stimuli on future behavior (decreased anterior CBF) while simultaneously enhancing the ability to recall the negative consequences associated with behaviors that were motivated by stimuli in past situations (increased posterior CBF). Baclofen's dual but opposing effects on resting blood flow in the functionally dichotomous cingulate may inform medications' development to correct vulnerabilities for addictive and other compulsive/impulsive disorders.

Although the evidence cited above theoretically supports the hypothesis that baclofen's effects on select brain regions influences behavior, it is equally possible that some of the observed effects are nonspecific. To test whether effects are related to drug-motivated behavior, one could acquire a RB perfusion fMRI scan and a brain scan acquired during exposure to drug cues. To demonstrate specificity, regional changes in RB should predict the responses to drug cues in *a priori* regions. We are currently acquiring data in this regard to enhance our understanding of the mechanism underlying baclofen's possible utility as a medication to treat addiction.

4.2. Strengths

This blinded placebo controlled study was specifically conducted in nontreatment seekers to reduce confounds in brain activation introduced by attempts to quit, or a change in nicotine/cigarette intake during the study. Interestingly, both placebo and baclofen groups reduced their number of cigarettes smoked per day (CPD), without differences between groups at Time 2. If indeed baclofen may aid in smoking cessation one might speculate that the baclofen group would spontaneously quit smoking or reduce their cigarette consumption. However, there is considerable variability in human smoking behavior (puff duration, puff

volume, puff interval, vent blocking) and it is conceivable that baclofen- and placebo-treated smokers did differ in the actual amount of nicotine and other tobacco constituents that were consumed over the course of the medication regimen. As all subjects smoked a cigarette prior to the scanning sessions, we feel that any potential differences in smoking behavior were minimized and any residual effects are unrelated to the findings.

4.3. Limitations

This study was conducted in a relatively small number of individuals, which may be considered a limitation. However, it was performed using a double-blind placebo-controlled design and results are strong and highly consistent with the animal literature, providing support that the findings are reliable.

The question arises as to whether the effects of baclofen on RB in smokers would generalize to nonsmokers without other addictions, or does it normalize tone in addicted individuals with vulnerabilities in the affected areas? This is an important question that could and should be tested with the appropriate control groups. However, the demonstration of baclofen's modulatory effects in brain regions involved in addictive processes is an important finding and relevant to the study of cigarette and other drug addictions.

4.4. Conclusions

This study and the convergence of existing preclinical, clinical and brain imaging data suggest that baclofen may be beneficial in aiding drug users to resist the urge to use, which should reduce relapse rates. Baclofen is FDA-approved; its long-acting formulations, which would improve compliance, have completed Phase III clinical trials in both Parkinson's and Multiple Sclerosis patients (<http://www.medicalnewstoday.com/articles/146910.php>, accessed, <http://impaxpharma.com/spasticity.php>, accessed); it shows no evidence of abuse potential (Addolorato et al., 2000; Griffiths et al., 1991; Haubenstock et al., 1983); it has few side effects other than initial mild sedation (Physician's Desk Reference, 1993), although see (Franklin et al., 2009a; Kahn et al., 2009) wherein no medication-related adverse events were observed; and its safety and tolerability has been clearly established in non-addicts and in nicotine, cocaine, and alcohol dependent individuals (Aisen et al., 1992; Johnson et al., 2005; Kahn et al., 2009; Taricco et al., 2000).

Minimizing relapse rates and maximizing abstinence is crucial to the health of our nation and may be hastened by exploiting existing (and safe) medications, such as baclofen, that are potentially beneficial for drug addiction. Moreover, this study highlights the feasibility that the use of perfusion fMRI of the resting state can be used to examine the effects of a pharmacological intervention on the brain, and potentially provide knowledge of underlying mechanism and its link with behavioral responses.

Acknowledgments

Role of funding source

Work supported by NIH grants DA015149, K01 DA 015426-01A1, 5-P60-DA-005186-18, and NS045839, BCS-0224007, RR02305, The Alexander Foundation and the GCRC of the University of Pennsylvania

The authors wish to acknowledge the nursing staff at the University of Pennsylvania Center for the Studies of Addiction for conducting physical evaluations and medication monitoring. We also would like to thank our clinicians Anita Hole Ph.D., Jesse Suh, Psy. D., and Marta MacDougal, Psy. D for conducting the psychological evaluations. And third, we take this opportunity to thank the MRI technicians at the Hospital of the University of Pennsylvania for conducting the scanning sessions.

We wish to thank Moo Park, Ph.D., Chemist and Nora Chiang, Ph.D. Chief of Chemistry & Pharmaceuticals Branch NIH/NIDA/DPMC and Murty Pharmaceuticals for providing baclofen and matching placebo tablets.

References

- Addolorato G, Caputo F, Capristo E, Colombo G, Gessa GL, Gasbarrini G. Ability of baclofen in reducing alcohol craving and intake: II—preliminary clinical evidence. *Alcohol Clin Exp Res*. 2000; 24:67–71. [PubMed: 10656195]
- Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet*. 2007; 370:1915–1922. [PubMed: 18068515]
- Agabio R, Marras P, Addolorato G, Carpiello B, Gessa GL. Baclofen suppresses alcohol intake and craving for alcohol in a schizophrenic alcohol-dependent patient: a case report. *J Clin Psychopharmacol*. 2007; 27:319–320. [PubMed: 17502794]
- Aguirre GK, Detre JA, Wang J. Perfusion fMRI for functional neuroimaging. *Int Rev Neurobiol*. 2005; 66:213–236. [PubMed: 16387205]
- Aisen ML, Dietz MA, Rossi P, Cedarbaum JM, Kutt H. Clinical and pharmacokinetic aspects of high dose oral baclofen therapy. *J Am Paraplegia Soc*. 1992; 15:211–216. [PubMed: 1431867]
- Alsop DC, Detre JA. Reduced transit-time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow. *J Cereb Blood Flow Metab*. 1996; 16:1236–1249. [PubMed: 8898697]
- Assadi SM, Radgoodarzi R, Ahmadi-Abhari SA. Baclofen for maintenance treatment of opioid dependence: a randomized double-blind placebo-controlled clinical trial [ISRCTN32121581]. *BMC Psychiatry*. 2003; 3:16. [PubMed: 14624703]
- Balfour DJ, Wright AE, Benwell ME, Birrell CE. The putative role of extra-synaptic mesolimbic dopamine in the neurobiology of nicotine dependence. *Behav Brain Res*. 2000; 113:73–83. [PubMed: 10942034]
- Bearden CE, Thompson PM, Dutton RA, Frey BN, Peluso MA, Nicoletti M, Dierschke N, Hayashi KM, Klunder AD, Glahn DC, Brambilla P, Sassi RB, Mallinger AG, Soares JC. Three-dimensional mapping of hippocampal anatomy in unmedicated and lithium-treated patients with bipolar disorder. *Neuropsychopharmacology*. 2008; 33:1229–1238. [PubMed: 17687266]
- Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol*. 1997; 29:1422–1431. [PubMed: 9180099]
- Bonson KR, Grant SJ, Contoreggi CS, Links JM, Metcalfe J, Weyl HL, Kurian V, Ernst M, London ED. Neural systems and cue-induced cocaine craving. *Neuropsychopharmacology*. 2002; 26:376–386. [PubMed: 11850152]
- Boyke J, Driemeyer J, Gaser C, Buchel C, May A. Training-induced brain structure changes in the elderly. *J Neurosci*. 2008; 28:7031–7035. [PubMed: 18614670]
- Brebner K, Childress AR, Roberts DC. A potential role for GABA(B) agonists in the treatment of psychostimulant addiction. *Alcohol Alcohol*. 2002; 37:478–484. [PubMed: 12217943]
- Brody AL, Mandelkern MA, Jarvik ME, Lee GS, Smith EC, Huang JC, Bota RG, Bartzokis G, London ED. Differences between smokers and nonsmokers in regional gray matter volumes and densities. *Biol Psychiatry*. 2004; 55:77–84. [PubMed: 14706428]
- Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. *Am J Psychiatry*. 1999; 156:11–18. [PubMed: 9892292]
- Colombo G, Agabio R, Carai MA, Lobina C, Pani M, Reali R, Addolorato G, Gessa GL. Ability of baclofen in reducing alcohol intake and withdrawal severity: I—preclinical evidence. *Alcohol Clin Exp Res*. 2000; 24:58–66. [PubMed: 10656194]
- Corrigall WA, Coen KM, Adamson KL, Chow BL, Zhang J. Response of nicotine self-administration in the rat to manipulations of mu-opioid and gamma-aminobutyric acid receptors in the ventral tegmental area. *Psychopharmacology (Berl)*. 2000; 149:107–114. [PubMed: 10805604]
- Corrigall WA, Coen KM, Zhang J, Adamson KL. GABA mechanisms in the pedunculopontine tegmental nucleus influence particular aspects of nicotine self-administration selectively in the rat. *Psychopharmacology (Berl)*. 2001; 158:190–197. [PubMed: 11702093]

- Craig AD. How do you feel-now? The anterior insula and human awareness. *Nat Rev Neurosci*. 2009; 10:59–70. [PubMed: 19096369]
- Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995; 118:279–306. [PubMed: 7895011]
- Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. *Eur J Pharmacol*. 2000; 393:295–314. [PubMed: 10771025]
- Domino EF, Minoshima S, Guthrie S, Ohl L, Ni L, Koeppe RA, Zubieta JK. Nicotine effects on regional cerebral blood flow in awake, resting tobacco smokers. *Synapse*. 2000; 38:313–321. [PubMed: 11020234]
- Driemeyer J, Boyke J, Gaser C, Buchel C, May A. Changes in gray matter induced by learning—revisited. *PLoS One*. 2008; 3:e2669. [PubMed: 18648501]
- Duvernoy, HM. *The Human Brain: Surface, Three-Dimensional Sectional Anatomy with Magnetic Resonance Imaging and Blood Supply*. Springer-Verlag; Wien, New York: 1999.
- Elliott R, Dolan RJ, Frith CD. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cereb Cortex*. 2000; 10:308–317. [PubMed: 10731225]
- Enrico P, Bouma M, de Vries JB, Westerink BH. The role of afferents to the ventral tegmental area in the handling stress-induced increase in the release of dopamine in the medial prefrontal cortex: a dual-probe microdialysis study in the rat brain. *Brain Res*. 1998; 779:205–213. [PubMed: 9473673]
- Fadda P, Scherma M, Fresu A, Collu M, Fratta W. Baclofen antagonizes nicotine-, cocaine-, and morphine-induced dopamine release in the nucleus accumbens of rat. *Synapse*. 2003; 50:1–6. [PubMed: 12872287]
- Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. *J Behav Med*. 1989; 12:159–182. [PubMed: 2668531]
- Fattore L, Cossu G, Martellotta MC, Fratta W. Baclofen antagonizes intravenous self-administration of nicotine in mice and rats. *Alcohol*. 2002; 37:495–498.
- Franklin TR, Wang Z, Wang J, Sciortino N, Harper D, Li Y, Ehrman R, Kampman K, O'Brien CP, Detre JA, Childress AR. Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. *Neuropsychopharmacology*. 2007; 32:2301–2309. [PubMed: 17375140]
- Franklin TR, Harper D, Kampman K, Kildea-McCrea S, Jens W, Lynch KG, O'Brien CP, Childress AR. The GABA B agonist baclofen reduces cigarette consumption in a preliminary double-blind placebo-controlled smoking reduction study. *Drug Alcohol Depend*. 2009a; 103:30–36. [PubMed: 19398283]
- Franklin TR, Lohoff FW, Wang Z, Sciortino N, Harper D, Li Y, Jens W, Cruz J, Kampman K, Ehrman R, Berrettini W, Detre JA, O'Brien CP, Childress AR. DAT genotype modulates brain and behavioral responses elicited by cigarette cues. *Neuropsychopharmacology*. 2009b; 34:717–728. [PubMed: 18704100]
- Franklin TR, Wang Z, Suh J, Hazan R, Cruz J, Li Y, Goldman M, Detre JA, O'Brien CP, Childress A. Effects of varenicline on smoking cue-triggered neural and craving responses. *Arch Gen Psychiatry*. 2011a10.1001/archgenpsychiatry.2010.190
- Franklin TR, Wang Z, Li Y, Suh J, Goldman M, Lohoff F, Cruz J, Hazan R, Jens W, Detre JA, Berrettini W, O'Brien CP, Childress AR. Dopamine transporter genotype modulation of neural responses to smoking cues: Confirmation in a new cohort. *Addiction Biology*. 2011b 2011. 10.1111/j.1369-1600.2010.00277.x
- Gazdzinski S, Durazzo TC, Studholme C, Song E, Banys P, Meyerhoff DJ. Quantitative brain MRI in alcohol dependence: preliminary evidence for effects of concurrent chronic cigarette smoking on regional brain volumes. *Alcohol Clin Exp Res*. 2005; 29:1484–1495. [PubMed: 16131857]
- Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, Phillips RL, Kimes AS, Margolin A. Activation of memory circuits during cue-elicited cocaine craving. *Proc Natl Acad Sci USA*. 1996; 93:12040–12045. [PubMed: 8876259]

- Griffiths RR, Lamb RJ, Sannerud CA, Ator NA, Brady JV. Self-injection of barbiturates, benzodiazepines and other sedative-anxiolytics in baboons. *Psychopharmacology (Berl)*. 1991; 103:154–161. [PubMed: 1674158]
- Gudeman, D.; Shoptaw, S.; Majewska, D.; Scherf, S.; Yeats, D.; Ling, W. Preliminary report of Baclofen as a cocaine craving medication. *Proceedings of the Problems of Drug Dependence* 1996, NIH, NIDA; Rockville, M.D. 1997.
- Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Cooper ZD, Foltin RW. Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. *Psychopharmacology (Berl)*. 2010; 211:233–244. [PubMed: 20521030]
- Haubenstock A, Hruby K, Jager U, Lenz K. Baclofen (Lioresal) intoxication report of 4 cases and review of the literature. *J Toxicol Clin Toxicol*. 1983; 20:59–68. [PubMed: 6887300]
- Heinzerling KG, Shoptaw S, Peck JA, Yang X, Liu J, Roll J, Ling W. Randomized, placebo-controlled trial of baclofen and gabapentin for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. 2006; 85:177–184. [PubMed: 16740370]
- Hermes M, Hagemann D, Britz P, Lieser S, Rock J, Naumann E, Walter C. Reproducibility of continuous arterial spin labeling perfusion MRI after 7 weeks. *MAGMA*. 2007; 20:103–115. [PubMed: 17429703]
- Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res*. 2007; 9:315–327. [PubMed: 17365764]
- Johnson BA, Swift RM, Addolorato G, Ciraulo DA, Myrick H. Safety and efficacy of GABAergic medications for treating alcoholism. *Alcohol Clin Exp Res*. 2005; 29:248–254. [PubMed: 15714047]
- Kahn R, Biswas K, Childress AR, Shoptaw S, Fudala PJ, Gorgon L, Montoya I, Collins J, McSherry F, Li SH, Chiang N, Alathari H, Watson D, Liberto J, Beresford T, Stock C, Wallace C, Gruber V, Elkashef A. Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug Alcohol Depend*. 2009; 103:59–64. [PubMed: 19414226]
- http://www.rxlist.com/cgi/generic/baclofen_ad.htm Index, R.T.i.D., 2010. *Kemstro, Side Effects and Drug Interactions*. Accessed on http://www.rxlist.com/cgi/generic/baclofen_ad.htm.
- Kilts CD, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F, Ely TD, Hoffman JM, Drexler KP. Neural activity related to drug craving in cocaine addiction. *Arch Gen Psychiatry*. 2001; 58:334–341. [PubMed: 11296093]
- Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol*. 2004; 72:341–372. [PubMed: 15157726]
- Kumari V, Gray JA, ffytche DH, Mitterschiffthaler MT, Das M, Zachariah E, Vythelingum GN, Williams SC, Simmons A, Sharma T. Cognitive effects of nicotine in humans: an fMRI study. *Neuroimage*. 2003; 19:1002–1013. [PubMed: 12880828]
- Ling W, Shoptaw S, Majewska D. Baclofen as a cocaine anti-craving medication: a preliminary clinical study. *Neuropsychopharmacology*. 1998; 18:403–404. [PubMed: 9536455]
- Mai, JK.; Voss, T.; Paxinos, G. *Atlas of the Human Brain*. Elsevier Academic Press; New York; London: 2008.
- Malcolm RJ. GABA systems, benzodiazepines, and substance dependence. *J Clin Psychiatry*. 2003; 64(Suppl 3):36–40. [PubMed: 12662132]
- Markou A, Paterson NE, Semenova S. Role of gamma-aminobutyric acid (GABA) and metabotropic glutamate receptors in nicotine reinforcement: potential pharmacotherapies for smoking cessation. *Ann N Y Acad Sci*. 2004; 1025:491–503. [PubMed: 15542754]
- McClernon FJ, Hiott FB, Huettel SA, Rose JE. Abstinence-induced changes in self-report craving correlate with event-related FMRI responses to smoking cues. *Neuropsychopharmacology*. 2005; 30 (10):1940–1947. [PubMed: 15920499]
- Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking. *Science*. 2007; 315:531–534. [PubMed: 17255515]
- Paterson NE, Froestl W, Markou A. The GABAB receptor agonists baclofen and CGP44532 decreased nicotine self-administration in the rat. *Psychopharmacology (Berl)*. 2004; 172:179–186. [PubMed: 14610636]

- Penny W, Friston K. Mixtures of general linear models for functional neuroimaging. *IEEE Trans Med Imaging*. 2003; 22 (4):504–514. [PubMed: 12774896]
- Montvale: Medical Economics Data. 47. 1993. Physician's Desk Reference.
- Robbins SJ, Ehrman RN, Childress AR, O'Brien CP. Relationships among physiological and self-report responses produced by cocaine-related cues. *Addict Behav*. 1997; 22:157–167. [PubMed: 9113211]
- Roberts DC, Andrews MM. Baclofen suppression of cocaine self-administration: demonstration using a discrete trials procedure. *Psychopharmacology (Berl)*. 1997; 131:271–277. [PubMed: 9203238]
- Rolls ET. The functions of the orbitofrontal cortex. *Brain Cogn*. 2004; 55:11–29. [PubMed: 15134840]
- Schneider F, Habel U, Wagner M, Franke P, Salloum JB, Shah NJ, Toni I, Sulzbach C, Honig K, Maier W, Gaebel W, Zilles K. Subcortical correlates of craving in recently abstinent alcoholic patients. *Am J Psychiatry*. 2001; 158:1075–1083. [PubMed: 11431229]
- Sheehan B, Lecrubier Y, Sheehan K. The Mini International Neuropsychiatric Interview (MINI): the development and validation of structured diagnostic interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998; 59:22–33. [PubMed: 9881538]
- Shoaib M, Swanner LS, Beyer CE, Goldberg SR, Schindler CW. The GABAB agonist baclofen modifies cocaine self-administration in rats. *Behav Pharmacol*. 1998; 9:195–206. [PubMed: 9832934]
- Shoptaw S, Yang X, Rotheram-Fuller EJ, Hsieh YC, Kintaudi PC, Charuvastra VC, Ling W. Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. *J Clin Psychiatry*. 2003; 64:1440–1448. [PubMed: 14728105]
- Sim ME, Lyoo IK, Streeter CC, Covell J, Sarid-Segal O, Ciraulo DA, Kim MJ, Kaufman MJ, Yurgelun-Todd DA, Renshaw PF. Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. *Neuropsychopharmacology*. 2007; 32:2229–2237. [PubMed: 17299505]
- Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Changes in brain activity related to eating chocolate: from pleasure to aversion. *Brain*. 2001; 124:1720–1733. [PubMed: 11522575]
- Spano MS, Fattore L, Fratta W, Fadda P. The GABAB receptor agonist baclofen prevents heroin-induced reinstatement of heroin-seeking behavior in rats. *Neuropharmacology*. 2007; 52:1555–1562. [PubMed: 17451755]
- Stein EA, Pankiewicz J, Harsch HH, Cho JK, Fuller SA, Hoffmann RG, Hawkins M, Rao SM, Bandettini PA, Bloom AS. Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. *Am J Psychiatry*. 1998; 155:1009–1015. [PubMed: 9699686]
- Taricco M, Adone R, Pagliacci C, Telaro E. 2000Pharmacological interventions for spasticity following spinal cord injury. *Cochrane Database Syst Rev*. :CD001131. [PubMed: 10796750]
- Vogt BA, Sikes RW. The medial pain system, cingulate cortex, and parallel processing of nociceptive information. *Prog Brain Res*. 2000; 122:223–235. [PubMed: 10737061]
- Wang Z, Faith M, Patterson F, Tang K, Kerrin K, Wileyto EP, Detre JA, Lerman C. Neural substrates of abstinence-induced cigarette cravings in chronic smokers. *J Neurosci*. 2007; 27:14035–14040. [PubMed: 18094242]
- Wang Z, Aguirre GK, Rao H, Wang J, Fernandez-Seara MA, Childress AR, Detre JA. Empirical optimization of ASL data analysis using an ASL data processing toolbox: ASLtbx. *Magn Reson Imaging*. 2008; 26:261–269. [PubMed: 17826940]
- Westerink BH, Enrico P, Feimann J, De Vries JB. The pharmacology of mesocortical dopamine neurons: a dual-probe microdialysis study in the ventral tegmental area and prefrontal cortex of the rat brain. *J Pharmacol Exp Ther*. 1998; 285:143–154. [PubMed: 9536004]
- Wilson SJ, Sayette MA, Delgado MR, Fiez JA. Instructed smoking expectancy modulates cue-elicited neural activity: a preliminary study. *Nicotine Tob Res*. 2005; 7:637–645. [PubMed: 16085533]
- Yoshida M, Yokoo H, Tanaka T, Emoto H, Tanaka M. Opposite changes in the mesolimbic dopamine metabolism in the nerve terminal and cell body sites induced by locally infused baclofen in the rat. *Brain Res*. 1994; 636:111–114. [PubMed: 8156399]

Yucel K, Taylor VH, McKinnon MC, Macdonald K, Alda M, Young LT, Mac-Queen GM. Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology*. 2008; 33:361–367. [PubMed: 17406649]

Fig. 1.

Representative fMR coronal and sagittal images of neural activity following 3 weeks chronic baclofen (80 mg per day, Time 2) compared to pre-baclofen administration (Time 1). Data were analysed in SPM2 and are displayed in MRICRO. Crosshairs are centered on the suprathreshold voxel of representative significant clusters. Images are displayed neurologically (left is left). Abbrev: A Cing, anterior cingulate; Cb, cerebellum; Lat, lateral; OFC, orbitofrontal cortex; P, posterior; V, ventral. Hot colors indicate areas of increased perfusion. Cool colors indicate areas of decreased perfusion. T values range from -7.26 to $+6.40$ at $p = 0.001$, 20 contiguous voxels. For an interactive visual display of all brain data in all three planes go to <http://franklinbrainimaging.com>.

Table 1General characteristics of study participants (means $\pm$ SEM).

Characteristics	All <i>N</i> = 21	Baclofen <i>N</i> = 10	Placebo <i>N</i> = 11	<i>p</i> value
Sex	Males: 9	Males: 4	Males: 5	
	Female: 12	Female: 6	Female: 6	
Race	Black: 13	Black: 6	Black: 7	
	White: 7	White: 4	White: 3	
	Multiple: 1	Multiple: 0	Multiple: 1	
Age	38.6 $\pm$ 2.15	34.3 $\pm$ 3.1	42.8 $\pm$ 2.6	0.05
Education	13.6 $\pm$ 0.46	13.0 $\pm$ 0.7	14.3 $\pm$ 0.6	0.15
BDI	4.8 $\pm$ 0.99	4.4 $\pm$ 1.7	5.2 $\pm$ 1.2	0.68
CPD at Time 1	21.4 $\pm$ 1.33	21.0 $\pm$ 2.0	21.8 $\pm$ 1.8	0.81
CPD at Time 2	11.9 $\pm$ 1.38	12.2 $\pm$ 2.6	11.6 $\pm$ 1.4	0.86
Years since initiating smoking	20.1 $\pm$ 2.03	17.7 $\pm$ 3.8	22.5 $\pm$ 1.8	0.29
Pack years	22.4 $\pm$ 3.11	19.3 $\pm$ 5.0	25.4 $\pm$ 3.9	0.45
FTND scores	5.3 $\pm$ 0.25	5.2 $\pm$ 0.5	5.4 $\pm$ 0.30	0.56

Table 2

Baclofen-induced modulation of the brain in the resting state.

	X	Y	Z	T value	Post > Pre
<i>Regional increases</i>					
Cerebellum	-3	-46	-38	5.03	5.96 ± 1.80
Cingulate					
Anterior	13	-28	47	3.52	4.88 ± 1.66
Posterior	-9	-56	42	6.40	5.00 ± 2.22
Frontal cortex					
Lateral OFC	37	48	-9	4.93	12.34 ± 3.40
Inferior, Left	-16	61	-3	5.52	15.31 ± 4.61
Superior, Right	16	-52	72	4.40	4.60 ± 1.00
Ventral medial prefrontal, Right	13	-28	47	5.62	17.02 ± 6.40
Dorsolateral prefrontal	-51	24	33	5.14	10.50 ± 3.55
<i>Regional decreases</i>					
Cingulate					Pre > Post
Dorsal supragenual	-1	1	31	-6.97	-7.28 ± 2.45
Frontal cortex					
Medial orbitofrontal					
Left	-14	43	-15	-6.97	-11.29 ± 4.33
Left	-5	18	-7	-7.26	-10.00 ± 6.66
Right	11	42	-15	-6.79	-7.19 ± 8.23
Right	12	45	-20	-4.82	-6.34 ± 6.33
Insula					
Anterior ventral					
Left	-55	9	-18	-6.47	-6.80 ± 2.1
Right	52	15	-18	-4.49	-7.21 ± 2.4
Temporal Cortex	-54	0	-26	-7.00	-5.96 ± 1.56
Ventral Striatum					
Left	-6	14	-9	-5.24	-5.02 ± 1.79
Right	7	14	-11	-3.45	-4.97 ± 3.45

Regions are listed in alphabetical order. $p = 0.0001$, corrected at the cluster level, extent threshold of 20 contiguous voxels. Coordinates are in MNI as provided by SPM and are those chosen from the suprathreshold voxel of each cluster. The means of the change scores in cerebral blood flow from Time 1 (following 21 days of medication) to Time 2 (prior to the medication regimen) are listed in ml of blood/100 g of tissue/min. $N = 10$ baclofen-treated subjects.