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Acute baclofen diminishes resting baseline blood flow to limbic structures: A perfusion fMRI study

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Abstract

Background—Preclinical and clinical evidence show that the GABA B agonist, baclofen is a promising treatment for addictive disorders; however, until recently its mechanism of action in the human brain was unknown. In previous work we utilized a laboratory model that included a medication *versus* placebo regimen to examine baclofen's actions on brain circuitry. Perfusion fMRI [measure of cerebral blood flow (CBF)] data acquired 'at rest' before and on the last day of the 21-day medication regimen showed that baclofen diminished CBF bilaterally in the VS, insula and medial orbitofrontal cortex (mOFC). In the present study, we hypothesized that a single dose of baclofen would have effects similar to repeated dosing.

Methods—To test our hypothesis, in a crossover design, CBF data were acquired using *pseudo* continuous arterial spin labeled (*pCASL*) perfusion fMRI. Subjects were either un-medicated or were administered a 20 mg dose of baclofen approximately 110 min prior to scanning.

Results—Acute baclofen diminished mOFC, amygdala, and ventral anterior insula CBF without causing sedation (family-wise error corrected at $p = 0.001$).

Conclusions—Results demonstrate that similar to repeated dosing, an acute dose of baclofen blunts the 'limbic' substrate that is hyper-responsive to drugs and drug cues. Smokers often manage their craving and can remain abstinent for extended periods after quitting, however the risk of eventual relapse approaches 90%. Given that chronic medication may not be a practical solution to the long-term risk of relapse, acute baclofen may be useful on an 'as-needed' basis to block craving during 'at risk' situations.

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Contributors

TF wrote the protocol. TF and ARC were responsible for study concept, design and implementation. TF, ZW, JJS, JAD and ARC interpreted findings. TF, JS and KJ managed the literature searches and summaries of previous related work. JS screened and consented subjects, conducted the imaging sessions, and entered behavioral data. ZW and JAD optimized and monitored perfusion fMRI data acquisition. ZW and KJ analyzed imaging data. TF wrote the first draft of the manuscript and is responsible for all of the manuscript content. All authors critically reviewed content and approved final version for publication.

Conflict of interest

Dr. J.A. Detre is an inventor on the University of Pennsylvania's patent for ASL MRI and has received royalties for its commercial licensure. None of the other authors have reported any potential conflicts of interest.

Keywords

Addiction; fMRI; GABA B agonist; Cerebral blood flow; Smoking cessation; Treatment; Baclofen

1. Introduction

Drug addiction, including nicotine dependence, is a chronic relapsing disorder, resulting in devastating social, economic and health consequences. Indeed, only 1–11% of cigarette smokers who seek treatment are smoke-free at one-year follow-up (Hughes et al., 2003). Typical treatments range from 6 to 12 weeks with follow-up at 6 and 12 months. Thus, individuals afflicted with cigarette addiction are left unprotected to combat their cravings, until most individuals ultimately relapse. Withdrawal-based and cue-based cravings are two primary motivators to relapse (Baker et al., 1986; Caggiula et al., 2001; Killen and Fortmann, 1997). Withdrawal abates within 4 weeks but cravings elicited by smoking reminders can continue months and even years after cessation (Hughes, 2007). Although remaining on medication throughout life is an option and could potentially reduce relapse rates, smokers who are initially successful in quitting often feel as if they conquered their addiction. Consequently, compliance with a chronic medication may be less than optimal. Lapses often occur in “risky” situations, such as circumstances and events that are repeatedly associated with smoking. The conditioned brain and behavioral responses resulting from past and repeated ‘pairings’ of smoking with these events/reminders precipitates a lapse, and in most cases, relapse. This pattern may recur multiple times in a remitted smokers life –or could it be prevented? If strategies existed for ‘cue-vulnerable’ smokers other than protracted pharmacological treatments, they could, in theory, enjoy a life free of smoking and improved health without life-long medication maintenance. One possible strategy is to use ‘targeted treatment’ (*i.e.*, on an “as-needed” basis), which has been used successfully with naltrexone in heavy drinkers who wanted to control their drinking in high-risk drinking situations (Kranzler et al., 1997, 2009). Smoking cessation has immediate and substantial health benefits and dramatically reduces the risk of most smoking-related diseases. For example, within one year after quitting, the risk of coronary heart disease decreases by 50%. Within 15 years of quitting, the relative risk of dying from this disease approaches that of a lifetime non-smoker (US Department of Health and Human Services). The improved health benefits received from quitting smoking underscore the importance of identifying effective treatments to battle this chronic relapsing disorder.

Baclofen is a gamma-aminobutyric acid subunit B (GABA B) agonist that has been studied extensively in animal models of addiction with consistent results. With over 30 preclinical investigations of effects on drug-seeking and drug-taking behavior, baclofen dose-dependently prevents 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 inhibits dopamine (DA) release in nicotine, cocaine and morphine-dependent rats (Fadda et al., 2003). Most recently, Fattore and colleagues reported that baclofen dose-dependently blocked nicotine-induced reinstatement of self-administration and conditioned place preference, both of which are animal models of relapse (Fattore et al., 2009). Baclofen reduces drug-reinforced behavior at doses that do not affect responding for food, water, or mobility suggesting that it is not sedating and does not disturb normal activity (Fattore et al., 2009; Roberts and Andrews, 1997; Roberts et al., 1996; Spano et al., 2007).

Clinically, baclofen (FDA-approved for other indications and available in generic form) has shown potential for reducing drug-motivated behaviors, including craving and relapse in opiate (Assadi et al., 2003), cocaine (Ling et al., 1998; Shoptaw et al., 2003) and

amphetamine (Heinzerling et al., 2006) addictions however, in a multi-site trial of baclofen for cocaine dependence treatment outcome was not different between baclofen-treated and placebo-treated subjects (Kahn et al., 2009). Baclofen has been studied more extensively in alcohol trials, showing promise in 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). In nicotine-dependent smokers, we previously observed reductions in the number of cigarettes smoked per day in a Baclofen for Smoking Reduction clinical trial, using a higher dose (80 mg/day) than that used in previous clinical trials of drug addiction (Franklin et al., 2009a). In other work, using positron emission tomography (PET), and O¹⁵ H₂O, we demonstrated that baclofen reduced cocaine cue-induced craving and brain blood flow in the limbic reward-responsive amygdala and orbitofrontal and dorsal anterior cingulate cortices (Brebner et al., 2002).

Based on baclofen's actions on the DA system and the previous findings in preclinical and clinical investigations, we hypothesized that baclofen might represent an effective agent to reduce reward-related brain activity in smokers. Thus, we utilized a laboratory model that included a 3-week medication *versus* placebo regimen to examine its actions on brain circuitry. Using arterial spin labeled perfusion functional magnetic resonance imaging (ASL perfusion fMRI), a quantitative method that allows the examination of longitudinal cerebral blood flow (CBF) changes in the brain at rest or during tasks (Franklin et al., 2011c), resting baseline data were acquired before and on the 21st day of the medication regimen. Chronic baclofen dampened resting CBF in the dorsal anterior cingulate and bilaterally in the ventral striatum, insula and medial orbitofrontal cortex, and selectively enhanced it in a circumscribed region of the posterior cingulate and the lateral orbitofrontal cortex (Franklin et al., 2011c). Blood perfusion was unchanged in placebo subjects and there were no differences between groups in side effects after the 3-week regimen. We concluded that baclofen's modulatory actions on regions involved in motivated drug-seeking behavior in humans are reflected in the resting state and provide insight into the mechanism behind its potential to block drug-reinforced behavior, in preclinical studies, and its putative effectiveness as an anti-craving/anti-relapse agent in humans. Given this prior work demonstrating baclofen's impact on reward-related brain structures we hypothesize here that one dose of baclofen may be sufficient to reduce brain perfusion in limbic structures. As protracted pharmacological treatment may not be a practical solution in remitted 'cue vulnerable' smokers, a single dose of baclofen may suffice to immediately block drug-motivated behavior during 'at risk' situations for several hours.

A priori brain regions were chosen based on the animal literature and our previous laboratory studies. These studies demonstrate baclofen-induced decreases in CBF to the ventral striatum, the dopaminergic substrate that attributes incentive salience to stimuli, and the final common pathway of all drugs of abuse (Robinson and Berridge, 1993); the medial orbitofrontal cortex, which encodes responses to reinforcers and their behavioral consequences (Elliott et al., 2010); the ventral anterior insula, an autonomic relay station strongly implicated in cigarette craving (Franklin et al., 2007, 2009b; Naqvi et al., 2007); the amygdala, which assigns hedonic valence to incoming stimuli (Cardinal et al., 2002); and the dorsal anterior cingulate cortex, involved in monitoring emotionality and behavioral restraint (Vogt et al., 1992). Based on the chronic baclofen study, increased perfusion may be expected in the posterior cingulate cortex which subserves evaluative processes such as monitoring sensory events (Vogt et al., 1992) and the lateral orbitofrontal cortex, a region known to re-evaluate previously rewarded behavior (Elliott et al., 2000).

2. Methods

2.1. Subjects

The study was conducted at the Center for the Studies of Addictions, a University of Pennsylvania Perelman School of Medicine-affiliated outpatient treatment center. All procedures were approved and monitored by the Institutional Review Board, and adhered to the Declaration of Helsinki. A subset of the data was reported previously in Franklin et al. (2012). Subjects were compensated \$25.00 for successful consent, \$6.00 for each study visit, \$75.00 for the first scanning session and \$100.00 for the second session.

Subjects were screened, tested on study knowledge, and consented prior to comprehensive 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. 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 other current substance dependence, current Axis I DSM-IV psychiatric diagnoses, significant medical conditions, an intellectual ability estimate score of <80 on the *Wechsler Abbreviated Scale of Intelligence* (Wechsler, 1999), 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 intra-cranial bleeding, or who had irremovable magnetically active objects on or within their body were excluded.

The initial sample consisted of 22 nicotine-dependent subjects. Two subjects were excluded due to exceptionally large ventricles (most likely related to unreported alcohol abuse). The remaining sample of 20 subjects ($N = 13$ female) were African American (3), Caucasian (12), Multiple Ethnicity (2), Asian (2), or Other (1). Subjects were between the ages of 18 and 54 (Mean $\pm$ SEM = 32.65 ± 2.59) and averaged 14.65 ± 0.57 years of education. Subjects smoked 14.13 ± 1.27 cigarettes per day and FTND scores ranged from 1.38 to 7.13, mean $\pm$ SEM: 4.66 ± 0.34 .

2.2. Design

Subjects participated in two scanning sessions that occurred on separate days and were interposed by 3 or more days. During the 'On Bac' condition, subjects received a 20 mg dose of baclofen approximately 110 min prior to scanning (peak plasma concentrations of baclofen are achieved within 2 h) (NOVARTIS, 2010). Subjects were unmedicated (Off Bac condition) prior to the second session. The On Bac scanning session always preceded the Off Bac session. Both 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. Prior to the scanning session, subjects were asked to rate their craving for a cigarette by responding to the question 'On a scale from 1 to 7 how do you rate your desire for a cigarette right now?' Subjects were also administered the Shiffman-Jarvik Withdrawal Questionnaire prior to scanning to examine whether withdrawal accrued over the course of scanning and determine whether sedation, a potential side-effect that has been associated with baclofen, differed across conditions. Imaging data were acquired approximately 15–20 min after smoking to ensure dissipation of the acute cardiovascular effects of smoking (Benowitz and Gourlay, 1997). For each session, a high-resolution structural scan and a 5-min *pseudo* arterial spin labeled (*pCASL*) perfusion fMRI scan were acquired in the brain 'at rest.' Perfusion fMRI provides a measure of CBF through the capillaries in milliliters of blood per 100 g of tissue per minute providing oxygen and nutrients to regions of the brain that are being utilized (Aguirre et al., 2005; Detre and

Alsop, 1999). This quantitative feature facilitates the examination of medication- or behaviorally induced changes in CBF in the brain at rest or during tasks (Franklin et al., 2011c; Hermes et al., 2007; Khalili-Mahani et al., 2011). Simply described, the basic principle of perfusion fMRI is based on the perfusion-weighted difference between magnetically labeled and non-labeled (control) images. *p*CASL is a relatively novel ASL technique that provides improved labeling efficiency, improved sensitivity and is easier to implement in ASL protocols (Dai et al., 2008).

2.3. Imaging parameters

Data were acquired on a 3.0T Trio whole-body scanner (Siemens AG, Erlangen, Germany), using a standard 8-channel receive-only array head coil. A T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) structural scan was acquired (FOV = 160 mm, TR/TE = 1510/3 ms, 192×256 matrix, slice thickness = 1 mm for co-registration of the functional data). *p*CASL perfusion fMRI was used to acquire the 5 min resting baseline brain CBF (45 acquisitions). Interleaved images with and without labeling were obtained using a gradient echo-planar imaging sequence with a delay of 700 ms inserted between the end of the labeling pulse and image acquisition (FOV = 130 mm, matrix = 64×64 , TR/TE = 3400/17 ms, flip angle = 90° , 18 sequential slices with thickness of 6 mm with a 1.2 mm inter-slice gap).

2.4. Data processing

An SPM-based ASL data processing toolbox (Wang et al., 2008) was used for *p*CASL perfusion 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 at 10 mm FWHM. Forty-five CBF image series were generated from the 45 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 SPM8. The same transformation parameters were applied to co-register the CBF map to each subject's anatomical image. Subsequently, the structural image was spatially normalized to the Montreal Neurological Institute (MNI) standard brain. The resulting transformation matrix was used to align the CBF images to MNI space. A binary brain mask was used to exclude the non-brain areas in the CBF maps. The final masked CBF map was used for calculating global CBF for each session. The whole brain CBF values were also calculated from each CBF map, resulting in a global CBF value time series with 45 time points.

2.5. Statistical 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 (On *versus* Off Bac) were defined in the GLM model to assess the voxel by voxel CBF difference.

Baclofen-induced changes in CBF are reported FWE corrected at the cluster level at $p < 0.04$ for *a priori* regions of interest (ROIs). Changes in blood flow were determined using the small volume correction (SVC) tool in SPM8 with radius $r = 5$ mm. Coordinates are in MNI as provided by SPM. Coordinates listed are those chosen from the peak voxel of each ROI.

Continuous demographic variables, craving scores and stimulation/sedation scores were summarized by calculating means and standard error measurements ($X \pm \text{SEMs}$). Paired t -tests were used to test for differences in craving and stimulation/sedation across conditions.

3. Results

Given that baclofen has a reputation for having sedating effects (though see Addolorato et al., 2012; Franklin et al., 2009a; Kahn et al., 2009), a sedation/stimulation score was acquired from the Shiffman–Jarvik Withdrawal Questionnaire administered prior to scanning. There were no differences in sedation across conditions in 19 subjects (data was missing from one subject; On Bac, 5.89 ± 0.19 , Off Bac: 5.78 ± 0.31 ; $p = 0.59$). Subjective reports of craving were not different across conditions, which was not unexpected as subjects smoked a cigarette immediately prior to scan acquisition.

3.1. Effects of acute baclofen on resting brain CBF

Paired t -tests were conducted comparing the On *versus* Off Bac conditions. Baclofen-induced decreases in CBF were observed selectively in several regions including *a priori* amygdala, dorsal anterior cingulate cortex, posterior cingulate cortex, ventral anterior insula, and medial and lateral orbitofrontal cortices (FWE cluster-corrected at $p < 0.04$). See Table 1 for coordinates of the peak voxel and structure-specific t and p values. Baclofen-induced regional increases in CBF were not observed. When sedation scores were included in the model as a covariate, results were unchanged. Two subjects were excluded from the mOFC ROI, as CBF data in this region was not captured (possibly due to inaccurate head position or movement) (Fig. 1).

An interactive visual display of all brain data in all three planes can be found at <http://franklinbrainimaging.com>.

4. Discussion

Here we demonstrate that a 20 mg acute dose of baclofen diminished blood perfusion in limbic reward-related brain regions including *a priori* amygdala, dorsal anterior cingulate cortex, ventral anterior insula, and medial orbitofrontal cortices. Results are similar to those obtained when baclofen was administered to smokers for 3 weeks at 80 mg/day (dorsal anterior cingulate and bilaterally in the ventral striatum, ventral anterior insula and medial orbitofrontal cortex; Franklin et al., 2011c) and to cocaine-addicted individuals during cocaine cue exposure receiving baclofen for 7–10 days at 10–20 mg/day (amygdala, mOFC, dorsal anterior cingulate; Brebner et al., 2002). This work corroborates a substantial preclinical literature demonstrating that baclofen inhibits DA release in drug-dependent rats (Fadda et al., 2003), prevents self-administration of drugs of abuse (Corrigall et al., 2000; Fattore et al., 2002; Markou et al., 2004; Paterson et al., 2004; Roberts and Andrews, 1997; Shoaib et al., 1998; Spano et al., 2007), and blocks drug-induced reinstatement (Campbell et al., 1999; Chaudhri et al., 2008; Fattore et al., 2009; Maccioni et al., 2008; Spano et al., 2007). The results of this study are also consistent with its potential therapeutic benefit for treating alcohol, cocaine, nicotine, amphetamine and opiate addictions (Assadi et al., 2003; Heinzerling et al., 2006; Ling et al., 1998; Shoptaw et al., 2003; Addolorato et al., 2000, 2012; Colombo et al., 2000; Johnson et al., 2005; Malcolm, 2003; Brebner et al., 2002; Franklin et al., 2009a). Thus, this report provides insight into the neurobiological mechanisms underlying an agent that shows promise in reducing relapse, craving and/or withdrawal in several of the addictions.

Preclinical studies using animal models of drug motivated behavior and relapse have elucidated the limbic brain substrates underlying the ability of baclofen to reduce self

administration and reinstatement. However, until the advent of neuroimaging tools such as the quantitative techniques of positron emission tomography (PET) and perfusion fMRI, knowledge of the neuromechanisms underlying a medication's potential effectiveness was inaccessible. Perfusion fMRI is more readily attainable, relatively inexpensive, and has greater temporal sensitivity than PET. It is stable across time (Hermes et al., 2007), which facilitates the measurement of brain responses at various time points, both in response to cognitive and emotional tasks, such as cue exposure (Franklin et al., 2007), and also in the brain in the resting condition (without provocation; Franklin et al., 2011c; Suh et al., 2009; Wang et al., 2007). Blood oxygen level dependent (BOLD) fMRI accurately examines regional changes that reflect relative changes in blood flow that occur within a scanning session during a task or other provocation; however, it is not a quantitative technique and thus cannot reveal regional CBF changes in the brain in the resting condition. As such perfusion fMRI is ideal for longitudinal studies examining brain modifications induced by pharmacological agents to provide knowledge of underlying mechanism.

4.1. A priori regions of interest

The ability of acute baclofen to diminish CBF in a network of regions that includes the limbic amygdala, insula, mOFC and anterior cingulate cortex compliments the known functions of these regions derived from preclinical and clinical studies. Evidence for a role of the amygdala in drug-seeking is clearly established (Reti et al., 2008). For example, in rats that were first trained to self administer cocaine that was 'paired' with cues presented when it was available, and then trained that cocaine was no longer available (an extinction period), baclofen infusions into the amygdala abolished the reinstatement of cocaine seeking behavior. This study, conducted in an animal model of relapse provides evidence of a strong role of the amygdala in cue-motivated drug-seeking behavior and suggests that baclofen's ability to diminish blood flow to this region may result in reduced motivation to smoke (Gabriele and See, 2010).

The cortico-limbic mOFC encodes responses to reinforcers and their behavioral consequences (Elliott et al., 2010) and is hyper-responsive to drugs and to drug predictors. In our previous smoking cue studies the most robust effects during cue exposure were found in the mOFC and interconnected rostral ventral striatum (Franklin et al., 2007, 2009b, 2011b). Activation of the mOFC during smoking cue exposure is supported by other fMRI studies (Brody et al., 2002; Janes et al., 2010). Baclofen-induced deactivation of the mOFC may signify an increased ability to monitor previously rewarding behavior to allow consideration of the future consequences of such behavior. Evidence to support this supposition is provided by previous work in our laboratory demonstrating that varenicline, a first-line smoking cessation agent, blunted blood flow to the mOFC during smoking cue exposure and reduced smoking-cue induced craving (Franklin et al., 2011a). Bupropion, another first-line smoking cessation medication showed similar effects (Culbertson et al., 2011).

Similar to 3 weeks of baclofen, acute baclofen reduced CBF in the ventral anterior insula in the brain at rest. Increased blood flow to the insula was observed in three previous studies in our laboratory using perfusion fMRI during smoking cue exposure demonstrating its role in modulating drug-cued responses (Franklin et al., 2007, 2009b, 2011b). A role for the insula in drug craving was also elucidated by Naqvi and colleagues who examined smoking behavior in individuals with brain lesions. Smokers who had lesions that were selective to the ventral anterior insula, reported an absence of craving for cigarettes and spontaneously quit smoking, while craving for other naturally rewarding substances, such as food, was left intact (Naqvi et al., 2007). One function of the ventral anterior insula relevant to addiction is to relay autonomic sensations to higher cortical processing structures (Craig, 2009). Hyperactive insulas may potentiate increased autonomic arousal to smoking reminders, and

increase vulnerability to 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 also reduced blood flow to the dorsal anterior cingulate cortex, a region implicated in monitoring emotionality and behavioral restraint (Vogt et al., 1992). Diminished CBF to this subregion of the cingulate may signify a reduced ability to monitor reward value (short-term immediate rewards *versus* long-term future rewards).

Acute baclofen-induced regional resting baseline CBF effects were similar but not identical to those observed in our chronic (3 weeks) baclofen study. In our previous study, 3 weeks of placebo did not alter CBF, thus we are confident that counterbalancing conditions in this experiment was not necessary. Further, given that we tested the effects of the medication on the brain at rest (untasked), rather than on task performance, order effects were not expected. In both studies reduced CBF was observed in the dorsal anterior cingulate, the ventral anterior insula and the medial orbitofrontal cortex. In the chronic study, baclofen induced decreases in CBF in the amygdala but not the ventral striatum, whereas when given acutely decreases were observed in the ventral striatum but not the amygdala. Further, there were no regions of increased blood flow following a single dose of baclofen, whereas chronic baclofen was associated with increased CBF in the posterior cingulate and lateral orbitofrontal cortex. These differences may be attributed to baclofen-induced modifications that occur over longer periods. Alternatively, and not mutually exclusive, pharmacoresponsivity may be altered by inter-individual variability between and within the populations studied.

Historically, baclofen has been associated with sedating effects, which has reduced enthusiasm for its use in treating addiction however, recent work in studies of cocaine, alcohol, marijuana and cigarette dependence suggest otherwise, even at doses higher than those used previously (Addolorato et al., 2011; Agabio et al., 2007; Haney et al., 2010; Heinzerling et al., 2006; Kahn et al., 2009). For example, in our *Baclofen for Smoking Reduction Trial*, wherein 80 mg baclofen was shown to be superior to placebo in reducing the number of cigarettes per day, we observed no differences in sedation or other side effects between placebo- and baclofen-treated subjects. We attribute the absence of medication-related adverse events to our dosing schedule which includes (1) an induction period, during which baclofen is titrated to full dose over a period of twelve days, and (2) a 7-day taper at study end (Franklin et al., 2009a). Further, in a large multi-site trial of baclofen for cocaine dependence, using the dosing schedule developed in our laboratory, no differences in side effects were observed (Kahn et al., 2009). The practice of gradually introducing a medication for smoking cessation or other psychiatric illness is widespread, as it eases the occurrence and intensity of side effects (Jorenby et al., 2006).

A caveat in the use of oral baclofen to aid smokers in combatting craving is that it can take up to 20 min to exert its effects. Thus, its benefits could only be realized in situations wherein a smoker has prior knowledge of upcoming risky circumstances that may increase relapse vulnerability. Although an oral dose may be beneficial under some circumstances, smoking cues are ubiquitous and advance notice of future exposure to 'at risk' situations is not always available. Other routes of administration do not exist at present, however it is conceivable that a baclofen inhaler may be an alternative strategy that would circumvent this caveat. In this way, baclofen would exert its effects on the brain in seconds rather than minutes. Nicotine inhalers (Hajek et al., 1999) and nicotine-containing electronic cigarettes (e-cigarettes; Polosa et al., 2011) are implemented examples of this principal and are beneficial to a subgroup of smokers in early abstinence whose relapse vulnerability may be influenced more by withdrawal symptoms. These developed routes of administration

demonstrate feasibility and suggest that a promising avenue could be developed with other medications, such as baclofen. The deleterious consequences of continued smoking underscore the need for novel and effective approaches to smoking cessation interventions.

5. Conclusions

The network of reward-related brain regions affected by a single dose of baclofen on brain blood perfusion and the convergence of existing preclinical, clinical and brain imaging data suggest it could be used as an anti-relapse medication in cue-vulnerable remitted smokers who find themselves in ‘at risk’ situations. Smokers can often control their craving as evinced by the fact that they can remain abstinent for months or even years after quitting however, eventual relapse is the rule rather than the exception (Hughes et al., 2003). Given that relapse may occur long after withdrawal symptoms abate and chronic medication may not be a practical solution, acute baclofen may suffice to immediately block drug-motivated behavior.

Baclofen is FDA-approved (for other indications) and available in generic form; it shows no evidence of abuse potential (Addolorato et al., 2000; Griffiths et al., 1991; Haubenstock et al., 1983); it has few side effects; and its safety and tolerability has been clearly established in non-addicts and in addicted individuals (Aisen et al., 1992; Johnson et al., 2005; Kahn et al., 2009;). Although we reported a reduction in the number of cigarettes smoked per day in our *Baclofen for Smoking Reduction* clinical trial, there are no published treatment trials of baclofen for smoking cessation [one clinical trial is ongoing (ClinicalTrials.gov Identifier: NCT01228994)]. The exploitation of available (and safe) medications, such as baclofen, that are potentially beneficial to treat drug addiction is advantageous and crucial to world health. Employing targeted treatment strategies such as those used successfully in heavy alcohol drinkers with naltrexone (Kranzler et al., 2009; 1997), baclofen may prove optimal in treating remitted smokers who find themselves in situations wherein the potential for relapse is high.

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Fig. 1.

(a) Resting baseline *p*CASL perfusion fMRI scans were acquired in a within subjects crossover design. In the brain at rest, CBF was greater in the On Bac compared to the Off Bac condition in the *a priori* regions shown. Units of blood flow are in milliliters of blood per 100 g of tissue per minute. Small volume correction using a 5 mm sphere was used to generate contrasts. (b) Illustrated are representative MRI images of the brain at rest in the On Bac compared to the Off Bac condition. Sagittal, axial and coronal views are shown with crosshairs centered on the peak voxel (MNI coordinates: 26 4–20) of the right amygdala. Data are analyzed and displayed neurologically (left is left) in SPM8. CBF differences are significant at $p < 0.04$ FWE cluster corrected. Rt, right; Ant, anterior; dor, dorsal; Vent, ventral; Cg, cingulate; l, lateral; m, medial; OFC, orbitofrontal cortex. An interactive visual display of all brain data in all three planes can be found at <http://franklinbrainimaging.com>.

Table 1

Regions showing CBF modulation by an acute dose of baclofen.

Baclofen Effects on RB	X	Y	Z	p	t value
Decreases in CBF					
Amygdala	26	4	-20	0.02	3.46
Cingulate cortex					
Anterior dorsal	6	12	34	0.02	3.40
Posterior	4	-28	32	0.03	3.48
Insula anterior ventral	52	24	-8	0.04	3.32
Orbitofrontal cortex					
Lateral	26	24	-22	0.03	5.49
Medial	0	44	-26	0.02	4.49
Increases in CBF	N.S.				

Listed are the coordinates X, Y, and Z from the peak voxel within a cluster and the p and t values in regions wherein resting baseline (RB) CBF was reduced by an acute dose of baclofen. There were no regions wherein baclofen increased CBF. CBF differences are significant at $p < 0.04$ family-wise error cluster corrected.