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# Cocaine-induced metabolic activation in cortico-limbic circuitry is increased after exposure to the histone deacetylase inhibitor, sodium butyrate

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ABSTRACT

Drug-induced inhibition of histone deacetylase (HDAC) results in the modification of many behavioral changes resulting from exposure to cocaine and other stimulant drugs-of-abuse, but a comprehensive map of the neuronal circuitries involved is lacking. The present study used blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI) in awake rats to determine the effects of the HDAC inhibitor, sodium butyrate (SBt) on brain metabolic activation patterns during the initial stage of repeated cocaine administration. Three groups of rats received cocaine during BOLD fMRI, (i) acutely for the first time, or pretreated for 2 days with either (ii) saline or (iii) SBt 30 min prior to cocaine. Acute but not repeated exposure to cocaine resulted in widespread BOLD activation in fore- and mid-brain. Pretreatment with SBt restored BOLD signals in the forebrain after repeated cocaine exposure, including a pronounced activation in the anterior thalamus, the hippocampus/amygdala and various portions of limbic and sensory cortex. Mesocorticolimbic areas showed a similar trend, but did not reach statistical significance. These findings suggest that HDACi modulation after repeated stimulant exposure involves cortico-limbic circuitry regulating emotion, motivation and memory.

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It is thought that [1] stimulant-induced changes in gene expression, particular in the core constituents of the mesolimbic circuitry – ventral tegmental area, ventral striatum/nucleus accumbens and prefrontal cortex – play a key role for the development and maintenance of the addicted state and chromatin remodeling [2], including the chemical modification of histone tail residues, is involved in cocaine-related behavioral and molecular adaptations [17]. To this end, the acetylation of histone lysine residues, which is associated with a loosening of chromatin structures and transcriptional activation, could become an attractive target for pharmacological interventions aimed at cocaine abuse. In particular, drugs that act as broad inhibitors of class I/II histone deacetylase (HDAC), profoundly affect the behavior of animals exposed to cocaine and other stimulants. For example, when cocaine, amphetamine or dopamine $D_1$-receptor agonist is co-administered with drugs acting as class I/II HDACi, there is robust enhancement of the stimulant's effects on locomotor sensitization and reward behavior [10,18].

Presently, little is known about the neuronal circuits mediating the enhancements in stimulant-related behaviors after HDACi treatment. Using blood-oxygen-level-dependent (BOLD) fMRI in fully awake rats [5,6], the goal of the present study was to obtain a comprehensive map of cocaine-sensitive neuronal circuits that are modified by sodium butyrate (SBt), a broad inhibitor of histone (protein) deacetylases previously shown to enhance the behavioral reinforcements of cocaine [10,18]. We report, for the first time, that SBt dramatically enhances the BOLD response to cocaine upon re-exposure in multiple brain regions. Unexpectedly, HDACi-mediated changes were not significant within in the mesocorticolimibc system, but pronounced in other cortico-limbic circuity including the hippocampus/amgydala, the anterior thalamus and multiple portions of the cerebral cortex. These findings suggest that cortico-limbic circuitry regulating emotion and memory is responsive to HDACi treatments in the context of cocaine exposure.

Adult Long Evans male rats were treated with cocaine hydrochloride and sodium butyrate acetate (SBt) dissolved in 0.9% sterile saline solution. Cocaine was prepared fresh at a dose of 15 mg kg$^{-1}$ and SBt at 200 mg kg$^{-1}$ and both were injected i.p. at a volume of 0.1 cm$^3$ 100 g$^{-1}$. The SBt and cocaine administration protocol used in the present study was partly adopted from a previous study [13]. For imaging experiments, cocaine was injected intracerebroventricularly (ICV) during functional scan acquisition at a concentration of 20 μg in 10 μL artificial cerebrospinal fluid as previously described [5,6]. A schematic of the treatment groups, dose regimen and imaging protocol is shown in Fig. 1. The activation maps shown in Fig. 2 are from the dose regimens shown in red in Fig. 1.

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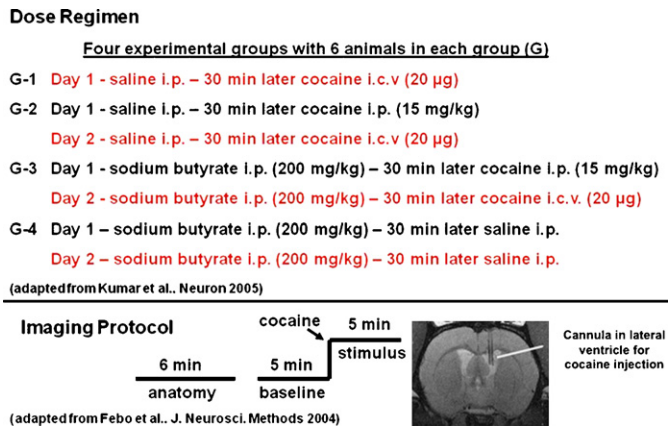


**Fig. 1.** Schematic diagram outlining drug treatment and imaging protocols. Imaging data acquired during treatment protocols shown in red are presented as activation maps in Fig. 2.

All imaging experiments were done in fully awake, unanesthetized male rats (see [5]). Animals were acclimated to the restrainer and imaging protocol prior to an imaging session as previously described [7]. Magnetic resonance imaging was conducted in a Bruker Biospec 4.7-T/40-cm horizontal magnet (Oxford Instrument, Oxford, U.K.) using multislice, fast spin echo (RARE) pulse sequences for both anatomical and functional data acquisitions (for details see Supplementary data, file 1). Random-effects analyses using a fully segmented, 3D rat MRI atlas was used for statistical comparisons between treatment groups [7]. Once each animal was fully registered and segmented in the atlas, the statistical responses for each were averaged on a voxel-by-voxel bases comparing control (32 scan repetitions) to experimental (32 scan repetitions) time periods (see Fig. 1). For each voxel (4800 in number) in the brain a significance test and false discovery test were applied (independent of other voxels) to deem them as activated. Once these voxels for each animal were identified they were assigned to different regions of interest (ROIs) based on atlas information. The mean volume of activation (number of voxels occupying a given ROI) between treatment groups were statistically analyzed using a non-parametric Neuman–Keuls test for multiple comparisons.

BOLD activation maps, co-registered on 2D, coronal sections for each of the four experimental conditions are shown in Fig. 2. These activation maps from the four conditions (day 1 saline/cocaine; day 2 saline/cocaine; day 2 SBt/cocaine; day 2 SBt/saline) are a composite of six subjects each, fully registered into a 3D rat MRI atlas and segmented for volumes of interest (VOI). Visual inspection shows overall much more robust activation in fore- and mid-brain of animals treated with a single dose of cocaine, or two once daily doses of SBt/cocaine (Fig. 2). In contrast, metabolic activation patterns after two daily doses of single drug cocaine or SBt/saline were overall less pronounced (Fig. 2). The increased signals in the SBt/cocaine treated animals include much of the cortical mantle, the medial temporal lobe including amygdala/entorhinal cortex/hippocampus and the anterior and medial dorsal nuclei of the thalamus (Fig. 2).

The only brain areas showing significant differences in BOLD signal between the three cocaine treatments, i.e. saline/cocaine and 1 and 2 day SBt/cocaine are listed in Table 1 and include the somatosensory cortex, CA3 and CA1 fields of the hippocampus, cortical nuclei of the amygdala, the anterior thalamic nuclei and the septum. These significant different sites were identified from 93 brain areas, including the substantia nigra, ventral tegmental area, nucleus accumbens, dorsal striatum, prefrontal areas such as the prelimbic, infralimbic and orbital cortices (not all listed in table). Metabolic activation in the amygdala and somatosensory cortex was also higher after 2 days of SBt/cocaine when compared to a single dose of the stimulant (Table 1). Shown in Fig. 3 are 3D renderings of BOLD activation in the reward circuitry and the Papez circuit. These 3D volumes of activation from the three experimental cocaine groups are a composite of six subjects each and provide a visual representation comparing the difference in the number of activated voxels across experimental conditions. There were no significant differences in any of the brain areas comprising the mesocorticolimbic dopaminergic system. In contrast, areas comprising the Papez circuit, e.g. amygdala, hippocampus, and anterior thalamus, were significantly different and show an ostensibly greater volume of activation in animals treated with 2 day SBt/cocaine.

**Table 1**
Activated voxels in regions of interest of rats treated with chromatin sodium butyrate or vehicle prior to ICV cocaine.

| Volume of interest | 1 day | 2 day | 2 day |
|---|---|---|---|
| | Saline/Coc | Saline/Coc | SBt/Coc |
| Somatosensory cortex | 90 (44.115)* | 98 (61.119)* | 149 (105.222) |
| CA3 hippocampus | 17 (10.34) | 9 (1.17)* | 20 (8.22) |
| CA1 hippocampus | 17 (8.33) | 8 (2.24)* | 20 (15.64) |
| Cortical n. amygdala | 4 (3.15)* | 7 (1.16)* | 15.5 (3.29) |
| Septum | 8 (2.14) | 6 (0.10)* | 14.5 (7.23) |
| Anterior n. thalamus | 0 (0.0) | 1 (0.1)* | 4.5 (0.3) |

Data for voxel activations presented as median and minimum-maximum values in parenthesis.
* Significance for between groups using Neuman–Keuls multiple comparison test ($p < 0.05$ compared to 2 day SBt/Coc).

The present study shows unexpected patterns of brain activation in awake rats exposed to SBt, using a 2 day treatment paradigm previously reported to increase cocaine sensitization [13]. An acute ICV dose of cocaine resulted in widespread BOLD activation in the fore- and mid-brain, but cocaine-induced activation was significantly reduced after repeated exposure to the stimulant, corroborating an earlier work [5] and consistent with related changes in glucose metabolism [9]. Interestingly, SBt co-treatment restored the pronounced and widespread BOLD activation to successive cocaine treatments. Taken together, these findings suggest that the brain's initial response to repeated cocaine exposure triggers an adaptive, desensitization-like mechanism which can be overturned by pretreating animals with SBt prior to receiving cocaine. Does this mechanism involve chromatin modification? To this point, a recent report identified HDAC1, a potential target of SBt [2], as an essential factor for the desensitization of the immediate early gene, *c-fos*, upon repeated exposure to the stimulant and drug-of-abuse, amphetamine [17].

Many of the areas responsive to the HDACi also play significant roles in learning, memory (CA3 and dentate gyrus of the hippocampus, anterior nucleus of the thalamus) and social recognition (central nucleus of the amygdala, septum). These same areas form an integrated neural circuit. The anterior thalamic nuclei of the rat receive synaptic projections through the subcommisural fornix from the pre- and para-subicular cortex but not the hippocampal subfields (CA1–CA4) [20]. This projection also extends in the rat to the mammillary nuclei of the hypothalamus [20]. The subfields of the hippocampus proper communicate directly with the septal nuclei [20]. A case can therefore be made that during the initial exposure to cocaine, chromatin alterations occur in specific brain circuitry to enhance associative learning and memory. However, this remains to be tested experimentally. With regards to the somatosensory cortex it is unclear what the role of cocaine-associated chromatin modifications with this region may be, however it has been shown to have a significant degree of synaptic plasticity in response to cocaine administration in the rat [3].

The neural circuitry underlying this putative epigenetic mechanism contributing to cocaine sensitivity was not the

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