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Cocaine administration increases angiotensin I-converting enzyme (ACE) expression and activity in the rat striatum and frontal cortex

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ABSTRACT

Some central effects of cocaine administration seem to be related to angiotensin II (Ang II) or its metabolites. Nonetheless, it is still an open question whether or not the levels of angiotensin I-converting enzyme (ACE), the main Ang II generating enzyme, are modified by cocaine administration. To evaluate the effect of acute and subchronic cocaine administration on ACE activity and mRNA expression, male rats were randomly assigned to saline or cocaine group. Acute and subchronic cocaine administration induced a significant increase in ACE activity and mRNA expression in the frontal cortex and striatum but not in the hippocampus. These results suggest that some of the Ang II related effects of cocaine upon the central nervous system can be mediated by changes on the expression and activity of ACE in the striatum and frontal cortex.

1. Introduction

Cocaine is one of the most commonly abused illicit drugs [18]. In 2007, the estimated worldwide total number of people, aged 15–64 years old, who used cocaine was 15.6–20.8 million (0.4–0.5% of those in this age group) [40].

It is well-documented that systemic acute cocaine administration induces autonomic responses mediated by the central nucleus of the amygdala (CeA) [39]. Peripheric injection of cocaine (7 mg/kg) induces significant alterations in a number of behaviors, such as stereotyped, locomotor, rearing and anxiety-like behaviors [5]. In addition, it has been shown that repeated administration of cocaine at a similar dose range (10 mg/kg for 5 days) can induce locomotor sensitization in rodents [15], an animal model of addiction [21,37]. Sakoori and Murphy using a 7.5 mg/kg dose showed cocaine-associated place preference [34]. Moreover, Reichel et al. demonstrated the effects of low doses of cocaine (5–7.5 mg/kg) in a modified variant of the place conditioning task, referred as a 'reference – conditioning' procedure that compared two potentially rewarding stimuli (high vs. low dose) [31]. Many of these activities are related to dopamine re-uptake blockade. However, the specific molecular mechanisms involved or whether this activation is due to the direct effects of cocaine on dopaminergic neurons and/or actions on other neuromodulatory systems are still under study [11].

Dopamine release in the striatum of the rat can be directly affected by angiotensin II (Ang II) [13,28] or through an Ang II metabolite like angiotensin IV (Ang IV) [8,9,38]. Ang II, increases corticotropin releasing factor (CRF) release [1] an effect also induced by cocaine withdrawal [12]. Of note, angiotensin I-converting enzyme (ACE, EC 3.4.15.1), the main Ang II generating enzyme, is an essential part of the renin-angiotensin system (RAS) present in the brain. A recent review emphasizes the importance and possible implications of the complete RAS in the brain, where it acts to regulate a number of physiological processes (e.g. cardiovascular maintenance, memory, fluid intake, energy balance) [3]. Angiotensin I-converting enzyme inhibitors (ACEi) are ligands that form a complex with Zn^{2+} at the active site of ACE. ACEi are effective in reducing blood pressure in hypertensive individuals as they block the conversion of angiotensin I to Ang II and reduce the degradation of bradykinin. As pointed out by Margolin et al. ACEi are able to increase dopamine release in the striatum, an effect probably

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mediated by the opioid system. As they indirectly could block CRF release and directly block Ang II production, ACEi have been suggested to be used in the treatment of cocaine abuse [27]. Moreover, it was observed that chronic administration of ACEi increased the turnover of dopamine in the striatum of rats [20].

It is still an open question whether or not the levels of ACE are modified by cocaine administration, potentially leading to an increase in the generation of Ang II and its metabolites. In an attempt to answer this question, following acute and subchronic cocaine administration in rats, we evaluated ACE activity and mRNA expression in different areas, in the central nervous system, known to have increased extracellular dopamine under Ang II effect or to be linked to motor activity.

2. Materials and methods

Male Wistar rats (3 months of age) were obtained from CEDEME – Universidade Federal de São Paulo (UNIFESP). The animals were housed in a room maintained at 22 °C in 12:12 h light–dark cycle (lights on at 07:00 a.m. and off at 19:00 h) inside standard polypropylene cages. All procedures used in the present study complied with the Guide for the Care and Use of Laboratory Animals [19]. The experimental protocol was approved by the Ethical Committee of UNIFESP (#1001/09).

Cocaine hydrochloride (Sigma Chemical Co., St. Louis, MO, USA) was freshly dissolved in saline solution. Intraperitoneal (ip) injections were given at a constant volume of 1 mL/kg. Naive subjects were randomly assigned to 2 treatment groups, saline and cocaine administration. A single dose of cocaine 7 mg/kg or saline was administered intraperitoneally to the rats at 7:30 a.m. only 1 day (acute) or during 5 days (subchronic) at the same time. Six hours after the single dose (acute) or 6 h after the fifth dose administration (subchronic), the animals were decapitated with minimum discomfort. Two additional groups (withdrawal and the respective control) received ip daily injections of cocaine (7 mg/kg) or saline for 5 consecutive days and were euthanized 24 h after the fifth administration. The dose of 7 mg/kg was chosen on the basis of previous studies [4,5].

After decapitation the frontal cortex, striatum and hippocampus were rapidly dissected for protein or total RNA extraction (Trizol, Invitrogen Life Technologies, Carlsbad, CA, USA). For protein extraction, tissues were homogenized in a buffer containing 50 mM Tris–HCl, pH 7.4, NaCl 100 mM and 0.1% Triton. Homogenates were centrifuged at 1000 *g* for 15 min and the supernatant was frozen at −20 °C. The protein contents of the samples were measured by the Bradford method [7] using bovine serum albumin as a standard.

ACE activity on tissue extracts was determined using the FRET peptide Abz-FRK(Dnp)P-OH (10 μM) as previously described [10]. The reactions were continuously followed in a Gemini XS fluorimeter (Molecular Devices Company, Sunnyvale, CA, USA) measuring the fluorescence at λ_{ex} = 320 nm and λ_{em} = 420 nm. Measurements were performed in duplicate and ACE activity values were reported as nanomolar of substrate hydrolyzed per minute per milligram of protein (nM min^{-1} mg^{-1}). In separate control experiments, cocaine concentrations up to 1 mM were added to incubation in order to verify the possibility of a direct action of cocaine on enzyme activity.

ACE, β-actin and GAPDH mRNA expression in tissue were assessed by SYBR Green real-time PCR using 10 ng of total cDNA, SYBR Green Universal Master Mix (Applied Biosystems, Carlsbad, CA, USA), and the following set of primers independently: ACE (5′CGGTTTTCATGAGGCTATTGG3′ and 5′TCGTAGCCACTGCCCTCACT3′ GenBank accession number NM_012544), β-actin (5′AGGCCAACCGTGAAAAGATG3′ and 5′CCAGAGGCATACAGGGACAAC3′ GenBank accession number NM_031144.2) and GAPDH (5′TGCCCCCATGTTTGTGATG3′ and 5′GCTGACAATCTTGAGGGAGTTGT3′ GenBank accession number NM_017008) [26]. ACE, β-actin and GAPDH mRNA expressions were obtained from the cycle threshold (Ct) associated with the exponential growth of the PCR products. Quantitative values for ACE mRNA expression were obtained by the parameter $2^{-\Delta\Delta Ct}$, in which ΔCt represents the subtraction of the β-actin or the GAPDH Ct values from the ACE Ct values.

Studentĭs-*t* test for independent samples by group was used to analyze the data. Values are expressed as the ± standard error of mean (SEM). $p < 0.05$ was considered statistically significant.

3. Results

Fig. 1 shows that acute cocaine treatment significantly increased ACE gene expression in the rat cortex (*t*: −2.99; df: 12; $p < 0.01$) and striatum (*t*: −4.48; df: 12; $p < 0.001$) compared to saline treatment. Similar alterations were seen in ACE mRNA after subchronic cocaine treatment (frontal cortex *t*: −2,36; df: 10; $p < 0.04$ and striatum *t*: −3.24; df: 10; $p < 0.009$). There were significant differences among groups in ACE expression relative to endogen controls β-actin or GAPDH (data not shown).ACE activity values are shown in Fig. 2. Acute and subchronic administration induced a significant increase in ACE activity in the frontal cortex (acute *t*: −10.24; df: 10; $p < 0.001$ and subchronic *t*: −4.69, df: 11; $p < 0.001$/Fig. 2A and D) and striatum (acute *t*: −3.80; df: 11; $p < 0.003$ and subchronic *t*: −3.53; df: 11; $p < 0.005$/Fig. 2B and E). In a separate control, there was no effect of cocaine alone, added up to 1 mM in the incubation medium, on ACE activity (data not shown). However, no significant difference was observed in ACE activity after 24 h withdrawal of repeated cocaine administration (frontal cortex *t*: 0.91; df: 12; $p = 0.37$; striatum *t*: 0.11; df: 13; $p = 0.91$ and hippocampus *t*: −1.08; df: 12; $p = 0.3$; Fig. 2G–I). In a separate control, there was no effect of cocaine alone, added up to 1 mM in the incubation medium, on ACE activity (data not shown).

No significant changes were obtained either for ACE activity (acute *t*: −1.54; df: 11; $p = 0.15$ and subchronic *t*: 0.85; df: 11; $p = 0.41$) or mRNA (acute *t*: −1.82; df: 12; $p = 0.09$ and subchronic *t*: −1.78; df: 10; $p = 0.10$) in tissue extracts from the hippocampus.

4. Discussion

The data reported in this study show that cocaine administration in rats exerts distinct effects upon the central nervous system. The results show that acute and subchronic cocaine administration induced a selective increase in relative mRNA in the frontal cortex and striatum. Moreover, acute cocaine produced a 3-fold and 2-fold increase of ACE activity in the frontal cortex and striatum, respectively. After subchronic cocaine administration, those differences remained significative (frontal cortex 1.8-fold and striatum 1.6-fold, Fig. 2A and B). No significant difference was observed in ACE activity after 24 h withdrawal of repeated cocaine administration in frontal cortex and striatum. In addition, no significant differences were observed in either condition in the hippocampus.

Regarding our data, there are many evidences that Ang II or its metabolites, like Ang IV, can modulate dopamine release in the striatum of the rat [8,9,13,28,38]. The found rise in ACE expression and activity probably implies in the generation of more Ang II and its metabolites, leading to the known involvement of angiotensin receptors in cocaine effects. It is known that cocaine administration induces increased extracellular dopamine in the striatum and the activation of specific intracellular pathways. These changes include the regulation of gene and protein expression that occur in specific areas of the brain and are related to changes in neural plasticity in response to the effects of conditioning and sensitization [6,22,30].

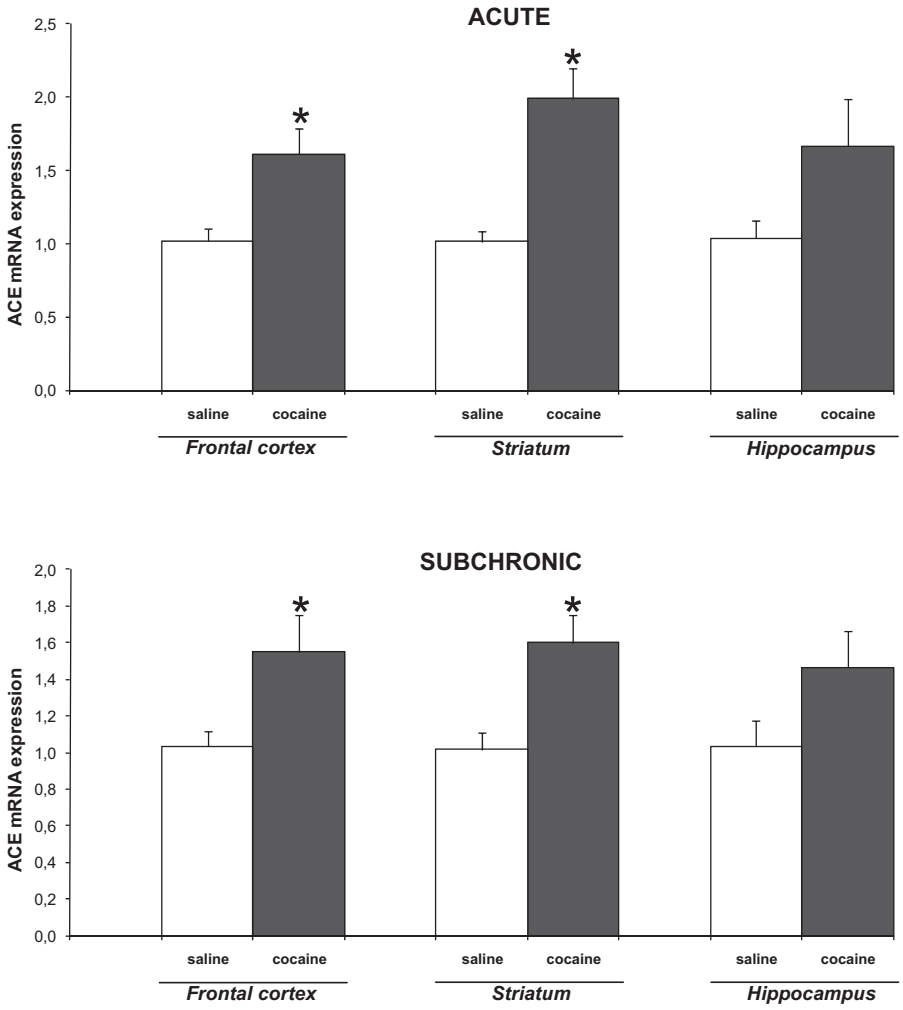

Fig. 1. Plot representation of ACE mRNA relative amount after (A) acute and subchronic (B) cocaine (7 mg/kg, i.p.) administration in the frontal cortex relative to β-actin (A) $^{*}p < 0.02$ and (B) $^{*}p < 0.04$, striatum relative to β-actin (A) $^{*}p < 0.001$ and (B) $^{*}p < 0.007$ and hippocampus relative to β-actin (A) $^{*}p = 0.09$ and (B) $^{*}p = 0.19$. Values are expressed as the mean ± standard error of mean (SEM).

Both cocaine regimens (acute and repeated) produced the same level of response not only at the ACE activity but also at the mRNA expression in the striatum and in the frontal cortex. In the case of the repeated regimen, it can also be interpreted as a response to the last cocaine injection and not to the repeated treatment. In line with the latter possibility, when another time point further away from the injection (i.e. 24 h) was considered in order to measure established long term effects, no effects on ACE activity was observed in either brain area. Both, striatum and the frontal cortex, seem to be related to the behavioral sensitization phenomenon and to drug addiction [17,23,25]; Given that the dose range and duration of cocaine repeated administration used here are effective at producing behavioral sensitization [15], one would expect that the effects of repeated cocaine on ACE activity and mRNA expression would also sensitize after repeated administration. Thus it is important to highlight here that any possible implication of the findings presented in cocaine behavioral effects would need further behavioral experiments to be corroborated.

Although not yet demonstrated in nervous tissues, beyond its ability to form Ang II and process many active peptides, ACE also acts as a signaling molecule by itself at the cell membrane, triggering intracellular phosphorylation events [14] and calcium entry [16]. These recent findings indicate that, potentially, an increase in ACE expression could not only affect Ang II formation, activating angiotensin receptors but also increase a possible signaling through ACE itself.

In vivo, ACE is able to hydrolyze bradykinin and substance P [36]. Opioid peptides, corticotrophin [33,35], hemopressin [32] and amyloid β-protein [29] were also shown to be in vitro ACE substrates. Opioid peptides, like endorphins and enkephalins, are ACE substrates whose dynamics are probably altered by changes in ACE activity with consequences in pain perception [2]. Moreover, modifications on ACE activity can potentially result in alterations in the metabolism of these neuropeptides and *in vivo* could be related to cocaine addiction. ACE inhibitors have been suggested to be used for treating cocaine addiction since they were able to stimulate the release of dopamine in the CNS [20]. Further studies also point to other of ACE inhibitors in the CNS that may have potential applicability for the treatment of cocaine addiction [24,27].

Our results suggest the involvement of brain ACE in the Ang II related effects of cocaine administration. Generation of Ang II and processing of opioid peptides could directly affect dopamine dynamics in regions where ACE increase is induced by cocaine. Ang IV, an Ang II metabolite, participates in memory and learning through a mechanism involving D1–D4 dopamine receptors and inhibition of the Insulin Regulated Aminopeptidase (IRAP) [8]. Ang IV could also be involved in the mechanisms of cocaine addiction adding on the memory consolidation of its rewarding effects. Further studies will allow us to specify the areas of tissues where the presented changes in ACE take place and evaluate the effect of these changes on the levels and activity of involved neuropeptides and receptors *in vivo*.

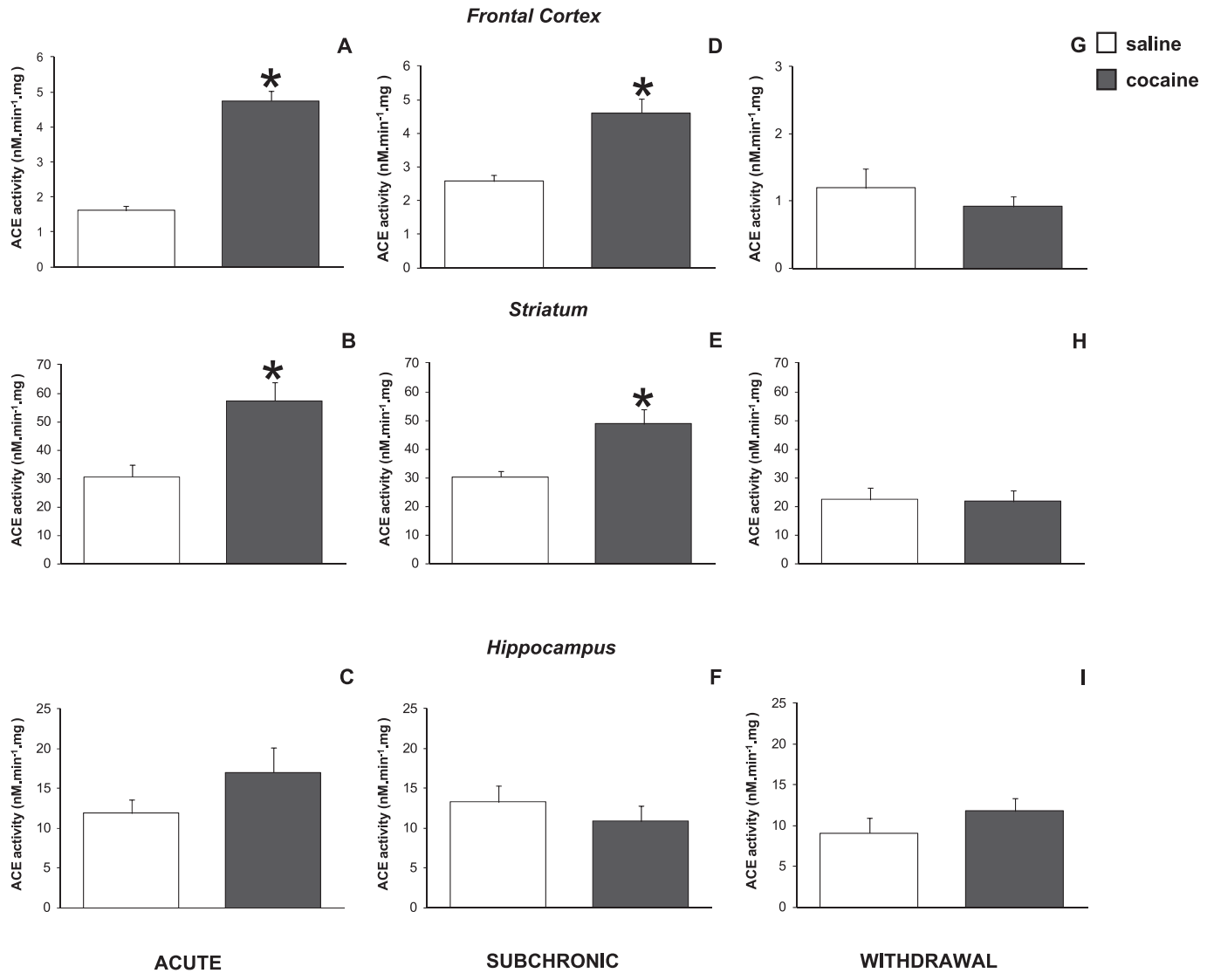

Fig. 2. Plot representation for ACE specific proteolytic activity in the control and in the acute cocaine treated animals in: (A) frontal cortex ($^{*}p < 0.001$), (B) striatum ($^{*}p < 0.003$) and (C) hippocampus ($p = 0.15$), subchronic cocaine treated animals in: (D) frontal cortex ($^{*}p < 0.001$), (E) striatum ($^{*}p < 0.005$) and (F) hippocampus ($p = 0.41$) and after 24 h withdrawal of repeated cocaine treated: (G) frontal cortex ($p = 0.37$), (H) striatum ($p = 0.91$) and (I) hippocampus ($p = 0.30$). Values are expressed as the mean ± standard error of mean (SEM).

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