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Research article

Effects of sodium butyrate on aversive memory in rats submitted to sepsis

Amanda V. Steckert[a,b], Clarissa M. Comim[d], Dhébora M. Dall Igna[b], Diogo Dominguini[a], Bruna P. Mendonça[a], Felipe Ornell[a], Gabriela D. Colpo[e], Carolina Gubert[e], Flávio Kapczinski[e], Tatiana Barichello[a,c], João Quevedo[a,c], Felipe Dal-Pizzol[b,*]

[a] Laboratory of Neurosciences, Graduate Program in Health Sciences, Health Sciences Unit, University of Southern Santa Catarina, Criciúma, SC, Brazil
[b] Laboratory of Experimental Pathophysiology, Graduate Program in Health Sciences, Health Sciences Unit, University of Southern Santa Catarina, Criciúma, SC, Brazil
[c] Center for Experimental Models in Psychiatry, Department of Psychiatry and Behavioral Sciences, Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA
[d] Laboratory of Experimental Neurosciences, Postgraduate Program in Health Sciences, University of South Santa Catarina, Palhoça, SC, Brazil
[e] Laboratory of Molecular Psychiatry and National Institute for Translational Medicine (INCT-TM), Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil

HIGHLIGHTS

- SB administration was able to reverse the impairment in aversive memory induced by CLP.
- SB administration inhibited the HDAC activity in brain regions 10 days after CLP.
- The results may contribute to understanding of cognitive damage in septic rats.
- The findings support HDACi as a possible adjunctive therapy for sepsis.

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ABSTRACT

Epigenetic mechanisms are involved in normal behavior and are implicated in several brain neurodegenerative conditions, psychiatric and inflammatory diseases as well. Moreover, it has been demonstrated that sepsis lead to an imbalance in acetylation of histones and that histone deacetylase inhibitors (HDACi) can reverse this condition. In the present study, we evaluated the effects of a microinjection of sodium butyrate (SB, HDACi) into cerebral ventricle on aversive memory in rats submitted to the sepsis. Rats were given a single intraventricular injection of artificial cerebrospinal fluid (ACSF) or SB and immediately after the stereotaxic surgery and the drug infusion, the animals were subjected to cecal ligation and perforation (CLP). The animals were killed twenty four hours or ten days after sepsis induction and the prefrontal cortex, hippocampus, striatum and cortex were obtained to the determination of histone deacetylase activity. In a separate cohort of animals 10 days after sepsis induction, it was performed the inhibitory avoidance task. SB administration was able to reverse the impairment in aversive memory and inhibited the HDAC activity in prefrontal cortex and hippocampus 10 days after CLP. These support a role for an epigenetic mechanism in the long-term cognitive impairments observed in sepsis survivors animals.

1. Introduction

Histone modifications are an important mechanism to modulate chromatin structure and gene expression [1]. Histone acetylation is reversibly and controlled by the balance of enzymes called histone acetyltransferase (HAT), which acetylates histones, and histone deacetylase (HDAC), which catalyzes the deacetylation of histones [2]. Histone acetylation at gene promoters is related to increased

Abbreviations: ACSF, artificial cerebrospinal fluid; BDNF, brain-derived neurotrophic factor; CLP, cecal ligation and perforation; DTT, dithiothreitol; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitors; NGF, nerve growth factor; SAHA, suberoylanilide hydroxamic acid; SB, sodium butyrate; TSA, trichostatin A; VPA, valproate.

* Corresponding author at: Universidade do Extremo Sul Catarinense, Criciúma, SC 88806-000, Brazil. Fax: +55 48 3431 2736.
E-mail address: fdpizzol@gmail.com (F. Dal-Pizzol).

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gene transcription, while deacetylation is connected with inactivation of gene expression [3].

Histone deacetylase inhibitors (HDACi), such as valproate (VPA), trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA), and sodium butyrate (SB) prevent deacetylation and typically up-regulate gene expression being implicated in the epigenetic programming associated with regulation of behavior and cognition [4,5]. Indeed, epigenetic mechanisms are also implicated in several brain neurodegenerative conditions, psychiatric disorders and inflammatory diseases [6,7]. Besides, the organization of chromatin appears to play a central role in the regulation of gene expression involved in the inflammatory process [8].

Sepsis is characterized by deregulated inflammation and immune responses [9]. Despite the relevance of sepsis its pathophysiology is not fully understood. It is a complex process that involves the immune system; coagulation, endocrine and metabolic pathways; and also linked to an imbalance between ROS formation and clearance [10]. Moreover, it has been demonstrated that sepsis lead to an imbalance in acetylation of histones and that HDACi can reverse this, [11] reducing the release of TNF-α, IL-1β and IFN-γ [12], and exerting anti-inflammatory effects. Indeed, HDACi, such as SB and TSA, have been reported to decrease LPS-induced inflammation in animals [13].

Evidences in the literature have demonstrated that later after cecal ligation and perforation (CLP) rats presented cognitive impairment [14,15]. However, there are no published studies relating neither HDAC activity alterations early or late in the brain of sepsis survivor rats nor its implications in late cognitive damage. Thus, considering the growing body of evidence of the involvement of histones in the pathophysiology of sepsis, the present study aims to evaluate the effects of HDACi on late cognitive impairment in rats submitted to sepsis.

2. Material and Methods

2.1. Animals

Seventy two adult male Wistar rats (60 days old, weighting 250–300 g) were obtained from the Universidade do Extremo Sul Catarinense (UNESC) breeding colony. They were caged (41 × 34 cm and 16 cm high) in groups of five with food and water available *ad libitum* and were maintained on a 12-h light–dark cycle (lights on at 7:00 am), at a temperature of 23 °C ± 1 °C. These conditions were maintained constant throughout the experiments. All experimental procedures were performed in accordance with the approval of the local Ethics Committee of Animals Use (Protocol 01/2012).

2.2. Surgical procedure

Animals were intraperitoneally anesthetized with ketamine (80 mg/kg) and xylazine (10 mg/kg). In a stereotaxic apparatus, the skin of the rat skull was removed for placement of a guide cannula (27 gage 9 mm) 1 mm above lateral ventricle, according to Paxinos and Watson [16]. In the ventricle, a single cannula was implanted in the animals at coordinates: posterior 0.9 mm, lateral 1.5 mm, and ventral 3.3 mm.

2.3. Drug and infusion procedure

The drug used in the study was sodium butyrate (SB, Sigma, St. Louis, MO, USA). SB (10 mM) was dissolved in artificial cerebrospinal fluid (ACSF) and injected directly into the ventricle in a volume of 5 μL once just before sepsis induction. Controls groups received ACSF infused intracerebroventricularly. The dose of SB was based on previous studies of Wang et al. [17] and Arent et al. [18].

2.4. Sepsis induction

Immediately after the stereotaxic surgery, the animals were subjected to CLP, as previously described [19]. Briefly, under aseptic conditions, a 3-cm midline laparotomy was performed to allow exposure of the cecum with the adjoining intestine. The cecum was tightly ligated with a 3.0-silk suture at its base, below the ileocecal valve, and perforated once with a 14-gage needle. The cecum was then gently squeezed to extrude a small amount of feces from the perforation site, returned to the peritoneal cavity, followed by the closure of the laparotomy with 4.0-silk sutures. Animals were resuscitated with normal saline (50 mL/kg subcutaneously) immediately and 12 h after CLP. All animals were returned to their cages with free access to food and water. In the sham operated group, the rats were submitted to all surgical procedures but the cecum was neither ligated nor perforated. After surgery, both groups received 30 mg/kg ceftriaxone and 25 mg/kg clindamycin subcutaneously every 6 h for a total of 3 days. Survival rates were 100% in the sham group and 40% in the sepsis group, which were in accordance with our previous reports [20,21]. Each experiment was performed by a same blinded person. In this study, the animals were divided in three experimental groups (with $n = 12$): (1) Sham + ACSF, (2) CLP + ACSF, and (3) CLP + SB.

2.5. Inhibitory avoidance

The animals were subjected to inhibitory avoidance procedure as previously described by Roesler et al. [22]. The apparatus was an acrylic box (50 × 25 × 25 cm) whose floor consisted of parallel-caliber stainless-steel bars (1 mm diameter) spaced 1 cm apart, and a platform that was 7 cm wide and 2.5 cm high. Animals were placed on the platform and their latency to step down on the grid with all four paws was measured with an automatic device. Training session was performed 10 days after surgery. Immediately after stepping down on the grid, animals received a foot shock of 0.3 mA and 2 s. In test session carried out 24 h after training, no foot shock was given and the step-down latency (maximum of 180 s) was used as a measure of retention. This behavioral test was performed by a same blinded person.

2.6. HDAC activity

Twenty four hours and ten days after surgeries, the animals were killed by decapitation and the brain transferred within 1 min to ice-cold isolation buffer (0.23 M mannitol, 0.07 M sucrose, 10 mM Tris–HCl and 1 mM EDTA, pH 7.4). The prefrontal cortex, hippocampus, striatum and cortex ($n = 7$ animals per group) were obtained.

Samples of brain tissue were submitted to a nuclear extraction protocol, according to Nuclear Extraction kit (Chemicon, USA). Briefly, the tissues were homogenized in cytoplasmic lysis buffer containing dithiothreitol (DTT) and protease inhibitors. The suspension was kept in ice for 15 min and was later centrifuged in 250 × *g* for 5 min at 4 °C. The supernatant was discarded and the pellet was resuspended in two volumes of cold cytoplasmic lysis buffer. The suspension was homogenized using a small gauge needle syringe and centrifuged in 8000 × *g* for 20 min at 4 °C. The resulting pellet contained the nuclear portion of the cellular lysate. The pellet was resuspended in a nuclear extraction buffer containing DTT and protease inhibitors, and the suspension was homogenized with a small gauge needle syringe. The resulting sample was kept in slow agitation for 30–60 min in an orbital shaker at 4 °C. Later, the nuclear suspension was centrifuged in 16,000 × *g* for 5 min at 4 °C and the nuclear extract-containing supernatant was transferred to a new tube and stored at −80 °C until further analysis.

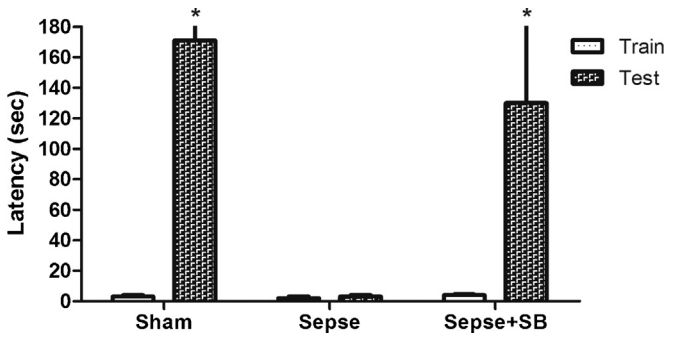

Fig. 1. The step-down inhibitory avoidance. Animals were submitted to CLP or sham-operated. They underwent the training test on the step-down inhibitory avoidance task 10 days after CLP and were tested 24 h later. Data are presented as median and interquartile ranges, $n = 12$ rats per group. $^{*}P < 0.05$ versus sham group.

The nuclear extracts were submitted to a HDAC activity assay with the use of HDAC Assay kit (Fluorometric Detection), according to the manufacturer's instructions (Upstate, USA). Briefly, 5 μL of nuclear extracts were mixed with 5 μL of HDAC Assay Buffer and 5 μL of HDAC Assay Substrate in a 384-well plate and incubated at 30 °C for 45 min. Concomitantly, a standard curve was performed with serial dilutions of deacetylated substrate and positive and negative controls were added to the plate. After, 10 μL of activator solution were added to the wells and the plate was incubated at room temperature for 15 min. The fluorescence reading was performed in a fluorescence plate reader, with 360 nm for excitation and 460 nm for emission. The calculation of the HDAC activity was performed based on the standard curve, and the values are presented as micromolars per microgram of protein. Protein content was measured by the method described by Lowry et al. [23] using bovine serum albumin as a standard.

2.7. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Science (SPSS) software. Data from the inhibitory avoidance task were reported as median and interquartile ranges and comparisons among groups were performed using Mann–Whitney *U* tests. The within individual groups were analyzed by Wilcoxon tests. All data from biochemical analyses were fitted in a standard distribution curve and were therefore, subjected to parametric analyses. For the comparisons between the groups, one-way analysis of variance (ANOVA) test was performed, followed by the LSD post-hoc test. Values of $P < 0.05$ were considered to be statistically significant.

3. Results

Fig. 1 demonstrates the test section step-down latency of the inhibitory avoidance. Ten days after CLP, it was significantly decreased in the sepsis group ($Z = 1.266$, $P = 0.002$) when compared to the sham group. SB administration was able to reverse the impairment in aversive memory ($Z = 2.194$, $P = 0{,}002$) observed in the sepsis group.

HDAC activity is shown in Fig. 2(A and B). It was observed an increase in the HDAC activity in hippocampus ($f = 4.879$, df = 2, $P = 0.023$) and cortex ($f = 3.087$, df = 2, $P = 0.026$) 24 h after CLP in septic animals when compared to sham (Fig. 2A). However, SB administration in sepsis group did not inhibited the HDAC activity in both structures (hippocampus and cortex). Additionally, in other brain structures (prefrontal cortex and striatum) there were no statistical differences between groups.

At longer times after sepsis induction (10 days, Fig. 2B), it was demonstrated an increase in the HDAC activity only in prefrontal cortex ($f = 7.951$, df = 2, $P = 0.003$) and hippocampus ($f = 6.617$, df = 2, $P = 0.006$) in sepsis group. In the others brain regions (striatum and cortex), there were no statistical differences between groups. SB administration in sepsis group inhibited the HDAC activity only in the prefrontal cortex and hippocampus, but not in striatum and cortex (10 days).

4. Discussion

Literature data shows that epigenetics mediates diverse environmental aspects involved in the pathophysiology of psychiatric and inflammatory diseases [24,25]. In this study, we observed that SB administration was able to reverse the impaired aversive memory and inhibited the HDAC activity in prefrontal cortex and hippocampus after 10 days CLP surgery, suggesting that HDAC activity could be associated to memory impairment.

Our results are in agreement with published data suggesting that inflammatory and immune responses evoked by sepsis may induce brain dysfunction and memory impairment [26,27]. It is also known that neurotrophins – such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) – play an important role in neuronal differentiation, survival and growth of neurons and control neuronal cell death during brain development [28]. In this context, BDNF levels [19] and hippocampal volume [29] are decreased after sepsis.

Some authors have explored the connection between HDACs and BDNF in nervous system dysfunction [30,31]. Additionally, HDACis have been shown to potentiate memory and synaptic plasticity and to ameliorate cognitive deficits and neurodegeneration [32,33]. In addition, histone acetylation is regulated during memory formation [34,35]. Accordingly, SB has been shown to increase BDNF levels in vitro [36]. Wu et al. [2] demonstrated that HDACi up-regulate astrocyte glial cell line-derived neurotrophic factor and BDNF gene transcription, protecting dopaminergic neurons. Subsequently, the same authors showed that chronic treatment with VPA reversed cognitive deficits probably by decreasing inflammation and apoptosis in the brain, as well as the activation of the BDNF-TrkB signaling pathway [37]. This was also demonstrated in animal models of traumatic brain injury and brain ischemia [38,39].

From a mechanistically point of view, it is not possible to ascertain if these observed effects were related to a decrease in systemic inflammation or were associated with an specific central effect. Thus, our results add to previously published since we administered HDACi directly into the CSF, avoiding in that way its systemic effects.

Moreover, pretreatment with HDACi, such as SB, VPA, and TSA decreased lipopolysaccharide-induced inflammatory responses and protected dopaminergic neurons from damage in cell culture [40].

Here, HDAC activity was increased in the sepsis group in hippocampus and cortex in 24 h after CLP induction; and in prefrontal cortex and hippocampus 10 days after sepsis. In fact, inflammatory diseases such as sepsis can induce increase HDAC activity, decreasing or inactivating gene transcription [37,41], but this is the first demonstration that HDAC activity is up-regulated in the brain longer after sepsis. However, SB administration reverses this only in prefrontal cortex and hippocampus at 10 days. This can be explained partly because regions of the brain may respond differently to sepsis, due to the heterogeneous subsets of cell population. Furthermore, even within a homogeneous population of cells, there is heterogeneity in terms of metabolic and physiological aspects [42].

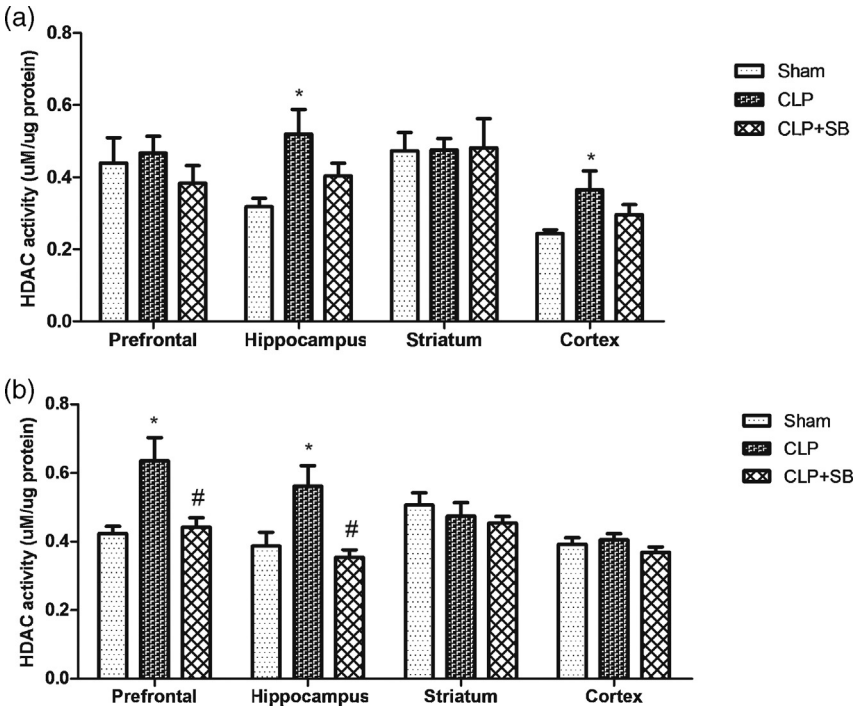

Fig. 2. Microinjection of SB or ACSF in the ventricle. HDAC activity in the brain (prefrontal cortex, hippocampus, striatum and cortex) of sepsis survivors rats 24 h (A) and 10 days (B) after CLP. Bars represent means ± SEM of 7 rats. $^{*}P < 0.05$ versus sham group. $\#P < 0.05$ versus CLP group.

Additionally, several factors that may influence HDAC activity could explain these differences, such as comorbidities and staging of sepsis. Likewise, in studies with animals, some variables could have a direct impact on the results [43]. In this study, the absence of alterations in HDAC activity is likely to be related to the duration of SB treatment, which was acute.

5. Conclusions

SB administration was able to reverse the impaired aversive memory and inhibited the HDAC activity in prefrontal cortex and hippocampus 10 after days CLP. These findings may contribute to a better understanding of cognitive damage in sepsis survivor and support HDACi as a possible adjunctive therapy for sepsis.

Conflict of interest

None of the authors or funding sources has conflict of interest.

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