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Research report

Further evidence that anxiety and memory are regionally dissociated within the hippocampus

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Abstract

The hippocampus has been implicated in the regulation of anxiety and memory processes. Nevertheless, the precise contribution of its ventral (VH) and dorsal (DH) division in these issues still remains a matter of debate. The Trial 1/2 protocol in the elevated plus-maze (EPM) is a suitable approach to assess features associated with anxiety and memory. Information about the spatial environment on initial (Trial 1) exploration leads to a subsequent increase in open-arm avoidance during retesting (Trial 2). The objective of the present study was to investigate whether transient VH or DH deactivation by lidocaine microinfusion would differently interfere with the performance of EPM-naive and EPM-experienced rats. Male Wistar rats were bilaterally-implanted with guide cannulas aimed at the VH or the DH. One-week after surgery, they received vehicle or lidocaine 2.0% in 1.0 μL (0.5 μL per side) at pre-Trial 1, post-Trial 1 or pre-Trial 2. There was an increase in open-arm exploration after the intra-VH lidocaine injection on Trial 1. Intra-DH pre-Trial 2 administration of lidocaine also reduced the open-arm avoidance. No significant changes were observed in enclosed-arm entries, an EPM index of general exploratory activity. The cautious exploration of potentially dangerous environment requires VH functional integrity, suggesting a specific role for this region in modulating anxiety-related behaviors. With regard to the DH, it may be preferentially involved in learning and memory since the acquired response of inhibitory avoidance was no longer observed when lidocaine was injected pre-Trial 2.

Keywords: Defensive behavior; Spatial learning; Transitory deactivation

1. Introduction

The hippocampus has a long established-role in spatial learning and memory [24,28]. It may also regulate defensive behaviors related to anxiety [4]. Electrolytic or excitotoxic lesions of the hippocampus produce anxiolytic-like behaviors in elevated mazes and social interaction tests [2,10]. Moreover, it is proposed that anxiolytic-like drugs induce their effects by acting on a behavioral inhibition system that includes the hippocampus [15].

There is considerable evidence to suggest that the hippocampus may be differentiated into dorsal (DH) and ventral (VH) poles [4,27]. The precise contribution of these two regions on anxiety and memory, however, still remains a matter of debate. With regard to the former process, research has frequently focused on avoidance behavior scored in the elevated plus-maze (EPM) test. Microinjection of the benzodiazepine midazolam into the DH decreased this response [19,20]. However, anxiolytic-like effects were also reported after either excitotoxic or electrolytic lesions of the VH, but not the DH [16]. VH lesions also reduced anxiety-related responses in the social interaction, the light/dark, the elevated T-maze and the cat-odor exposure tests [18,26,32]. These findings suggest that defensive behaviors related to anxiety are preferentially regulated by the VH. In relation to spatial learning aspects, a wealth of evidence suggests that it depends preferentially on DH function [4,21]. For instance, the degree of impairment of spatial learning in a water-maze correlates with DH, but not VH lesions [22,23,33].

The objective of the present study was to further investigate a possible hippocampal regional dissociation regarding the modulation of anxiety and memory processes. Since prior studies have usually assessed this issue by using lesion techniques, the current

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study adopted acute bilateral lidocaine microinfusion into the VH or the DH to transiently interfere with normal hippocampal activity. In addition, since behavioral measures related to anxiety and memory has been usually assessed by different tests, the present study used the EPM Trial 1/2 protocol. In the EPM test, after the initial (Trial 1) exploration of the whole apparatus, rodents express increased inhibitory avoidance response during retesting (Trial 2). This latter finding is thought to reflect the acquisition of spatial memory related to exploration of potentially dangerous areas of the maze—the open-arms [6,9]. This approach, therefore, was selected based on its capacity of evaluating either anxiety- and memory-related behavioral responses. Our hypothesis is that lidocaine microinfusion into the VH would interfere with the former whereas the latter responses would be prudentially affected by DH inactivation.

2. Materials and methods

2.1. Animals

One-hundred and fifty-five male Wistar rats weighing 250–270 g at the time of testing were housed in pairs in a temperature-controlled room (23 ± 1 °C), under standard laboratory conditions with free access to food and water, and with a 12 h light/12 h dark cycle (lights on at 06:30 h a.m.). Procedures were conducted in conformity with the Brazilian Society of Neuroscience and Behavior guidelines for the care and use of laboratory animals, which are in compliance with international laws and politics. The local Ethical Committee approved the experimental protocol and all efforts were made to minimize animal suffering.

2.2. Drugs

Lidocaine (2-diethyl-*N*-[2,6-diethyphenyl]-acetamide HCl; Probem, Brazil) was dissolved to a concentration of 2.0% (20 mg/mL) in saline (NaCl 0.9%), which alone served as vehicle solution. The dose of lidocaine was chosen based on a previous dose–response study [17]. A 0.5 μL volume of lidocaine was selected for these experiments so as to ensure maximum effective diffusion based on the estimate formula outlined in Tehovnik and Somner [30]. According to this estimate of effective radial spread, this volume of lidocaine infusion would block sodium channels within a ∼0.50 mm radial distance from the injector tip. This effect would last for approximately 15 min. Thus, drug injections were performed either 10 min before, or immediately after, the EPM test exposure.

2.3. Apparatus

The EPM was made of wood and consisted of two opposite open-arms, 50 cm × 10 cm (surrounded by a 1 cm high Plexiglas ledge), and two enclosed-arms, 50 cm × 10 cm × 40 cm, set up 50 cm above the floor [9]. The junction area of the four arms (central platform) measured 10 cm × 10 cm. In order to avoid urine impregnation the floor of the apparatus was painted with impermeable epoxy resin.

2.4. Stereotaxic surgery and drug administration

Rats were anaesthetized with 2.5% of 2,2,2 tribromoethanol (10 mL/kg, i.p.; Sigma, USA) associated with local anesthesia (3.0% lidocaine with norepinephrine 1:50,000; Harvey, Brazil) and fixed in a stereotaxic frame (David Kopf, USA). Two stainless steel guide cannulas (outer diameter = 0.6 mm), made locally using needles for parenteral injection (Becton Dickinson, Brazil), were implanted bilaterally aimed at the DH (coordinates: AP = −4.0 mm from Bregma, *L* = 2.8 mm, *D* = 2.1 mm) or the VH (coordinates: AP = −5.0 mm from Bregma, *L* = 5.2 mm, *D* = 4.0 mm), following the coordinates from the rat brain atlas by Paxinos and Watson [25]. The cannula tips were 1.5 and 3.0 mm above the site of injection, respectively. The guide cannulas were fixed to the skull with acrylic resin and two stainless steel screws. After this, a stylet was introduced inside each guide cannula to reduce the incidence of occlusion. At the end of the surgery, animals were injected (i.m.) with an antibiotic association containing benzylpenicillin and streptomycin (Pentabiótico®, Fort Dodge, Brazil; 1.0 mL/kg) to prevent possible infections. In addition, flunixin meglumine (Schering–Plough, Brazil; 2.5 mg/kg), a drug with analgesic, antipyretic and anti-inflammatory properties, was administered subcutaneously for post-surgery analgesia.

Five to seven days after the stereotaxic surgery each rat received a bilateral injection with thin dental needles (outer diameter = 0.3 mm) introduced through the guide cannulas until their tips were 1.5 or 3.0 mm (DH and VH, respectively) below the cannula end. A total volume of 1.0 μL (0.5 μL per side) of either saline or lidocaine 2.0% was injected during 30 s using two microsyringes connected to an infusion pump (KD Scientific, USA). A polyethylene catheter was interposed between the upper end of the dental needles and the microsyringes. The displacement of an air bubble inside the polyethylene catheters connecting the infusion pump apparatus to the intracerebral needles was used to monitor drug flow. The intracerebral needles were removed 1 min after the end of injections.

2.5. Experimental design

Rats were assigned for one of the 12 groups (*n* = 9–13/group), according to the drug treatment given (saline or lidocaine 2.0%), the local of the bilateral injection (DH or VH), and the time in which the injections took place (pre-Trial 1, post-Trial 1 or pre-Trial 2). Pre-Trial 1 means that rats were injected 10 min prior to the first EPM exposure. Twenty-four hours later, these groups were retested undrugged in the EPM. Animals from post-Trial 1 experiment were injected immediately after the first EPM test exposure. Twenty-four hours later, they were retested undrugged in the EPM. Finally, rats from pre-Trial 2 experiments were tested undrugged in the first EPM, but that were injected 10 min prior to the second EPM exposure.

2.6. Behavioral measures

Behavioral tests were carried out in a low illumination (40 lx) condition room, during the diurnal phase (between 13:00 and 17:00 h). EPM sessions last for 5 min, and were recorded by a video camera while a monitor and a video-recording system were installed in an adjacent room. A trained observer scored the following behavioral parameters from the videotape: the number of open- and enclosed-arms entries (EAE) with the four paws, and the time spent in the central platform, open- and enclosed-arms. These data were used to calculate the percentage of open-arm entries {%OAE; [open-entries/(open + enclosed-entries)] × 100}, the percentage of time spent in the open [%OAT; (open time/300) × 100] and the enclosed [%EAT; (enclosed time/300) × 100] arms, as well as on the central platform [%CT; (central platform time/300) × 100)]. The number of stretched attend postures (SAPs), defined as an exploratory posture in which the rat stretches forward and then retracts to its original position, performed by rats from the central platform or enclosed-arms towards open-arm, was also recorded.

2.7. Histology

After the behavioral tests, the animals were anesthetized with 25% of urethane (10 mL/kg i.p.; Sigma, USA) and injected through the guide cannulas with 0.5 μL of Evans Blue (Sigma, USA). Their brains were then perfused through the left ventricle of the heart with isotonic saline (0.9%), followed by 10% formalin solution. After removing the brains, and following a minimum period of 2 days immersed in a 10% formalin solution, frozen sections of 50 μm were obtained in a cryostat (Leica, USA). The microinjection sites were localized in diagrams from Paxinos and Watson's [25] rat brain atlas.

2.8. Statistical analysis

Data were analyzed by two-way analysis of variance (ANOVA), with drug treatment and site of injection as independent factors. When variances among

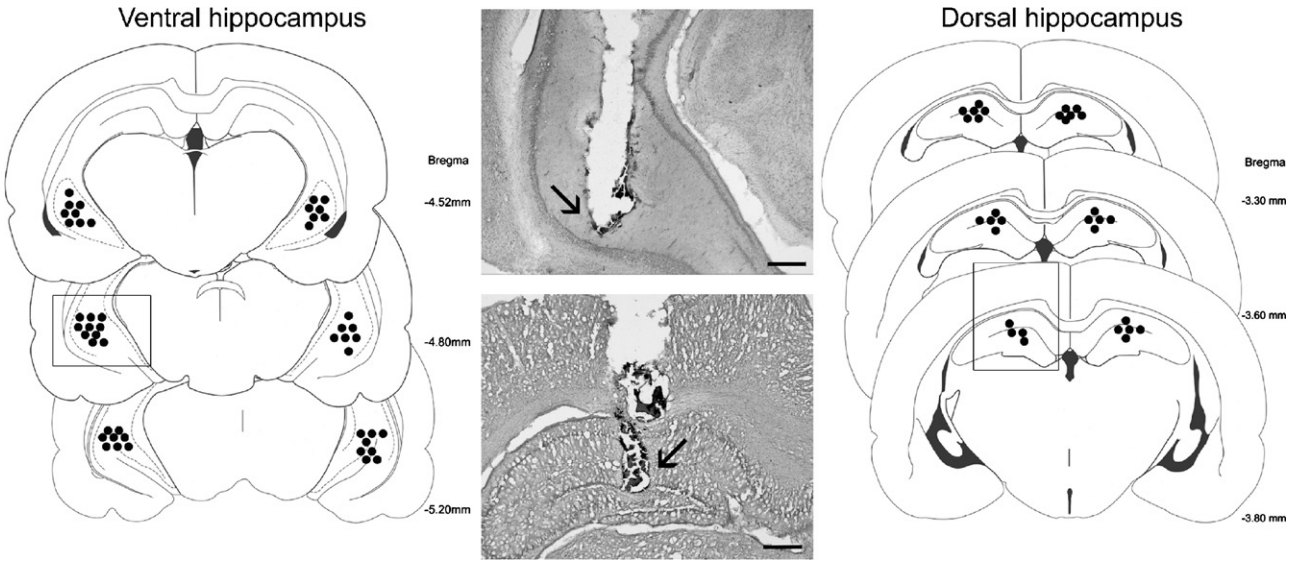

Fig. 1. Diagrams modified from Paxinos and Watson [25] showing injections sites (filled circles) into the ventral (4.52–5.20 mm posterior to Bregma) or the dorsal (3.30–3.80 mm posterior to Bregma) hippocampus. Due to overlapping, the number of points represented is fewer than the number of rats actually injected. On the middle of the figure are presented photomicrographs (scale bar: 500 μm) showing a typical injection site (indicated by an arrow) within the ventral (top) or the dorsal (bottom) hippocampus.

groups were not homogenous, the raw data were log transformed. The Duncan's test was used for post-hoc comparisons when appropriated.

3. Results

Pictures showing representative injection sites into the VH and the DH can be seen in Fig. 1. Animals receiving microinjections outside these hippocampal poles (27% and 14%, respectively) were excluded from the analysis.

3.1. Effects of temporary deactivation of VH and DH at pre-Trial 1

There was an interaction between drug treatment and site of injection for %OAE [$F(1, 39) = 5.84$, $p < 0.02$]. Further pairwise comparison showed an increase ($p < 0.05$) in this behavioral parameter when lidocaine was given into the VH prior to Trial 1 (Fig. 2A). The interaction between these factors for %OAT (Fig. 2B) was only marginally significant ($p < 0.10$). However,

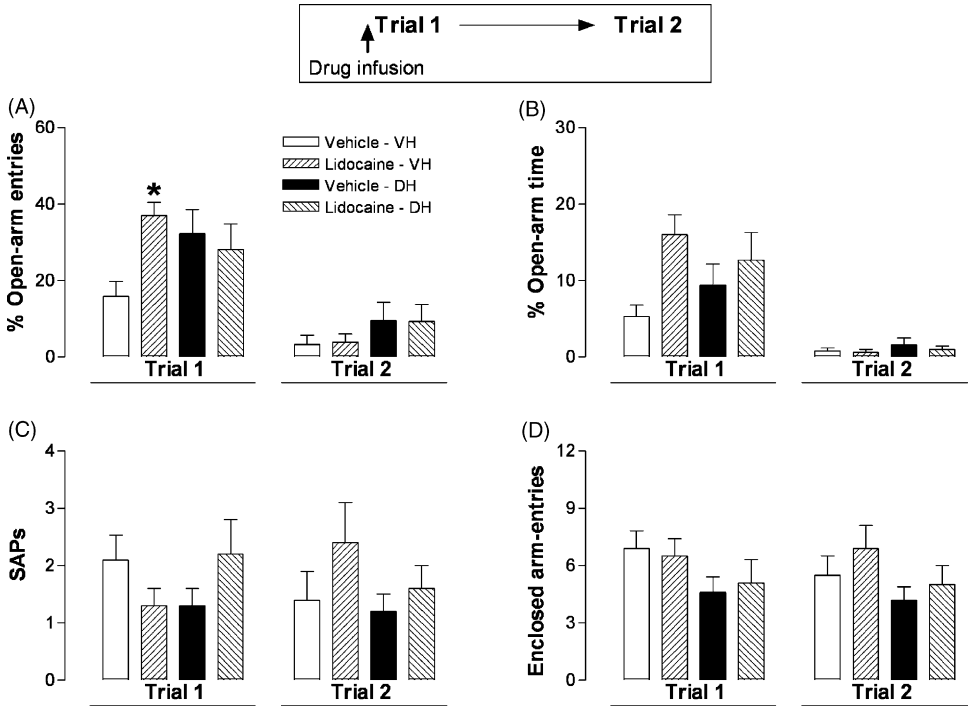

Fig. 2. Effects on the open-arm exploration (A and B), on risk assessment (C), as well as on enclosed-arm entries (D), of vehicle or lidocaine 2.0% given prior to Trial 1 into the ventral or the dorsal hippocampus (VH and DH, respectively) of rats tested in the elevated plus-maze ($n = 9$–12). Data are presented as mean + S.E.M. *$p < 0.05$ vs. respective control group.

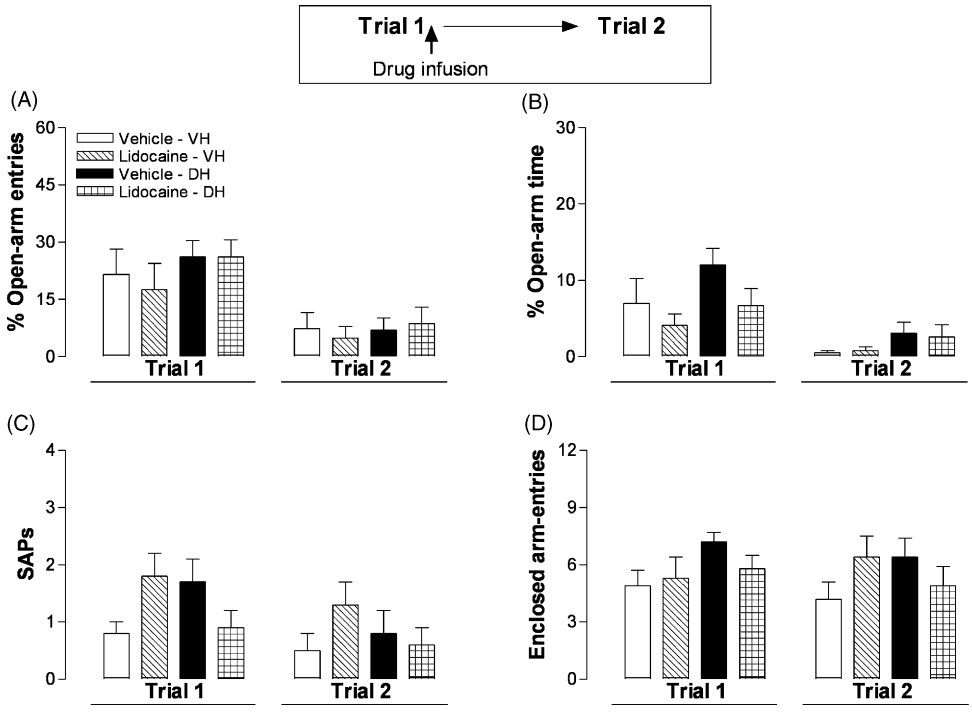

Fig. 3. Effects on the open-arm exploration (A and B), on risk assessment (C), as well as on enclosed-arm entries (D), of vehicle or lidocaine 2.0% given immediately after Trial 1 into the ventral or the dorsal hippocampus (VH and DH, respectively) of rats tested in the elevated plus-maze ($n = 8$–11). Data are presented as mean + S.E.M.

drug treatment increased the %OAT independently of injection site [$F(1, 39) = 6.89$, $p < 0.01$].

Regarding SAPs (Fig. 2C) and EAE (Fig. 2D), no statistically significant effect of drug treatment, site of injection, as well as their interaction, was found on Trial 1. Moreover, independent of the site of injection, behaviors scored on Trial 2 were similar in lidocaine- and saline-treated groups (Fig. 2).

3.2. Effects of temporary deactivation of VH and DH at post-Trial 1

There was no statistically significant effect of drug treatment, site of injection, or an interaction between these factors on behaviors monitored during Trials 1 and 2 (Fig. 3).

3.3. Effects of temporary deactivation of VH and DH at pre-Trial 2

With regard to Trial 1 VH and DH data, there was no statistically significant effect of drug treatment, injection site, as well as their interaction (Fig. 4). During Trial 2, however, the interaction between these factors was significant for %OAE [$F(1, 31) = 4.52$, $p < 0.04$] and %OAT [$F(1, 31) = 5.06$, $p < 0.03$]. Further comparison using Duncan's test showed that lidocaine increased ($p < 0.05$) both %OAE and %OAT when given into the DH, but not into the VH (Fig. 4A and B). In relation to SAPs and EAE (Fig. 4C and D, respectively), no statistically significant effect of drug treatment, site of injection, as well as their interaction, was found during Trial 2.

4. Discussion

The main experimental findings of the present study are that: (1) lidocaine injected into the VH prior to Trial 1 increased open-arm exploration. No effect was found, however, when the same treatment was given at post-Trial 1 or pre-Trial 2 and (2) lidocaine injected into the DH reduced the open-arm avoidance when given at pre-Trial 2, but not at pre-Trial 1 or post-Trial 1.

These findings are consistent with studies implicating the VH, but not the DH, in the regulation of anxiety-related behaviors [11,31]. While Bannerman et al. [3] found anxiolytic-like effects in the EPM with both VH and DH electrolytic lesions, they reported hyperactivity only in the DH group. When excitotoxic lesions were utilized in the successive alleys test, which represents a modified version of the EPM, the anxiolytic effect was restricted to the VH [18]. The EPM general locomotor activity index (enclosed-arm entries) was not changed by the intra-VH lidocaine-treatment, indicating that the reduction in avoidance behavior was not due to general effect in locomotion.

It was recently reported by Pentkowski et al. [26] that VH lesions did not change rat behavior during cat exposure. This suggests that the modulation of defensive behaviors during exposure to overt threat stimuli is not dependent of this region, and that other neural systems can support defensiveness to a clearly present predator. However, during cat-odor exposure animals with VH lesions displayed less defensive behaviors [26]. Blanchard and Blanchard [7] have suggested that situations in which rats are exposed to specific, immediate threat stimuli (cat exposure), elicit fear-like responses, whereas tests exposing rats to situations of potential or anticipated threat (cat-odor) elicit

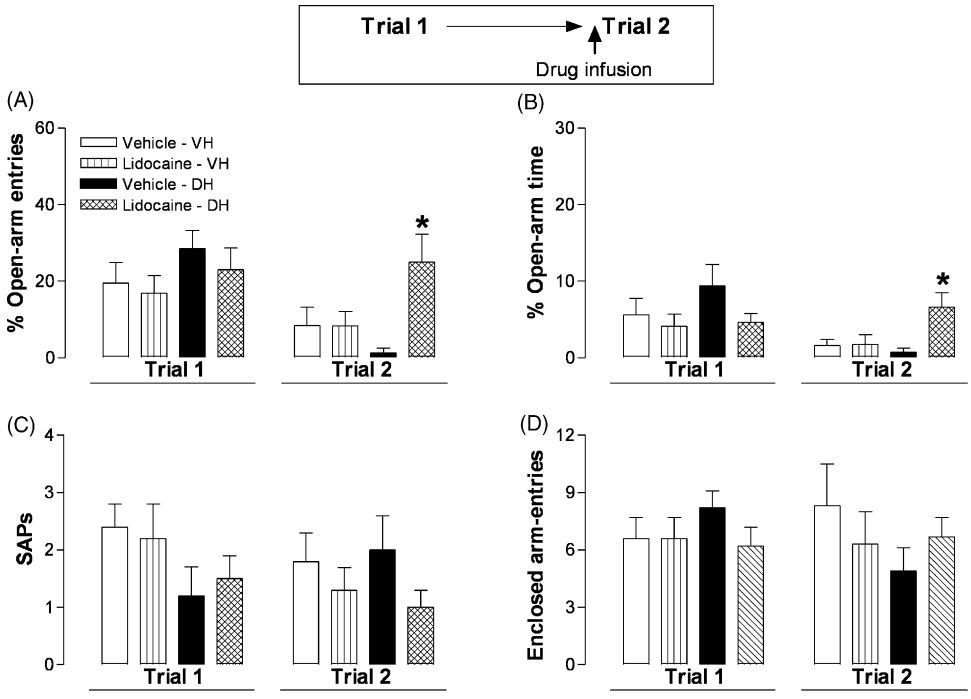

Fig. 4. Effects on the open-arm exploration (A and B), on risk assessment (C), as well as on enclosed-arm entries (D), of vehicle or lidocaine 2.0% given prior to Trial 2 into the ventral or the dorsal hippocampus (VH and DH, respectively) of rats tested in the elevated plus-maze ($n = 8$–11). Data are presented as mean + S.E.M. *$p < 0.05$ vs. respective control group.

anxiety-like behaviors. The contrasting effects of VH lesions during cat-odor and cat exposure may indicate, therefore, that this region modulates defensive behaviors sensitive to tests of anxiety, without affecting behaviors responsive to experimental tests of fear. This idea is supported by our results showing that temporary deactivation of the VH increased open-arm exploration similar to that induced by benzodiazepines [15,20]. It appears, therefore, that one of the VH function is to modulate defensive behaviors in tests that make use of potential threat stimuli such as open-spaces and odor of a predator. If so, one could suppose that lidocaine given into the VH at pre-Trial 2 would have a similar result as pre-Trial 1. The current findings are at odd with this supposition. In this regard, it is worth mentioning that the anxiolytic-like effect of drugs is likewise abolished after prior EPM test experience (for a review, see [9]). An explanation to the latter phenomenon is that, because of the initial overall EPM exploration, subjects would develop and adopt non-conflicting (and thus anxiolytic-insensitive) behavioral responses such as enclosed-arm preference during Trial 2 [6]. Taking into account this fact, the VH role may be in fact less prominent in EPM-experienced rats.

Risk assessment is also considered a significant behavioral measure closely related to anxiety [7,9]. Contrary to our prediction, bilateral infusion of lidocaine into the VH did not significantly reduced SAPs in the EPM test. In our experimental conditions, however, the control group showed a small number of SAPs, which could have prevented significant drug effects. Actually, a specific comparison between vehicle and lidocaine-VH groups suggests that the former treatment might be decreasing SAPs ($p = 0.11$).

Prior EPM test experience also produces enduring changes in behavioral responses [9]. After the initial apparatus exploration rodents acquire, consolidate and retrieve some kind of memory related to exploration of potentially dangerous areas [14]. As a consequence, EPM-experienced rats frequently express an increase in open-arm avoidance on Trial 2 [5]. In this regard, data showing that this response is compromised by the systemic administration of scopolamine, a drug that impairs/disrupts learning acquisition, supports the assumption that it incorporates spatial learning and memory aspects [6]. The present results also found a decrease in open-arm avoidance in EPM-experienced rats after the bilateral microinfusion of lidocaine into the DH at pre-Trial 2. In contrast, the same procedure in the VH left this response unaffected. This result supports the proposition that the DH has a preferential role in spatial learning and memory.

These findings, showing a dissociation of anxiety and memory processes within the hippocampus, may be reflecting the differential afferent and efferent connectivity of its ventral and dorsal poles [29]. A mechanism by which the VH may regulate unconditioned defense behavior is through its connections with the hypothalamus and amygdaloid complex [26]. On the other hand, a preferential role for DH in spatial learning and memory is consistent with the fact that the major input of visual and spatial information to the hippocampus from primary sensory cortical areas, via association cortex, and perirhinal and entorhinal areas, is mainly to the DH [1,13]. However, other types of sensory input, such as olfactory cues, appear to be more equally distributed along these hippocampus poles [21]. It implies that the DH may be less important when other types of information are considered [8,26]. Likewise, the VH may contribute to

spatial learning at least under some conditions. For example, De Hoz et al. [12] reported that rats with excitotoxic DH lesions acquire a spatial reference memory task in the water-maze if sufficient training is given. Moreover, the extensive connectivity between DH and VH [1] also predicts some degree of functional interdependence between these hippocampal aspects.

In conclusion, the present results corroborate the hypothesis that the DH and VH may preferentially regulate memory and anxiety-related processes, respectively.

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