CHRONIC NICOTINE ATTENUATES BEHAVIORAL AND SYNAPTIC PLASTICITY IMPAIRMENTS IN A STREPTOZOTOCIN MODEL OF ALZHEIMER'S DISEASE

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Abstract—Brain glucose metabolism is altered in sporadic Alzheimer's disease (sAD), whose pathologies are reproduced in rodents by intracerebroventricular (icv) infusion of streptozotocin (STZ) in subdiabetogenic doses. The icv-STZ model also culminates in central cholinergic dysfunctions, which in turn are known to underlie both the sAD cognitive decline, and synaptic plasticity impairments. Considering the cognitive-enhancing potential of chronic nicotine (Nic), we investigated whether it attenuates icv-STZ-induced impairments in recognition memory and synaptic plasticity in a cognition-relevant substrate: the hippocampal CA1-medial prefrontal cortex (mPFC) pathway. Rats treated with icv-STZ were submitted to a chronic Nic regime, and were evaluated for recognition memory. We then examined long-term potentiation (LTP), paired-pulse facilitation (PPF) under urethane anesthesia, and brains were also evaluated for hippocampus-mPFC cell density. We found that Nic treatment prevents icv-STZ-induced disruptions in recognition memory and LTP. STZ did not precipitate neuronal death, while Nic alone was associated with higher neuronal density in CA1 when compared to vehicle-injected animals. Through combining behavioral, neurophysiological, and neuropathological observations into the Nic-STZ interplay, our study reinforces that cholinergic treatments are of clinical importance against early-

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Key words: Alzheimer's disease, streptozotocin, nicotine, recognition memory, synaptic plasticity, long-term potentiation.

INTRODUCTION

Dysfunctional insulin signaling in the brain triggers the sporadic type of Alzheimer's disease (sAD) (de la Monte and Tong, 2014), which is characterized by decreased brain glucose metabolism (Hoyer, 1998; Frölich et al., 1998; Watson and Craft, 2003). Disturbances in central insulin signaling have also been shown to affect amyloid-beta (A β) levels and tau protein hyperphosphorylation (Hoyer, 2004; Salkovic-Petrisic et al., 2009), supporting the notion that sAD may be considered to be the brain type of diabetes (Hoyer, 2002; de la Monte, 2014). The intracerebroventricular (icv) administration of the diabetes-inducing drug streptozotocin (icv-STZ) has been investigated as a non-transgenic model of sAD (Lester-Coll et al., 2006; Salkovic-Petrisic and Hoyer, 2007). Subdiabetogenic doses of icv-STZ (1–3 mg/kg) mimic features of human sAD, such as metabolic dysfunctions (Hoyer and Lannert, 2007), brain insulin resistance associated with tau protein hyperphosphorylation (Grünblatt et al., 2007; Barilar et al., 2015), A β -like aggregation in meningeal vessels (Salkovic-Petrisic et al., 2011), cholinergic deficits (Blokland and Jolles, 1993), and memory impairments (Lannert and Hoyer, 1998; Agrawal et al., 2011). Taking into consideration that STZ does not cross the blood–brain barrier, icv-STZ decrease cerebral glucose uptake without altering blood glucose level (Grieb, 2016). However, it remains to be investigated whether the icv-STZ model can mimic functional connectivity alterations observed in sAD (Morgen and Frölich, 2015).

The earliest pathological events in Alzheimer's disease are thought to be the degeneration of basal forebrain cholinergic neurons, whose severity could positively correlate with memory impairments (Auld et al., 2002; Schliebs and Arendt, 2011). This finding has led to pro-cognitive therapeutic strategies via acetylcholine (ACh) neurotransmission, either by enhancing its endogenous level, or by reducing the activity of choli-

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Abbreviations: HFS, high-frequency stimulation; icv, intracerebroventricular; LTP, long-term potentiation; mPFC, medial prefrontal cortex; Nic, nicotine; PPF, paired-pulse facilitation; sAD, sporadic Alzheimer's disease; STZ, streptozotocin.

nesterase inhibitors (Anand et al., 2014). Modulating cholinergic receptors is another attractive approach. *In vivo* studies have indicated that agonists of muscarinic acetylcholine receptors (mAChRs) reverse cognitive impairments, while decreasing tau protein phosphorylation and A β processing (Fisher, 2012). Because nicotinic agonists are known as memory enhancers (Leiser et al., 2009; Levin, 2012), nicotinic acetylcholine receptors (nAChRs) are also potential targets against cognitive decline in Alzheimer's disease (Wallace and Bertrand, 2013). The nAChR agonist nicotine (Nic) is of particular interest, given its pro-cognitive effects on learning, memory, and attention (Kenney and Gould, 2008; Changeux, 2010; Gould and Leach, 2014), as well as its modulatory influence on synaptic plasticity and glutamatergic transmission in cortico-limbic circuits (Lambe et al., 2003; Poorthuis and Mansvelder, 2013). Nic treatments could, therefore, modulate cognitive and neurophysiological variables in animal models of Alzheimer's disease, which requires further investigation.

Synaptic plasticity is thought to be a cellular model of learning and memory (Bliss and Collingridge, 1993; Citri and Malenka, 2008). Limbic–cortical synaptic plasticity can be dysfunctional in prodromal Alzheimer's disease, which could explain its mild cognitive alterations (Scheff et al., 2006; Arendt, 2009). In this context, the hippocampal CA1–medial prefrontal cortex (mPFC) communication is prone to long-term plasticity (Lopes-Aguiar et al., 2008, 2013; Takita et al., 2013), is implicated in working memory (Spellman et al., 2015; Blot et al., 2015) and memory consolidation (Laroche et al., 2000; Taylor et al., 2016; Maingret et al., 2016; Jadhav et al., 2016; Barker et al., 2017). Thus, synaptic plasticity in this circuit could be increasingly altered as Alzheimer's disease develops, which can be experimentally studied using the icv-STZ model of SAD. Given the potential interplay between SAD and nicotinic modulation, we used rats to investigate the effects of icv-STZ – with or without chronic Nic treatment – on recognition memory, as well as CA1–mPFC synaptic plasticity. We also evaluated how these pharmacological manipulations affect cell density in the mPFC and hippocampus.

EXPERIMENTAL PROCEDURES

Animals

Male Wistar rats aged between 35 and 42 days (140–160 g) were housed in standard rodent cages under 24 °C and 12-h light/dark cycle (lights on at 7 AM) with free access to food and water. All behavioral experiments were performed between 7 AM and 7 PM. Procedures were in accordance with the Brazilian Council for Animal Experimentation (CONCEA) guidelines, and were approved by the Ethics Committee of the Ribeirão Preto Medical School, University of São Paulo. These guidelines also abide by the National Institutes of Health rules for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978).

A total of 40 rats were employed (starting with 10 animals per group), 12 of which were excluded because

of technical issues: usually, electrical noise, inconsistent evoked field postsynaptic potentials (fPSP), and loss of coronal specimens during the antigenic retrieval process. Such issues explain the variation in group size.

STZ injection and Nic treatment

Animals were anesthetized with ketamine and xylazine (0.75 and 0.38 mg/kg intraperitoneal, then 0.5 and 0.25 mg/kg intramuscular) and placed in a stereotaxic frame for bilateral icv injection of STZ (Sigma–Aldrich, USA). We used the following bregma-referenced coordinates: 0.5 mm posterior, 1.4 mm bilateral, 3.5 mm ventral from dura-mater, according to Paxinos and Watson (2007). STZ (3 mg/kg) was dissolved in 4 μ L of artificial cerebrospinal fluid (aCSF; in mM 1.2 CaCl₂, 2.7 KCl, 1.0 MgCl₂, 135.0 NaCl). Each hemisphere received 2 μ L of this solution through a 10 μ L microsyringe (Hamilton, USA) connected to a polyethylene tube (30 cm) and a gingival needle (13 mm, 30G; Injex, Brazil) at 0.5 μ L/min flow (Barilar et al., 2015). Control animals received aCSF instead. The surgery was concluded with scalp suture, subcutaneous flunixin meglumine (2.5 mg/kg; analgesic, anti-inflammatory, antipyretic) and intramuscular benzylpenicillin benzathine (0.2 ml/kg; antibiotic).

Rats were allowed to recover for two days before the chronic Nic treatment. This decision was based on Santos et al. (2012), who reported working memory disruptions three hours after icv-STZ injection, followed by degenerative processes already at day 1 post-injection. Nevertheless, all of our subjects were showing normal behavioral signs (including eating and drinking) at day 2 post-STZ, and care was taken to minimize their suffering.

For the chronic Nic treatment, we used the (–)-nicotine hydrogen tartrate salt (Sigma–Aldrich, USA) dissolved in sterile saline to a freebase concentration of 50 mg/mL. This solution was intraperitoneally injected (1 mg/kg) once per day over 20 days in STZ and aCSF animals (STZ-Nic and aCSF-Nic groups, respectively). Intraperitoneal saline was used for control (STZ-Sal and aCSF-Sal groups) (Fig. 1A). This Nic dose (1 mg/kg) is based on studies showing that chronic Nic prevents the effects from amyloid beta, and reduces the CSF levels of the amyloid precursor protein (Utsuki et al., 2002; Alkadhi et al., 2010). Furthermore, this dose did not induce visible behavioral abnormalities, such as seizure-like tremors, differently from a higher dose (3 mg/kg) we tested in a pilot study.

Behavioral assessment

A 65-day washout was allowed between the Nic regime and the behavioral testing period (Fig. 1A), which in turn lasted three days. This delay was meant to exclude withdrawal symptoms, and to evaluate Nic effects over an extended period. The first behavioral measurement was the locomotion on a white-floored open-field arena (46 $\times$ 46 cm) bounded by transparent acrylic walls and infrared sensors (Insight, Brazil). Beam breaks were collected over a 15-min period for analysis in 3-min bins. Our objective was to rule out locomotor alterations prior to the object recognition test.

Fig. 1. Experimental design and stimulation procedures. (A) Once recovered from the icv injection (streptozotocin, STZ, or artificial cerebrospinal fluid, aCSF), chronic treatment was performed (nicotine, Nic, or saline, Sal). A 65-day washout was allowed, and the rats were submitted to a battery of behavioral assessments (open-field locomotion and novel object recognition). At completion of the behavioral testing, the rats were anesthetized with urethane and submitted to acute electrophysiology *in vivo*. (B) Electrophysiological sessions consisted of a 30-min baseline, high-frequency stimulation (HFS) for induction of long-term potentiation (LTP), and an additional 240-min recording. Paired pulses (80-ms inter-pulse interval) were delivered into hippocampal CA1 every 20 s while recording field post-synaptic potentials (fPSP) from the medial prefrontal cortex (mPFC), except during HFS.

On the following two days, we employed the novel object recognition (NOR) paradigm. It consisted of three phases: habituation on day 1, and training followed by test on day 2. For habituation, animals were allowed to roam on a lab-made, black-floored wooden box (30 × 30 cm) for 15 min. For training, the rats were allowed to explore two identical objects (yellow cylindrical cups with blue lids, 3-cm diameter - 4-cm height) during 4 min, and were then returned to their home cages. After a 20-min interval, the animals were placed back onto the arena for the test phase, in which they were exposed to a novel object (white cylindrical cups with orange lids, 3-cm diameter, 3-cm height) and the familiar one (same from the training phase) for an additional 4 min (Bevins and Besheer, 2006; Warburton et al., 2013). Sessions were filmed by a webcam on the top of the box and all objects were wiped with 70% ethanol after each session. The object exploration was calculated as the percentage of time spent at each object divided by the time exploring both objects. Similarly, recognition index was calculated as the time spent at the novel object divided by the time exploring both objects. The discrimination ratio, in turn, was calculated as the difference between novel and familiar object exploration divided by the time exploring both objects. Quantification of object exploration time was performed by a blind observer.

Electrophysiology

On day 91 (Fig. 1A), rats were anesthetized with urethane (1.2 mg/kg i.p. in sterile saline; Sigma–Aldrich, USA) and placed back on the stereotaxic frame for electrode implantation with body temperature maintained at $37 \pm 0.5^\circ\text{C}$ through a heating pad (Insight, Brazil). When necessary, the level of anesthesia was maintained with supplementary injections of the anesthetic (10% of the initial dose) after checking the tail pinch reflex. Once the skull was exposed, two bregma-referenced holes were drilled (Paxinos and Watson, 2007): over the prelimbic (PL) region of mPFC (3.0 mm anterior, 0.5 mm lateral, 3.1–3.4 mm ventral from dura-mater) and the ipsilateral dorsal region of CA1 (4.7 mm posterior, 4.0 mm lateral, 2.5–2.8 mm ventral), each receiving a monopolar recording electrode. A third ipsilateral hole was drilled over the intermediate region of CA1 (5.7 mm posterior, 4.6 mm lateral, 2.5–2.8 mm ventral) for the bipolar stimulating electrode. Lastly, a fourth hole was drilled over the contralateral parietal cortex (no precise coordinate) to implant a microscrew for recording reference.

The bipolar electrode was made from twisted wires (Teflon-coated tungsten, 60 μm bare diameter, $\sim 500 \mu\text{m}$ inter-pole distance) for CA1 stimulation with a paired-pulse protocol (monophasic square pulses, 200- μs duration each pulse, 80-ms inter-pulse interval, 0.05 Hz

rate), while recording basal and facilitated field post-synaptic potentials (respectively fPSP1 and fPSP2) from the mPFC monopolar electrode (Teflon-coated tungsten, 60- μ m diameter) (Fig. 1B). Electrical pulses were generated from an S88X stimulator and photoelectrically isolated (PSIUX, Grass Technologies, West Warwick, RI, USA). Analogical signals were amplified, filtered ($\times 100$, 0.3–3 kHz, P55 pre-amplifier, Grass Technologies), digitized (10 kHz, PowerLab, AD Instruments), and recorded on LabChart 7.2 software (ADInstruments, Australia).

Before the experiment, the mPFC and intermediate CA1 implants were finely adjusted for optimal fPSP evoking and, therefore, electrophysiological validation of electrode positioning. We then delivered pulses at increasing intensities (60–500 μ A, 0.05 Hz) to probe the input–output curve, and to identify the stimulus intensity that would be used in the experiment (i.e., the intensity able to evoke fPSP amplitudes at $\sim 50\%$ of the maximum input–output amplitude).

We then started the experiment, comprising a 30-min baseline recording, long-term potentiation (LTP) induction, and an additional 240-min recording (Fig. 1B). Paired pulses were delivered throughout this timeline for probing the paired-pulse facilitation (PPF: fPSP2/fPSP1 amplitude ratio), except during LTP induction, when stimulation parameters were set to a high-frequency stimulation (HFS) protocol. It consisted of two series (10 min apart) of 10 trains (10 s apart), each train with 50 pulses at 250 Hz. LTP was evaluated in 10 min averaged fPSP amplitudes, which were plotted as ratios from the baseline mean amplitude (Lopes-Aguiar et al., 2008).

Cell density analysis

After electrophysiological recordings, rats were perfused with saline followed by phosphate-buffered 4% paraformaldehyde. Brains were removed from the skull, dehydrated in 70% ethanol, and embedded in paraffin for microtome sectioning (8 μ m) and hematoxylin and eosin staining (Laborclin, Brazil). Coronal specimens were obtained from the following anterior–posterior segments: +4.68 to +2.76 mm (prefrontal cortex), and –4.44 to –4.80 mm (intermediate hippocampus) (Paxinos and Watson, 2007). Images from the PL area of the mPFC, and CA1 of the hippocampus were captured through a video monochrome charge-coupled device camera (Model 2400, Hamamatsu Photonics, Tokyo, Japan) attached to a microscope (Model BX60, Olympus, Tokyo, Japan). Images were averaged and digitized using the Scion Image frame grabber, and were then analyzed using the public-domain software ImageJ (NIH, Bethesda, MD, USA). Five squares of 50 $\times$ 50 μ m were randomly placed on each analyzed brain area (right and left hemispheres) from all animals of each group, and then averaged after the counting. We performed neuron counts (neurons per cubic millimeter) estimated at 200 $\times$ magnification using a morphometric grid methodology and Abercrombie's correction (Abercrombie, 1946) as previously described and extensively used by our group and others (Andrade-Valença et al., 2008; Kandratavicius et al.,

2013, 2014; Rodrigues et al., 2015; Wolf et al., 2015). Neurons were distinguished from glial cells by their clearly distinct morphological appearance. The experimenter was blinded to group allocation.

Statistical analysis

One-way ANOVA was used to compare averaged (i.e., single value) variables between groups, namely: open field total distance, recognition index, baseline fPSP properties (latency, amplitude and PPF), average power spectra bands, and cell density. Two-way ANOVA was used to compare repeated measure variables between groups over time: open field data, discrimination ratio, input–output curve, and time dependent power spectra bands. Tukey's post hoc comparisons were made when ANOVA returned significant effects at the $p < 0.05$ criterion.

RESULTS

Locomotor activity is not altered by Nic or STZ

During the chronic Nic treatment, increased grooming and locomotion was observed only within 5 min after each injection. However, spontaneous activity in the open field test, i.e., 65 days after the Nic treatment, did not differ among groups, either by measuring the total (whole 15-min session) (Fig. 2A₁) or the binned (3-min) distance traveled (Fig. 2A₂).

Nic prevents STZ-induced recognition memory deficits

Performance in the NOR task showed that STZ rats had a significant impairment in recognition memory, which was reverted by the chronic Nic treatment. Recognition indices of STZ-Sal rats were at least 25% lower than those of other groups ($F_{(3,24)} = 12.643$, $p < 0.001$) (Fig. 2B₁). The same can be seen in the discrimination ratio, which revealed no preference of STZ-Sal rats for either object during both training and test phases. Lastly, aCSF-Nic and STZ-Nic discrimination ratio were similar to the aCSF-Sal group (training vs. test: $F_{(1,24)} = 48.261$, $p < 0.001$; Fig. 2B₂). All groups explored both objects equally during the training phase. However, in the test phase only STZ-Sal animals did not show differences in the exploration of object A and B, while others groups revealed an increased exploration of the novel object B (training A vs. test B, $p < 0.001$; Fig. 2B₃).

STZ diminishes LTP without altering PPF, and Nic attenuates the effect

No significant differences in the input–output curve, baseline fPSPs latency, or baseline fPSPs amplitude were found among groups (Fig. 3), indicating that the basal hippocampal CA1-mPFC neurotransmission was not affected by any drug treatment prior to the synaptic plasticity experiment. In agreement with the literature, a negative peak at 14–17-ms latency from each pulse characterized all fPSP (Laroche et al., 1990; Takita

Fig. 2. Effects of streptozotocin (STZ) and nicotine (Nic) on locomotor activity and novel object recognition (NOR). (A₁) Neither STZ nor Nic affected the total distance traveled, as measured in the open-field test. (A₂) Locomotor activity throughout 3-min bins indicates that all four groups explored less over time ($p < 0.001$). (B) Detrimental effects of STZ on recognition memory were reverted by Nic. (B₁) Recognition index ($p = 0.002$). (B₂) Discrimination ratio ($p < 0.001$). (B₃) Training vs. test object exploration percentages of each experimental group ($p < 0.001$). Values expressed as mean $\pm$ standard error.

et al., 1999) (Fig. 3A, D). The average baseline PPF ratio (fPSP2/fPSP1) was of 2.47 ± 0.14 across all groups, and the fPSP1 amplitudes, in particular, were always above $150 \mu V$ (Fig. 3C–E).

fPSPs and PPF amplitudes of aCSF-Sal animals were compared with the remaining groups in order to investigate time-dependent effects of STZ and chronic Nic in LTP (Fig. 4). Our results show that STZ decreased induction and maintenance of fPSP1 LTP by at least 30% (treatment vs. time interaction:

$F_{(26,260)} = 3.605$, $p < 0.001$). A similar LTP reduction of at least 25% was found in fPSP2 amplitudes (treatment vs. time interaction: $F_{(26,260)} = 2.763$, $p < 0.001$). We also observed that STZ did not affect PPF when comparing STZ-Sal and aCSF-Sal rats (Fig. 4-Left).

Interestingly, chronic Nic reversed the LTP effect caused by STZ, as seen in the fPSP1 results from the STZ-Nic group. In fact, 50 min after HFS there were still no differences in fPSP1 amplitude between STZ-Nic and aCSF-Sal animals. During the initial 50 min, STZ-Nic vs.

Fig. 3. Field postsynaptic potentials (fPSP1 and fPSP2) properties recorded from the medial prefrontal cortex (mPFC). (A) Averaged fPSP1 and fPSP2. (B) Input-output curves showing no significant differences among groups. Values expressed as mean $\pm$ standard error. (C) Baseline paired-pulse facilitation (PPF) in the mPFC. (D) Baseline fPSP1 and fPSP2 latencies. (E) Baseline fPSP1 and fPSP2 amplitudes. No differences were found among groups. Values expressed as mean and dispersion.

aCSF-Sal differences were about 10% lower than between STZ-Sal and aCSF-Sal (treatment vs. time interaction: $F_{(26,286)} = 2.796$, $p < 0.001$). Likewise, STZ-Nic vs. aCSF-Sal comparisons regarding fPSP2 and PPF returned no significant differences (Fig. 4-middle). Nic treatment, per se, did not affect LTP or PPF when comparing aCSF-Nic and aCSF-Sal groups (Fig. 4-right).

When STZ-Nic rats were compared to STZ-Sal ones, we observed that Nic treatment enhanced LTP induction and maintenance of both fPSP1 (effect of treatment: $F_{(1,286)} = 8.061$, $p = 0.015$) and fPSP2 (effect of treatment: $F_{(1,286)} = 9.302$, $p = 0.015$) (Fig. 5A, B-right). We also found that interaction effect from fPSP2 data (treatment vs. time interaction: $F_{(26,286)} = 1.693$, $p = 0.021$) (Fig. 5B-left). Additionally, Nic treatment did not affect PPF when comparing STZ-Sal and STZ-Nic rats (Fig. 5C).

Chronic Nic prevents neuronal loss in CA1

Cell density in CA1 and the PL region of mPFC showed no differences between STZ and aCSF-Sal animals (Fig. 6). However, aCSF-Nic rats showed a significantly higher cell density in CA1 when compared with other groups ($F_{(3,17)} = 6.519$, $p < 0.05$). This finding suggests that chronic Nic exerted an STZ-unrelated neuroprotective effect against age-related cell loss in CA1. Increased neuron density was also observed in the mPFC of

aCSF-Nic animals, as we found a significant difference between them and STZ-treated animals ($F_{(3,17)} = 4.887$, $p < 0.05$; Fig. 6B).

DISCUSSION

Through employing a straightforward behavioral paradigm followed by *in vivo* electrophysiology, our study reveals detrimental effects of icv-STZ to recognition memory, as well as hippocampal-prefrontal LTP. Noteworthy, we demonstrated that chronic Nic treatment prevents these STZ-induced dysfunctions.

Our findings are consistent with the literature concerning behavioral aspects of sAD rodent models (Lannert and Hoyer, 1998). Shoham et al. (2007) and Espinosa et al. (2013) have reported recognition memory impairments in icv-STZ-treated rats, and a comparative study between rodent models of sAD (Chen et al., 2013) has shown that the icv-STZ model is even more detrimental to short-term memory than the transgenic 3xTg-AD mouse model. In line with the icv-STZ impact on cognition, spatial discrimination impairments in STZ-treated animals were shown to correlate with reduced choline acetyltransferase (ChAT) activity in the hippocampus (Blokland and Jolles, 1993; Prickaerts et al., 1999). Because of the cholinergic involvement in both cognition and cortico-limbic plasticity (Poorthuis and Mansvelder, 2013; Gould and Leach, 2014), our findings are further

Fig. 4. Field postsynaptic potentials (fPSP1 and fPSP2) and paired-pulse facilitation (PPF) recorded from medial prefrontal cortical (mPFC) during long-term potentiation (LTP). Streptozotocin (STZ) weakened the LTP induction and maintenance, as measured from the amplitudes of fPSP1 (A, left) and fPSP2 (B, left; $p < 0.05$). (C, left) In turn, PPF was not affected by STZ. The middle graphs follow the same organization, this time showing that nicotine (Nic) treatment attenuated the STZ effects on LTP, as measured from both fPSP1 and fPSP2 amplitudes. The right graphs contain direct comparisons between STZ-untreated groups, showing that Nic, per se, did not affect LTP in a significant manner. Values expressed as mean $\pm$ standard error.

linking behavior and neurophysiology in the icv-STZ model.

It has been hypothesized that LTP-like alterations of synaptic efficacy underlie memory consolidation processes at the systems level (Takeuchi et al., 2013). Particularly, the hippocampus and prefrontal cortex act in synchrony during spatial working memory tasks and are reactivated during rest or non-REM sleep, supporting episodic memory consolidation (Maingret et al., 2016; Jadhav et al., 2016; Barker et al., 2017). Thus, synaptic plasticity in the CA1-mPFC pathway is a possible substrate for episodic memory storage (Laroche et al., 2000). To our knowledge, the present work is the first to demonstrate that icv-STZ reduces the hippocampal-

prefrontal LTP *in vivo* with no significant effects on the short-term synaptic plasticity. Synaptic dysfunctions in animal models of Alzheimer's disease have been well addressed in transgenic models (Chakroborty et al., 2012; Sancheti et al., 2013; Clark et al., 2015). Additionally, Xu et al. (2014) have reported that icv-STZ decreases the dendritic spine density, which was in turn associated with alterations in spatial memory and hippocampal LTP *in vitro*. As our study differentiates between affected LTP and unaffected PPF, we suggest that both the icv-STZ model and human SAD may present postsynaptic – rather than presynaptic – plasticity dysfunctions. This would be consistent with Shonesy et al. (2012), which have indicated that brain insulin resistance

Fig. 5. Effects of nicotine (Nic) treatment on streptozotocin (STZ) rats on field postsynaptic potentials (fPSP1 and fPSP2) and paired-pulse facilitation (PPF). Direct comparisons between STZ-treated groups additionally show that nicotine (Nic) attenuated the STZ effects on long-term potentiation (LTP), as measured from fPSP1 and fPSP2 amplitudes (A, B). (C) In turn, PPF did not differ between groups. The bar graphs on the right are from averaged post-HFS data, reinforcing conclusions from the curve graphs on the left (* $p < 0.05$). Values expressed as mean $\pm$ standard error.

does not result in presynaptic impairments. [Srivareerat et al. \(2011\)](#) have also assessed chronic Nic's effects in the A β infusion model of Alzheimer's disease. The study has shown that chronic Nic prevents CA1 LTP deficits in A β -infused rats. [Srivareerat et al. \(2011\)](#) have additionally found that Nic prevents spatial learning and short-term memory impairments from A β infusion. Besides, Nic neither enhanced nor decreased HFS-induced LTP in non-A β -infused rats, in agreement with our work. Subsequently, [Ardiles et al. \(2012\)](#) have shown that decreases in recognition memory are correlated with postsynaptic deficits in the Schaffer collateral–CA1 pathway in *Octodon degus*, a rodent species known for spontaneously developing pathological signs of Alzheimer's disease.

Hypofunction of classical cholinergic markers (e.g., ChAT, ACh, and ACh receptors) throughout the basal forebrain, neocortex, and hippocampus, has been related to the progressive cognitive deficit in early Alzheimer's ([Schliebs and Arendt, 2006, 2011](#); [Hernandez and Dineley, 2012](#)). Such changes have led to the cholinergic hypothesis of memory dysfunction ([Bartus, 2000](#); [Craig et al., 2011](#)). In fact, enhancing cholinergic function by continued use of cholinesterase inhibitor drugs is the currently accepted treatment against the onset of Alzheimer's disease ([Anand et al., 2014](#)). However, several studies indicate that directly activating

Fig. 6. Cell density in CA1 and the prelimbic (PL) region of the medial prefrontal cortex (mPFC) following streptozotocin (STZ). (A) Representative CA1 and mPFC images from each experimental group. (B) STZ per se did not alter CA1 or mPFC cell densities. Nicotine (Nic) alone increased CA1 cell density when analyzing STZ-untreated groups. The mPFC also showed increased neuronal density in the aCSF-Nic group when compared to the STZ-Sal and STZ-Nic groups (* $p < 0.05$ vs. aCSF-Nic). Values expressed as mean $\pm$ standard error.

the $\alpha 7$ and $\alpha 4\beta 2$ subtypes of nAChR can improve both synaptic transmission and cognition ([Wallace and Porter, 2011](#); [Kroker et al., 2011](#); [Ondrejcek et al., 2012](#)). Thus, direct nAChR targeting has emerged as an alternative approach for treating Alzheimer's disease, as well as other cognitive disorders ([Haydar and Dunlop, 2010](#)). The agonism of $\alpha 7$ and $\alpha 4\beta 2$ nAChR subtypes can be among the Nic-mediated changes we observed here. In fact, chronic Nic exposure may trigger a cascade of events involving nicotinic receptor desensitization followed by long-lasting up-regulation ([Gould and Leach, 2014](#); [Markou, 2008](#); [Dani and Bertrand, 2007](#); [DiFranza and Wellman, 2007](#)). We suggest that these processes could compensate for the disrupted cholinergic transmis-

sion in icv-STZ, thus ameliorating mnemonic and synaptic plasticity deficits.

Finally, we also found that Nic per se may exert neuroprotective effects in CA1 against age-related cell loss. Saxena et al. (2011) have shown that a 14-day chronic Nic treatment in icv-STZ-treated animals avoids mitochondrial dysfunctions and caspase-3 activity, evidencing the Nic protective influence against apoptosis-related processes. Our findings, together with those from Srivareerat et al. (2011), are in agreement with multiple reports on Nic neuroprotective roles (Fujii and Sumikawa, 2001; Picciotto and Zoli, 2002; Liu and Zhao, 2004; Unger et al., 2006; Poorthuis et al., 2009). In addition, it has been shown that neuroprotection is blocked by nAChR antagonists (Akaike et al., 2010), and that nicotinic receptors can modulate mnemonic processes involving ACh release and Ca^{2+} homeostasis (Séguéla et al., 1993; McGehee et al., 1995).

In summary, we show that Nic effectively prevents recognition memory and hippocampal-prefrontal LTP deficits from icv-STZ. Targeting nAChR might represent a useful strategy against the cognitive deficits of prodromal Alzheimer's disease, but more studies are needed to identify nicotinic regimes devoid of addictive side effects, either using Nic or other nicotinic drugs. Moreover, as suggested by the distinct LTP and PPF effects to icv-STZ, each form of synaptic plasticity might undergo particular perturbations as Alzheimer's disease progresses, which deserves detailed investigation.

FINANCIAL DISCLOSURES

None of the authors have any potential or actual financial interests or conflict of interest.

Acknowledgments—We thank Renata Caldo Scanduzzi and Antonio Renato Meirelles e Silva for their technical support. Further, we thank Calvin K. Young and Christopher Kushmerick for valuable comments. This work was supported by grants from CNPq [#161239/2011-0; #2012/23918-0], São Paulo Research Foundation (FAPESP) [#2014/18211-0; #2015/25275-8], and CNPq/MS/SCTIE/DECIT [#466995/2014-8].

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(Received 15 February 2017, Accepted 10 April 2017)
(Available online 19 April 2017)