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Original Article

Dopamine depletion in wistar rats with epilepsy

Depleção da dopamina em ratos wistar com epilepsia

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Abstract

The dopamine content in cerebral structures has been related to neuronal excitability and several approaches have been used to study this phenomenon during seizure vulnerability period. In the present work, we describe the effects of dopamine depletion after the administration of 6-hidroxidopamine (6-OHDA) into the substantia nigra pars compacta of male rats submitted to the pilocarpine model of epilepsy. Susceptibility to pilocarpine-induced *status epilepticus* (SE), as well as spontaneous and recurrent seizures (SRSs) frequency during the chronic period of the model were determined. Since the hippocampus is one of main structures in the development of this experimental model of epilepsy, the dopamine levels in this region were also determined after drug administration. In the first experiment, 62% (15/24) of 6-OHDA pre-treated rats and 45% (11/24) of those receiving ascorbic acid as control solution progressed to motor limbic seizures evolving to SE, after the administration of pilocarpine. Severeness of seizures during the model´s the acute period, was significantly higher in epileptic experimental rats (56.52%), than in controls (4.16%). In the second experiment, the frequency of seizures in the model's chronic phase did not significantly change between groups. Our data show that dopamine may play an important role on seizure severity in the pilo's model acute period, which seems to be due to dopamine inhibitory action on motor expression of seizure.

Keywords: dopamine, pilocarpine, epilepsy, substantia nigra, hippocampus.

Resumo

O conteúdo de dopamina nas estruturas cerebrais tem sido relacionado à excitabilidade neuronal e várias abordagens têm sido utilizadas para estudar este fenômeno durante o período de vulnerabilidade às crises. No presente trabalho, descrevemos os efeitos da depleção de dopamina após a administração de 6-hidroxidopamina (6-OHDA) na região pars compacta da substância negra de ratos submetidos ao modelo de epilepsia com pilocarpina. A susceptibilidade ao estado de mal epiléptico induzido pela pilocarpina, bem como a frequência de crises espontâneas e recorrentes durante o período crônico do modelo foi determinada. Sendo o hipocampo uma das principais estruturas afetadas no desenvolvimento desse modelo experimental de epilepsia, os níveis de dopamina nessa região foram determinados após a administração da droga. No primeiro experimento, 62% (15/24) dos ratos pré-tratados com 6-OHDA e 45% (11/24) daqueles que receberam ácido ascórbico como solução controle evoluíram para crises límbicas motoras e para o estado de mal epiléptico, após a administração de pilocarpina. A gravidade das crises durante o período agudo do modelo foi significativamente maior nos ratos epilépticos experimentais (56,52%) do que nos ratos controle (4,16%). No segundo experimento, não houve diferença significante entre os grupos quanto à frequência de crises na fase crônica do modelo. Nossos dados mostraram que a dopamina pode desempenhar um papel importante na gravidade das crises na fase aguda da pilo, o que parece ser exercido por sua ação inibitória da dopamina sobre a expressão motora das crises.

Palavras-chave: dopamina, pilocarpina, epilepsia, substantia nigra, hipocampo.

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1. Introduction

The relationship between underlying mechanism and the neurotransmitter system is a two-way road and it has been investigated during the last decades. On one hand, this relation can be concentrated in verifying the changes induced by epileptic condition on neurotransmitter synthesis, released content and receptor activity. On the other hand, the investigation can be aimed at verifying the effects of direct or indirect stimulation or inhibition of a given neurotransmitter system on the establishment or spreading of an epileptic event. In general terms, epileptic discharge, seizure-like behaviors in the chronic phase of Pilocarpine experimental model, sudden unexpected death in epilepsy and consequently epileptic seizures have been associated with an imbalance between excitation and inhibition in specific brain circuitries (Bozzi and Borrelli, 2013; Dal Pai et al., 2022; Alharbi, 2021; Scorza et al., 2010). This hypothesis has been repeatedly tested in experiments where agonists or antagonists of specific receptor sites were able to interfere with the occurrence of an epileptic event. The role of catecholamines in seizure susceptibility have been demonstrated in several models of epilepsy (Bozzi and Borrelli, 2013; Trindade-Filho et al., 2008). The use of dopaminergic ligands specific for different subclasses of dopamine (DA) receptors allowed to demonstrate that DA has an anti-epileptic action in a wide variety of animal models. Dopamine has been implicated in the modulation of seizure threshold in animal models of epilepsy (Weinshenker and Szot, 2002). Furthermore, reduced dopamine transporter binding has been reported for juvenile myoclonic epilepsy in the substantia nigra and ventral tegmentum and epilepsy with tonic-clonic seizures in the putamen suggesting that dopaminergic alterations may be related to the pronounced motor manifestation of syndrome-related seizures (Ciumas et al., 2008; Odano et al., 2012; Ciumas et al., 2010). Further studies have focused on the role of the dopaminergic system within the basal ganglia-thalamocortical circuitry and its assumed ability to control the propagation of seizures (Deransart and Depaulis, 2002).

In this context, the aim of this work was to investigate the effect of dopaminergic pathway depletion in the development of acute and chronic phases of pilocarpine-induced temporal lobe epilepsy in rodents.

2. Materials and Methods

2.1. Chemical and drugs

Analytical grade chemicals were used in sample and mobile-phase preparations. Perchloric acid (HClO4), Na2S2)2, EDTA-disodium salt (titriplex III) citric acid, orthophosphoric acid, hydrochloric acid, sodium chloride, methanol (Lichorov), Na2HPO4, and 2-mercaptoethanol were purchased from Merck (Darmstadt). Dihydroxybenzilamine (DHBA), 6-hidroxydopamine, pilocarpine hydrochloride, and scopolamine methylnitrate were purchased from Sigma (St. Louis, MO, USA).

2.2. Animals

For at least 1 week before the experiments (after approved for Committee of ethics n°: 16A/2019), adult male Wistar rats, randomly selected from the same pool, weighting 220-280 g were housed in groups of five on a standard light/dark cycle of 12 h (night at 7:00 pm). Room temperature and humidity were controlled between 20 and 24 °C and 45-55%, respectively. Rat Chow pellet and water was given *ad libitum*. The experiments were performed with institutional approval of ethical protocols and all efforts were made to minimize animal suffering. Moreover, assisted feeding and hydration were carried out during the initial recovery of the acute period (status epilepticus) to improve the animal's general physical state and survival.

2.3. Procedures

For stereotaxic surgery purposes, animals were anaesthetized with a chloral hydrate/pentobarbital mixture and placed in the stereotaxic frame. A 30-gauge needle was lowered into the substantia nigra pars compacta (AP: -5.3; L: 1.9; H: -8.1), according to the Paxinos and Watson atlas (2007), and a 0.2 ul of a solution containing 1 $mg.ml^{-1}$ 6-hydroxydopamine (6-OHDA) dissolved in 1% ascorbic acid (20 $ug.ul^{-1}$ concentration) was infused in a speed of 0.1 l/min (around 2 minutes long). Ascorbic acid was used as a solvent to maintain the 6-OHDA neurotoxicity. Pilo model of epilepsy was performed in all animals receiving, first, an injection of scopolamine methylnitrate (1 $mg.kg^{-1}$, s.c.) with the purpose of limiting peripheral cholinergic effects; and, 30 minutes after, an injection of pilo (350 $mg.kg^{-1}$, i.p.). All procedures were performed between 8 at 10 a.m. During the recovery period of *status epilepticus* (SE), animals were assisted with feeding and hydration by mouth, to assure their general physical state and survival.

2.3.1. Experiment 1

The aim of this experiment was to test the effect of dopamine depletion on the development of pilo-induced SE (experimental model's acute period). For that, 72 animals were randomly distributed in 3 groups of 24 rats: 6-OHDA and ascorbic acid received the substance into the substantia nigra pars compacta, via stereotaxic surgery. One week after surgery, all groups were submitted to pilo model of epilepsy- see procedures section. After treatment with pilo, all groups were continuously monitored (for 72h) for the observation of the main characteristics of the model's acute phase. After this period, animals were euthanized for hippocampal neurochemical analysis (Figure 1).

2.3.2. Experiment 2

This experiment was designed to study the effect of dopamine depletion on the frequency of spontaneous and recurrent seizures (SRS) (experimental model's chronic period). For that, 27 rats received pilo injection followed by a closer monitoring for 4 h. After that, rats were settled in the video-monitoring room, where they were recorded 24 h/day for 3 weeks, while, during this period, the first spontaneous seizure and recurrent seizures were observed and recorded. The first spontaneous seizure is the landmark

of this model, meaning that animals became epileptic. After that, epileptic animals were randomly assigned to two groups: 6-OHDA: 16 epileptic rats, received 6-OHDA into the substantia nigra stereotaxically; and, Control: 11 epileptic rats, received ascorbic acid in the same nucleus. Aiming to avoid inflammatory interference in the occurrence of seizure frequency, animals were let to rest for 2 weeks, when they returned to the video-monitoring room for additional 3 weeks. In this period, the frequency of SRSs was recorded. After this period, the seizure frequency of each animal was compared with that observed before receiving 6-OHDA treatment (Figure 1).

2.3.3. Neurotransmitter analysis

Dopaminergic content in the hippocampus of animals after being induced to the pilo model of epilepsy were not performed once important changes in this monoamine content were previously demonstrated by Cavalheiro et al. (1994) in the acute and chronic model's periods. For control purposes of the effect of 6-OHDA injection into the substantia nigra pars compacta, on the hippocampal dopamine content, 10 animals were sacrificed right after the end of each experiment and had both hippocampi removed. Hippocampi were then placed on an ice-chilled plate, weighted, and stored at -80 °C until the neurochemical assay was accomplished. Assay procedure was performed by ultrasonically homogenizing the tissue in a 0.1 M solution of HClO4 containing 0.02% Na2S2O2 and DHBA (as internal standard) at a proportion of 15µl solution for each milligram of tissue. Samples were then centrifuged at 11.000 g, for 50 min, at 4 °C. The supernatant was filtered and injected into the high-performance liquid chromatography system (HPLC) and the dopamine content was quantified as previously described by Cavalheiro et al. (1994).

2.3.4. Data analysis

Statistical differences in hippocampal dopamine levels were evaluated using Student's t-test. Comparisons of seizure frequency between groups were made using Mann-Witney test and the effects of 6-OHDA on the acute effects of pilocarpine were analyzed using the chi-square test. A value of p≤0.05 was accepted as significant. GraphPad Software Prism 4.0, San Diego, USA, was used to analyze the data.

3. Results

3.1. Experiment 1

After pilo administration, 62% (15/24) of 6-OHDA pretreated rats and 45% (11/24) of those receiving ascorbic acid as control solution, progressed to motor limbic seizures evolving to SE. Animals from all groups remained in SE for approximately 11 hours, when they gradually started to exhibit normal behavior. It was observed that the severity of motor seizures behaviors was significantly higher in the 6-OHDA group (p= 0.0014). Thirteen animals pretreated with 6-OHDA and only 1 animal pretreated with ascorbic acid showed tonic seizures and died (Table 1).

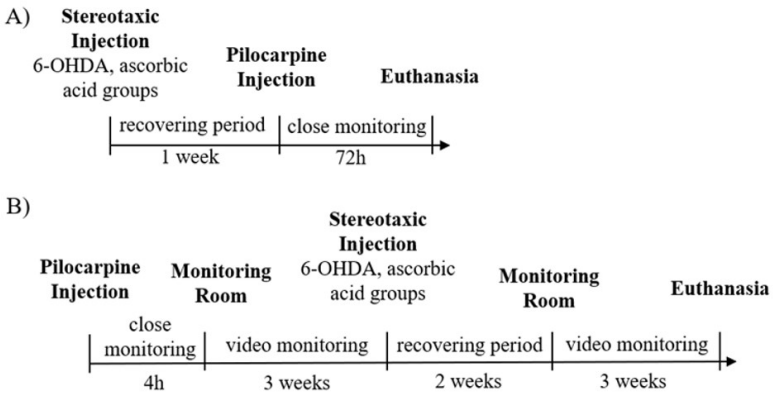

Figure 1. Time line of experiments 1 (A) and 2 (B).

Table 1. Seizure severity in rats injected with ascorbic acid (control group) and 6-OHDA (6-OHDA group) after pilocarpine injection.

Grupos	Tonic Seizures		Total	% Tonic Seizures
	Yes	No		
Controle	1	23	24	4.16
6-OHDA	13*	10	24	56.52
Total	14	33	48	29.78

*p=0.0014.

Table 2. Seizure frequency in control rats before and after acid ascorbic injection (CTL/B and CTL/A, respectively) and experimental rats before and after 6-OHDA injection (6-OHDA/B and 6-OHDA/A, respectively).

Groups	CTL/B	CTL/A	6-OHDA/B	6-OHDA/A
Media	11.16	9.5	9.83	12.16
Stander deviation	5.7	4.92	5.7	5.84

3.2. Experiment 2

6-OHDA injection significantly decreased dopamine levels in the hippocampus, 7 days after surgery. A reduction of 58% of DA was observed in experimental animals, when compared to controls. Hippocampal levels of noradrenaline and serotonin remained unchanged. The effects of 6-OHDA and ascorbic acid intracerebral injection into the substantia nigra, in the frequency of SRSs, in epileptic rats are presented below. The 6-OHDA group presented a tendency to show higher number of SRSs after drug injection, however, no significance was observed. Values of SRSs obtained were, epileptic rats before 6-OHDA, 9.45 ± 4.92 and, epileptic rats after 6-OHDA injection: 12.16 ± 5.8. Similarly, the 6-OHDA injection did not alter the presentation of the epileptic seizures, animals showed regular pattern of clonic seizures in the model's chronic phase. Regarding control epileptic animals, values of SRSs obtained before and after ascorbic acid administration, are shown in Table 2.

4. Discussion

In this study we evaluated the behavioral effects of the reduction of dopamine levels in the brain of animal that went through the experimental model of epilepsy using pilo. 6-OHDA injection into the substantia nigra pars compacta was effective in reducing hippocampal levels of dopamine, while levels of other monoamines remained unchanged. Regarding model's acute phase, after pilo injection in animals previously depleted of dopamine, we observed stronger and severe motor seizures, as tonic ones. This finding suggests that dopamine depletion may have facilitated the induction of SE, which invariably led few animals to death. The possible main cause of deaths was hypoxia once apnea occurred during tonic seizures and a marked cyanosis was also evident during and after seizure. Concerning the frequency and the pattern of SRSs in epileptic animals before and after depletion of hippocampal dopaminergic levels, no differences was observed.

Our findings are in accordance with other studies, reinforcing the systematic use of the neurotoxin 6-OHDA in the functional comprehension of the dopaminergic system (Zhang et al., 2014; Yang et al., 2014; Wen et al., 2015). According to literature, biochemical evidence of dysfunction of the dopaminergic system in the brain of patients with epilepsy have been contradictory. Some studies have demonstrated reduction in dopamine levels and in its main metabolite, homovanillic acid in the cerebrospinal fluid of patients with idiopathic epilepsy (Rocha et al., 2012; Paredes et al., 2015). Such works are consistent, considering that reduction of dopaminergic transmission might be important in the expression of epilepsy. However, others have not observed alterations in dopamine release or in its metabolism, in experimental models of epilepsy (Szabó et al., 2015). Previous studies from Cavalheiro and Turski (1986), Ikonomidou-Turski et al. (1987), Cavalheiro et al. (1987) and Turski et al. (1988), have demonstrated that injection of picomoles of apomorphine, a dopaminergic agonist, bilaterally in the animal striatum, provided protection against pilo-induced seizures. Our study corroborates such authors, suggesting that dopaminergic transmission in the substantia nigra play a fundamental role in modulating the susceptibility of neurons do seizures. Results obtained in experiment one, point to the protective role of dopamine in the susceptibility and severity of seizures induced by pilo injection. On the other hand, once animals became epileptic (model's chronic phase) and the epileptogenic process have been established, the depletion of dopamine had no effect on altering seizure parameters.

Our results are similar to those obtained by Michelson and Buterbaugh (1985), in which 6-OHDA was injected into the cerebral ventricles of rats and were induced to the kindling model of seizures. In this work, authors observed that kindling behaviors were shown earlier than expected. Researchers suggested that catecholamines would play a role in limiting the spread of seizures in the model's acquisition phase, but once generalization of seizures have started, this system would not be able to limit it's spread. Mintz and Herberg (1986) showed evidence of the protective effect of dopaminergic system when amphetamine was given to animals induced to the kindling model. Authors observed that kindling occurred more rapidly when performed in the hemisphere with low amphetamine content, than in the contralateral hemisphere. Rotational body behaviors were also observed, which helped in determining which hemisphere contained naturally lower dopamine content. The use of dopaminergic agonists has reinforced the hypothesis of a protective role played by dopamine. In humans, apomorphine is effective in decreasing the occurrence of high-frequency graphotypes associated with myoclonus caused by intermittent stimulation. Apomorphine is also strongly anticonvulsive in genetically prone mice. Similarly, apomorphine injection protects animals against generalized seizures after systemic injection of pilo (Ujihara et al., 1991; Hara et al., 1993). In general, it seems that dopaminergic system has a protective effect against stimuli that trigger seizures. However, there are examples of deleterious effects of apomorphine on the progression of seizures, since it is suggested that endogenous dopamine could be anti or pro-convulsive, and these actions would depend, in part, on brain structures involved and the preferred

action of dopaminergic agonists on D1 or D2 receptors (Fariello et al., 1987).

Cavalheiro et al. (1994) demonstrated increased levels of dopamine in the rat hippocampus in all phases of the pilo model, suggesting that dopamine does not play a major role in pilo-induced convulsions and thus contradicting the behavioral results obtained in this experiment. It is known, however, that dopaminergic neurons receive dense GABAergic afferent fibers from rostromedial tegmental nucleus, also known as tail of the ventral tegmental area rostromedial tegmental nucleus (Matsui and Williams, 2011).

During the acute phase of pilo model, the activation of such GABAergic neurons, due to intense epileptic activity, could be inhibiting dopaminergic neurons, which would be responsible for increased content and decreased dopamine release observed by Cavalheiro et al. (1994) in the pilo model. This same effect could also be observed in the chronic phase of the model resulting from the interictal epileptic activity. In any case, it is possible that the protective effect of dopamine on the pilo model is materialized in other structures, than in the hippocampus. Alam and Star (1996) suggested the striatum as one of those structures, once authors observed an increase in the rate of dopamine turnover in the striatum, nucleus accumbens and cingulate gyrus when using systemic pilo and intra-hippocampal carbachol was applied. These results demonstrated that nigral pathways respond differently during epileptic activity causing increased dopamine release in the mesocortical and mesoaccumbens systems, leaving unchanged or having an opposite effect on the meso hippocampal system.

Other studies have suggested the striatum as an important site of mediating dopaminergic activity in the control of convulsive activity. Injection of D2 receptor agonists into the nucleus accumbens and olfactory tubercle, abolished convulsive activity from a behavioral and electrographic point of view, as well as avoiding the neuropathological alterations resulting from the injection of pilo (Al-Tajir et al., 1990; Al-Tajir and Starr, 1991).

Such results tend to reinforce the idea that dopaminergic action on epileptic activity of pilo model would be due to its action on cerebral structures other than the hippocampus. This idea, however, has strong opposition in the results of studies with the intrahippocampal use of selective agonists and antagonists at dopaminergic receptors. Alam and Starr (1996) have shown that intrahippocampal injection of the selective D2 receptor antagonist raclopride caused the animal to have status epilepticus with doses of pilo normally subconvulsive. These results therefore indicate that tonic release of dopamine in the hippocampus is essential to avoid excessive synchronization of hippocampal neuronal activity, thus avoiding epileptic seizures.

The complexity of dopaminergic role in the control of epileptic phenomenon is evidenced by the diversity of types of receptors. Several authors have observed a protective effect of dopamine on limbic seizures mediated by D2 receptors (Barone et al., 1991; Alam and Starr, 1993; Vallar et al., 1988) demonstrating that this inhibitory effect was mediated by the decrease in adenyl cyclase activity and consequently decrease of endogenous levels of cyclic AMP. Adding to it, they observed activation of potassium channels and inhibition of calcium channels. On the other hand, D1 type receptors have been implicated as a probable exacerbator of epileptic activity (Barone et al., 1992). Turski et al. (1990) demonstrated that the use of selective agonist D1 receptors, SKF 38393, caused an increase in the frequency, severity and lethality of seizures following pilo injection. All effects cause by SKF 38393 were avoided using the selective D2 receptor antagonist SCH 23390 (Turski et al., 1990).

In vitro electrophysiological studies have brought more complexity to the interpretation of effects of dopaminergic system on epileptic activity. Although initial studies reinforced the idea of a protective effect by demonstrating a reduction in the frequency of firing of pyramidal neurons of the hippocampal CA1 region with solutions containing DA; others, with the use of selective antagonists, have shown paradoxical responses to those found with behavioral studies (Suppes et al., 1985). The use of selective D1 receptor antagonists increased epileptiform activity in hippocampal slices induced by the withdrawal of calcium ion from the perfusion solution, which was blocked using selective D1 receptor agonists (Alam and Starr, 1993).

Results obtained here suggest that dopamine plays an important role in the acute phase of the pilo-induced epilepsy model, which was not observed in the model's chronic phase. Additionally with results provided in the literature, we observe the need for further studies to the characterization of the role played by dopamine in the epileptic phenomena.

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