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Intracerebroventricular administration of cigarette smoke condensate induced generalized seizures reduced by muscarinic receptor antagonist in rats

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ABSTRACT

Tobacco smoking is considered the greatest risk factor for early death caused by noncommunicable diseases. Currently, there are more than one billion tobacco smokers in the world predisposed to many diseases including heart attack, stroke, cancer, and premature birth or birth defects related to the consumption of cigarettes. However, studies on the association between tobacco smoking and seizures or epilepsy are insufficient and not well documented. In the present study, the authors examined the convulsive effects of the intracerebroventricular administration of cigarette smoke condensate (CSC, 2 μl/Rat) in rats and compared it with the intensity of seizures in the kainic acid (KA)-induced seizure model of epilepsy. The role of the cholinergic system was also investigated by testing the effect of the muscarinic acetylcholine receptors (mAChRs) antagonist atropine (2 ml/kg) on CSC-induced seizures.

The results indicate that a central injection of CSC produces an epileptic behavior similar to that induced by KA, the similarities include the following parameters: time latency of seizures, latency and duration of tonic–clonic seizures, duration of seizures, survival, and tonic–clonic rate. However, a pretreatment with atropine reduced seizures and all their parameters.

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1. Introduction

Approximately 1% of the world's population suffers from epilepsy [1]. Epilepsy can usually be controlled by modern anticonvulsants that can prevent or reduce the intensity of convulsions. However, even with the best available drugs, about 30% of people with epilepsy have uncontrollable seizures. This may be due to the difficulty of the treatment procedure of epilepsy, which is characterized by the ineffectiveness and chronic toxicity of antiepileptic drugs in nearly 20% of the patients [2].

Epilepsy is largely divided into two etiological classes: on the one hand, symptomatic epilepsies that are characterized by seizures resulting from significant disturbances in neuronal physiology are usually associated with brain atrophy induced by progressive death of neurons. On the other hand, in the idiopathic epilepsies, the primordial factors are genetic because the mutations appear to intervene selectively with the threshold of crisis, without disturbance of the other neuronal functions [3].

However, seizure control in more than half of patients with epilepsy is achieved primarily by the pharmacotherapeutic action of drugs targeting membrane ion channels or glutamatergic or GABAergic (GABA) neurotransmission [4], leading to a wide variety of changes in biochemical disorders affecting neurotransmitters such as dopamine, serotonin, glutamate, and GABA [5]. For example, low activation of the GABAergic system induces epilepsy [6].

Theoretically, the risks of epilepsy should be higher in chronic tobacco smokers. This risk comes from the toxic components of tobacco smoke that can lead to epileptic behavior in humans and animals, such as lead, hexane, toluene, cresol, arsenic, and acetone [7–11]. Nicotine, a parasympathomimetic and major alkaloid in tobacco, causes seizures in humans when overdosed [12]. Carbon monoxide can also cause convulsions in children and adults [13,14].

Animals are a useful tool for elucidating the association between tobacco smoking or nicotine use and seizures or epilepsy. Making animals imitate human tobacco-smoking behavior is technically challenging. Additionally, the nicotine doses used in animal models are much higher than the amounts obtained by humans via cigarette smoking. Currently,

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tobacco delivery methods in animals include the automatic smoking machine (ASM) [15]; injecting pure nicotine intracerebroventricularly (ICV) [16], subcutaneously (SC), or intraperitoneally (IP) [17,18]; and subcutaneous infusion [19]. Nicotine-induced seizure models include cats, mice, and rats [18,19].

Recently, various studies have shown that the activation of cholinergic receptors modulates convulsions generated by the hippocampus. These seizures are not only related to the imbalance between excitatory glutamatergic neurons and inhibitory GABAergic neurons, but also related to anomalous central cholinergic regulation. On the cellular level, various types of epilepsy are thought to be associated with aberrant metabotropic muscarinic receptors in diverse brain areas, while the mutations of ionotropic nicotinic receptors have been reported to result in a specific type of epilepsy, i.e., autosomal dominant nocturnal frontal lobe epilepsy. On the network level, cholinergic projection neurons and their interaction with other neurons may regulate the development of epilepsy, particularly the cholinergic circuit from the basal forebrain to the hippocampus, whereas cholinergic local interneurons have not been reported to be associated with epilepsy [20,21].

It was also reported that animals developed seizures when they received nicotine via injection but not through the ASM. Other studies have inspected the effects of pretreatment with nicotine prior to the administration of seizure-inducing chemicals such as pentylenetetrazole [17], kainic acid (KA), pilocarpine, and nicotine itself [19].

On the other hand, KA is an important agent for studying excitatory amino acid transmission and production of convulsions in small rodents. It has been extensively used in rats over the past 20 years for neuropathological, behavioral, neurochemical, and pharmacological studies and is considered an activator of inhibitory neurotransmission of gamma aminobutyric acid in the central nervous system [22,23].

In the present study, we focused on assessing a convulsive effect of cigarette smoke condensate (CSC) as a model of seizures and compared its intensity with the KA model of epilepsy in rats. Thus, our study was designed to examine the role of the cholinergic system in cigarette condensate- and KA-induced seizures. The interventions of mAChRs were investigated by a pure muscarinic cholinergic ligand treatment and by the observation of KA-induced seizure behavior.

2. Materials and methods

2.1. Experimental animals

Male Sprague–Dawley rats (3–4 months old, 230–250 g weight) are from the animal breeding facility of the Faculty of Sciences Semlalia, Marrakesh, Morocco. The animals were housed in individual plastic cages and kept at a constant room temperature (23 ± 2 °C), with a 12 h dark/light cycle, and had free access to food and water. All animals were treated with procedures conforming to European legislation related to the ethical evaluation and use of laboratory animals, 1st February 2013 NOR: AGRG1238767A. Thus, all efforts were made to minimize animal suffering and reduce the number of animals used. For every group we used 6 animals.

2.2. Drug treatment

In this study, the drugs used included atropine (2 ml/kg) and KA purchased from Sigma-Aldrich (Saint-Quentin-Fallavier, France). Atropine was administered (1 ml/kg) IP; KA was injected (1 μg/1 μl saline) into the cerebral ventricles (ICV).

2.3. CSC preparation

Mechanical CSC preparation was performed using VP800 vacuum pump to generate and withdraw a cigarette smoke through a tube surrounded by a cooling system, which passes cold water over the surface of the tube, and a balloon in which the cigarette condensate is recovered. A total of 6 commercial cigarettes containing 1 mg of nicotine each and 12 mg of tar produce a volume of 1.2 ml of the cigarette condensate.

2.4. Gas chromatography analyses

The gas chromatography analysis of CSC was realized using a Shimadzu GC 2010 Gas Chromatography Plus with a split/splitless injector system, and a flame ionization detector (FID), equipped with a capillary column 65% methyl–35% diphenylpolysiloxane and polar Rtx-5 column (30 m × 0.32 mm id.) with 0.25 μm stationary film thickness (Phenomenex, USA). Helium gas was used as the carrier gas at a constant flow rate of 3 ml/min at a constant linear velocity of 18.5 cm/s. The injection port was held at 230 °C and used in the splitless mode with splitless time of 0.5 min. The oven temperature was programmed as follows: initial 100 °C, from 100 °C (held 3 min) to 195 °C at rate of 10 °C/min, from 195 to 250 °C at rate of 4 °C/min (held 10 min). Total time for one gas chromatography run was 40 min. The FID temperature was maintained at 280 °C, hydrogen gas was generated for FID at a flow of 40 ml/min. The flow of zero air (99.99%, air products) for FID was 400 ml/min. Diluted sample (1/100 v/v, in methanol) of 0.2 μl was manually injected in the splitless mode by using a 1 ml syringe (gas tight, Hamilton, USA). The identification of compounds of crude CSC was focused on gas chromatography retention time on capillary column. The reference compound, nicotine, was used as marker.

The gas chromatography method applied in this work is a modification of that mentioned by Hossain and Salehuddin [46] for the analysis of nicotine present in tobacco. The peak of nicotine was confirmed by comparison of the retention times of condensate with reference nicotine peak [24] (Fig. 1). The chromatographic analysis shows the appearance of an intense peak in the chromatographic profile of CSC sample (Fig. 2).

2.5. Surgical procedures and postsurgical recovery

Rats were anesthetized with an intraperitoneal injection of hydrate chloral (400 mg/kg (6%)), and positioned in a Horsley–Clarke stereotaxic apparatus while maintaining the incisor bar at about 3.2 mm under horizontal zero to attain a horizontal position of the skull.

After incising the skin and cleaning the skull, stainless steel guide cannulae of approximately 23 gauge were implanted (unilaterally) 1 mm above the injection site according to the Paxinos and Watson [25]. The stereotactic coordinates of the ventricle were the incisor bar −0.92 mm posterior to Bregma, ±1.5 mm laterally to the sagittal suture and 3.2 mm from the top of the skull. Then the cannulae were fixed with stainless steel anchor screws and dental acrylics. Stainless steel stylets (30 gauges) have been placed to prevent the debris from dripping into the guide cannulae. Finally, the rats were allowed 8 days to recover from surgery and eliminate anesthesia.

2.6. Treatment

A total of N = 24 rats were used in our study. The animals were divided into four groups of six animals each. Control (saline 9%°), KA (1 μl/Rat), CSC extract (2 μl/Rat), Atropine + CSC (Atr + CSC), and CSC were injected 30 min before an IP injection of atropine (1 ml/kg).

For the KA and CSC infusions, the animals were gently retained by hand, and the styles were removed from the guide cannulae and introduced 27 gauge injection needles (1 mm below the tip of the guiding cannulae). Each injection unit was connected by polyethylene tubes to a 10 μl Hamilton syringe. The injected solutions were administered in a total volume of 1 μl/Rat for KA and 2 μl/Rat for CSC in a period of 60 s at the same time (13 h00 and 14 h00), and then the injection needles were left in the guide cannulae for a supplementary period of 60 s to facilitate drug delivery.

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