Therapeutics, Pharmacology and Clinical Toxicology
Vol XIII, Number 2, June 2009
Pages 147-149

ORIGINAL PAPER

THE CARDIOVASCULAR SYSTEM EFFECTS OF ALUMINUM SALTS

Dana Goşa[1], Anca Dana Buzoianu[2], Ruxandra Schiotis[1], Ş. Vlaicu[1], Corina Neculiță[2]

[1.] *Department of Pharmacology and Toxicology „Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca*
[2.] *Department of Clinical Pharmacology „Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca*

Abstract. Introduction. The ionic mechanism that stands at the base of the central arrhythmias it is not known exactly yet. The current researches at the UMF Cluj-Napoca, Department of Pharmacology and Toxicology showed that there are substances which could cause changes of cardiac rhythm and cardiac frequency when were administrated by microinjections into the cerebral lateral ventricle of rats in narcosis. In this study we examined the effects of aluminium chloride on central cardiac arrhythmia using pharmacological means. **Material and methods.** We used for the study Wistar white rats, with weight between 130-180 grams, in narcosis produced by ethyl urethane. **Results.** We obtained central caused cardiac arrhythmias by giving aluminium chloride into the cerebral lateral ventricle. **Conclusion** Aluminium chloride is not a protective agent against the arrhythmic effect of sodium glutamate which is known as the reference arrhythmic substance
Keywords: aluminium chloride, intracerebroventricular, central arrhythmias

Introduction

Field literature contains few references regarding the possibility of inducing centrogenic cardiac arrhythmia by microinjection or by iontophoretic application.

Previous researches of the Department of Pharmacology have shown the possibility of producing cardiac arrhythmias in the disturbance of hypothalamic nuclei or injection of chemical compounds in the lateral cerebral ventricle.

Following electrical stimulation of hypothalamic nuclei:

Dana Goşa
„Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca
6, Pasteur Str, 400349 Cluj-Napoca
Phone/Fax: 0264.595629
danagosa@yahoo.com

- mammillary medial nucleus
- mammillary lateral nucleus, medial posterior nucleus;
- ventro-medial nucleus;
- arcuate nucleus;
- periventricular nucleus;

With a current of low intensity would not cause significant electrocardiography changes but would probably lead to mild bradycardia. At high intensity, there would be subsequent emphasized bradyarrhythmias with or without ventricular extrasystole. All these changes are reversible.

These changes occurred in cardiac electrical stimulation, regardless of the place or the nucleus where the electrodes were located. Respiratory movements were engaging transit. The electroencephalogram showed resynchronization of hypothalamic post nucleus stimulation and no changes to the core of the previous stimulation. There were stereotypes of arrhythmias, cardiac bradycardia (ap-

parently characteristic are bradyarrhythmias).

Chemical stimulation of hypothalamic nuclei in rats produces the same type of disturbance input and electrical stimulation.

There are many classification criteria of cardiac arrhythmias. One of the criteria refers to the localization of the arrhythmogenic stimulus. The arrhythmogenic stimuli could entail cardiac tissue (arrhythmias caused by biochemical or morphological lesions of the heart), or could be extra cardiac, and this arrhythmogenic stimulus has become the most frequent among those of the Central Nervous System.

The pathogenesis of these cardiac rhythm disorders consists in the release of cerebral neurotransmitters (acetylcholine, noradrenalin) from the cerebral structures. The last link is represented by stimulation of β_1 central receptors. The ionic mechanism that lies at the origin of central arrhythmogenesis has not been clarified yet. In the experiments carried out on animals we aimed to study the effect of aluminum chloride upon cardiac arrhythmia induced by sodium glutamate.

Material and methods

The experiments were carried out in Wistar white rats of both sexes, from the Biobase of the „Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj Napoca. They weighed between 130-180 g. The animals were put on a standard balanced diet and were given water ad libitum. Before the experiment, the animals were kept under normal laboratory conditions, at room humidity and temperature. The rats were anesthetized with ethylic urethane 1.25 g/kg intraperitoneum (i.p.), in a 10% solution. After the insertion of the cannula into the trachea, the animals were connected to an artificial respiration pump „UGO BASILE" (Ugo Basile Rodent Ventilator – model 7025). The animals were fixed in the the Kovacs stereotaxic device, which was made by „MEDICOR". The signs of lateral cerebral ventricle were established by means of stereotaxic coordinates according to the Szentagothai atlas. The parameters were as follows: posterior (P) = 1 mm; lateral (L) = 1.5 mm (point 0 represents bregma) and vertical (H) = 4.5 mm. The electrocardiogram was carbon copy mechanically recorded with an 8-channel electroencephalograph (type BIOSCRIPT BST-1). The paper rolled at a speed of 7.5 mm/sec.

The experimental protocol that we used was the one designed by Cuparencu et al. This same protocol was employed in the laboratory of stereotaxia at the Department of Pharmacology, the „Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj Napoca, where the experiments were carried out. The studied substance was microinjected into the left lateral cerebral ventricle, according to the stereotaxic signs mentioned above. The animals were injected intracerebroventricular (icvt) with a Hamilton micro syringe, with a modified needle that permits attachment to the stereotaxic device. Before the administering of the substances, control records of the studied parameters were made. The next step consisted in observing the modifications caused by the studied substance. Sodium glutamate in a dose of 6000 μg/10 μl was employed to induce arrhythmia. If the animals presented arrhythmia their monitoring was continued in order to clarify the central effects of aluminum chloride. Aluminum chloride was administered icvt in three decreasing doses of 48.28 μg/10μl; 24.14 μg/10μl and 12.07 μg/10μl. Each study group included 6 animals. The results were statistically processed with the non-parametric test of ranks with the Wilcoxon sign. The following parameters were calculated: cardiac frequency (CF) and arrythmogenic index (AI). The statistical significance threshold was of $p \leq 0.05$*

Results

Intracerebroventricular (icvt) administration of sodium glutamate produces, after approximately 30-45 seconds, heart rhythm disorders similar to those obtained by electrical or chemical stimulation of the brain, namely: sinus pause, sinus arrhythmia, atrioventricular block, ventricular extrasystole.

In rats, it was observed that these arrhythmias are preceded in all cases by sinus bradycardia.

The arrhythmias could be prevented in all cases by intracerebroventricular administration in advance of aluminum chloride ($AlCl_3$) in different doses: 48.28 μg, 24.14 μg and 12.07 μg in a volume of 10 μl.

In animals first batch aluminum chloride does not produce centrogenic arrhythmias AI was 0 and it conferred protection against arrhythmias produced by administration of sodium glutamate.

In the second lot, intracerebroventricular administration of aluminum chloride and sodium glutamate (the initial dose) caused a significant decrease in cardiac frequency ($p<0.05$).

In all animals from the third lot, we noted a

decrease in the frequency of failure in intracerebroventricular administration of arrhythmogenic substances (sodium glutamate) and a substance included in the study (aluminum chloride).

Discussion

The pathogenesis of centrogenic cardiac arrhythmias it is not well known yet. The causes that frequently determine these centrogenic arrhythmias are: cerebral tumors, traumas, infections, subarachnoid space hemorrhages and epilepsy. We can add to these, the so-called "reflex arrhythmias" produced by stimulation of different organs (stomach, gall bladder, intestine, urinary tract). The huge release of cerebral neurotransmitters has an important role. Accumulation of the neurotransmitters produces a prolongation and excessive stimulation of the areas from CNS which are responsible for the control of cardiovascular activity. The concentration of neurotransmitters from different cerebral areas during centrogenic arrhythmias was not positively known, but it is hypothesized that these have high levels, many times exceeding normal values. Centrogenic arrhythmias were the subject of many experimental researches. It was not yet known whether the transmission of the arrhythmogenic stimulus from the CNS to the heart is intermediated by the vagus nerve, by the sympathetic system or by both.

Icvt administration of sodium glutamate causes centrogenic cardiac arrhythmias by endogenous release of acetylcholine which activates the muscarinic receptors; from this effect is released endogenous NA which acts on beta1-adrenergic receptor neurons in the hypothalamic nuclei, thus causing occurrence of cardiac arrhythmias.

The experiments made for this paper have shown that aluminum chloride in high doses is not statistically significant for changes in heart rate and confers protection against arrhythmias produced by the icvt administration of sodium glutamate.

Probably, the aluminum chloride blocks the entry of calcium ions through the channels and thus blocks the release of acetylcholine produced by sodium glutamate.

Blocking calcium entry provides a protection against the neural arrhythmogenic effect of sodium glutamate. In low doses, the aluminum chloride probably does not entirely block the entry of calcium ions and thus does not confer protection against arrhythmias caused by sodium glutamate.

Conclusions

1. Sodium glutamate administered icvt in rats narcotized with ethyl urethane produces characteristic cardiac rhythm disorders. These arrhythmias could reiterate.
2. Aluminum chloride administered icvt in high doses does not confer protection against arrhythmia caused by the icvt administration of sodium glutamate.

References

1. Benno I, Cuparencu B, Safta L, et al Do the central beta-adrenoceptors play any role in the genesis of centrogenic cardiac arrhythmias in anesthetized rats. *Curr. Ther. Res,* **1991, 49: 289-290.**

2. Cuparencu B Efectele medicamentelor cardiovasculare mediate prin sistemul nervos central. **Bucureşti, Editura Medicala, 1998.**

3. Szentagothai J *Stereotaxic Koordinata Atlas.* In Kovacs red. Vol III, Akademia Kiado, Budapest, **1980.**

4. Safta I, Cuparencu B Aplicaţii ale tehnicii sterotaxice în medicina experimentală. *Clujul Medical,* **1992, 3: 57-65.**

5. Cabarvdic A Condition for experiment in pharmacology. *Med. Arh,* **2006, 60 (2): 96-98.**

6. Sánchez-Iglesias S, Méndez-Alvarez E, Iglesias-González J. et al. Brain oxidative stress and selective behaviour of aluminum in specific areas of rat brain: potential effects in a 6-OHDA-induced model of Parkinson's disease. *J Neurochem.* **2009 May; 109 (3): 879-88.**

7. Prakash A, Kumar A. Effect of N-Acetyl Cysteine against Aluminum-induced Cognitive Dysfunction and Oxidative Damage in Rats. *Basic Clin Pharmacol Toxicol.* **2009 Mar 27.**

8. Stevanović ID, Jovanović MD, Jelenković A, et al. Effects of L-NAME, a non-specific nitric oxide synthase inhibitor, on AlCl3-induced toxicity in the rat forebrain cortex. *J Vet Sci.* **2009 Mar; 10(1):15-22.**

9. Bhalla P, Dhawan DK Protective Role of Lithium in Ameliorating the Aluminum-induced Oxidative Stress and Histological Changes in Rat Brain. *Cell Mol Neurobiol.* **2009 Jan 29.**

10. Sethi P, Jyoti A, Singh R, Hussain E, Sharma D Aluminum-induced electrophysiological, biochemical and cognitive modifications in the hippocampus of aging rats. *Neurotoxicology.* **2008 Nov; 29 (6):1069-79. Epub 2008 Sep 5.**

11. Jovicić ME, Popović M, Nesić KJ. et al. Aging, aluminum and basal forebrain lesions modify substrate kinetics of erythrocyte membrane Na,K-ATPase in the rat. *J Alzheimers Dis.* **2008 May; 14(1):85-93.**