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The Neurotoxic Effects of 2-Nitropropane on Nerve Conduction are Reversible, *In Vitro*

Sergio Lucio Becerra-Torres[1,2]* and Luis Castillo-Hernández[1]

[1]*Departamento de Fisiología y Farmacología, Centro de Ciencias Básicas, Universidad Autónoma De Aguascalientes, Aguascalientes, México*
[2]*Escuela de Medicina, Universidad Cuauhtémoc Campus Aguascalientes, Aguascalientes, México*

Abstract

In general, the scientific evidence points to organic solvents as substances capable of affecting the nervous system, both central and peripheral level. The aim was to measure the effect of 2-nitropropane on the sciatic nerve of the frog *in vitro*. We found significant effects on parameters such as nerve conduction velocity, amplitude and duration of the compound action potential, and nerve impulse conduction. The importance of our results is that there was a reversible behavior simulating the effect of the anesthetics used in medical practice. Due to the depressive effect shown by this solvent we strongly recommend health surveillance of those who are in constant exposure to organic solvents and the use of personal protective equipment indicated in the corresponding safety sheets to manipulate these xenobiotics.

Keywords: Toxic effects; Nerve conduction; 2-nitropropane; Frog; Organic solvent; Reversible effect

Introduction

The symptoms manifested by humans exposed to a wide variety of organic solvents like 2-nitropropane (2-NP) (CAS No. 79-46-9) indicates neurological disorders in the central and peripheral system that characterized by encephalopathy, polyneuropathy, paresthesias, neuropsychiatric disorders, memory loss, personality changes, and narcotic effects, among other [1-4]. The number of investigations on neurotoxicity and exposure to organic solvents is limited and has not investigated the effect of 2-NP on nerve conduction. The nervous conduction velocity (NCV) is a measure of the excitability of the nerve, and this parameter has been extensively used to classify and diagnose peripheral neuropathy [5]. Scientific evidence shows an association between exposure to solvents and a lower neurobehavioral performance. Some studies have reported assessing of persons occupationally exposed to solvents, and they have shown effects on memory, attention, and motor dexterity [6-9]. Skin absorption and inhalation are the usual routes of exposure. It has been reported that some organic solvents causes a distal axonopathy consisting of sensorial loss and weakness, and that workers exposed to organic solvents typically develop a mild form of chronic toxic encephalopathy characterized by neurobehavioral defects in psychomotor, perceptual, and memory function with frequent disturbances in mood [10]. Solvents represent a heterogeneous category of chemicals, and millions of people are in risk of exposure. Poor workplace conditions may contribute significantly to solvents exposure. Molecules produced during the metabolism of many solvents are usually more toxic than the original substance [11]. Propane 2-nitronate (CAS No. 20846-00-8) is the major genotoxic form of 2-NP [12], and its genotoxicity could be due to generation of reactive free radical species [13]. It has been demonstrated a distal peripheral neuropathy following exposure of humans and animals to solvents such as n-hexane (CAS No. 110-54-3), methyl-butyl-ketone (CAS No. 591-78-6), or carbon-disulfide (CAS No. 75-15-0). This disorder has histological features such as focal axonal swelling with distal axonal degeneration [14]. For example, the NCV of the tail nerve decreased significantly in alcohol acute administration [15]. In this regard, there have been studies in workplaces in which people are exposed to certain types of organic solvents. Some parameters related to peripheral nerve conduction were measured in them, observing significant changes in all those workers chronically exposed to these substances [16]. Likewise, it has been reported that in exposed workers a reduced sensitive of the NCV was correlated with duration of exposure to solvents, and more frequently accompanied of fatigue, hand numbness, enhanced excitation, concentration difficulties, forgetfulness, and headaches [17]. This study demonstrates the occurrence of two events raised by the 2-NP, in its natural state *in vitro*:

1. This solvent inhibits the NCV (in the sciatic nerve), behavior consistent with information reported in some studies with propanes like 2-bromopropane (2-BP) (CAS No. 75-26-3) which causes damage in myelin sheath [18]. Coincidentally, also it has been reported that the long term exposure to the trichloroethene (TCE) (CAS No. 79-01-6), at threshold limit, may affect slightly the trigeminal nerves [19].

2. This solvent blocks the nerve impulse conduction (NIC). Both effects were reversibly. In contrast, the effect found in this study is similar or equal to that which characterizes the local anesthetics because the inhibitory effect caused by the 2-NP was reversible. In this regard, we recommend constant medical monitoring of people who are at risk of exposure to solvents. Similarly, we suggest the use of protective equipment indicated in the data sheet for the 2-NP. It is obvious the lack of research regarding this issue. It must seek and find the mechanisms by which the nervous system is affected by organic solvents as well as the interactions between the metabolites and/or molecules of solvent with the cell structures involved in this process.

Materials and Methods

The 2-NP was purchased from Sigma-Aldrich Chemical S. A. de C. V. (Toluca, Estado de Mexico, Mexico).

***Corresponding author:** Sergio Lucio Becerra-Torres, Departamento de Fisiología y Farmacología, Centro de Ciencias Básicas, Universidad Autónoma de Aguascalientes. Av. Universidad No. 940, C.P. 20100, Aguascalientes, Ags., México. Tel: (524) 49910-7400 Ext. 345; Fax: (524) 49910-840; E-mail: luciobecerratorres@hotmail.com

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Compound action potential (CAP). For obtaining and recording the CAP (extracellular recording of action potentials of all fibers included in a nerve) the sciatic nerve of the frog was dissected. Then it was placed in a special chamber with electrodes separated from one another 5 mm, and covered with a glass to prevent dehydration. The proximal end of the nerve was subjected to a stimulation protocol with a frequency equal to 1 Hz and with supramaximal-intensity stimuli with duration equal than 0.1 ms. Then we proceeded to place electrodes for recording (monopolar) in the distal end. Also, to evaluate the effect of 2-NP on the NIC was placed a small piece of cotton soaked with 2-NP was placed on the nerve, between stimulating and recording electrodes. In this regard, records were obtained in the absence and presence of the solvent studied, and after submitting the nerve to washing with deionized water.

The results were analyzed and all records obtained in this study were digitized and stored in an analog-digital converter (TL-125 Labmaster, Axon Instruments Inc., USA) for further analysis.

Statistical Analysis

Data were analyzed by one-way analysis of variance, and expressed as the mean ± standard error of the mean. A p-value less than 0.05 was considered statistically significant (*), n = 10.

Results

The sciatic nerve was exposed to 2-NP showing an inhibitory effect (gradual) on the NIC. This effect is characterized by the following events: Diminution of NCV, gradual reduction of the amplitude of the CAP, increased duration of CAP, and total blockade of the NIC. The corresponding record is displayed in Figure 1.

The findings of the CAP recorded obtained the following values on the effect of 2-NP (Table 1).

Discussion

Previously we have reported that 2-NP is able to completely block chemical neurotransmission (spontaneous and evoked). *In vitro*, similar to what happened in the evoked neurotransmission, suggesting that the faults in transmission during evoked release were caused necessarily by the absence of action potential in the nerve terminal, without ruling out another possible mechanism [20]. Furthermore, in this study we found that the inhibitory effect of 2-NP on the NCV and the NIC is reversible. This may mean that the effect is due to some mechanism of action similar to the observed in local anesthetics, affecting any of the ion conductance responsible for the generation and conduction of the CAP in the nerve fibers, as are mainly those of sodium and potassium. Thus, the increase in the duration of CAP may reflect alterations in the kinetics of the events of the corresponding ion channels, suggesting a reduction in that. Specifically, we could also propose that 2-NP exerts a low-affinity contact with the proteins that form ion channels in nerve fiber, thereby altering their functioning. Similarly, we believe that the effect of 2-NP might have been greater in our experimental model if we had used a systemic route of administration, because the metabolites generated during metabolism of these substances are usually more toxic than the original substance [11]. On the other hand, the anesthetic effect observed in this study is consistent with previous reports indicating that some organic solvents cause numb hands in workers exposed to these substances [17]. It is important to note that has not been published any work about the 2-NP and the experimental model used by us. Part of the importance of the results found in this research lies in the inhibitory and reversible properties shown by the 2-NP on

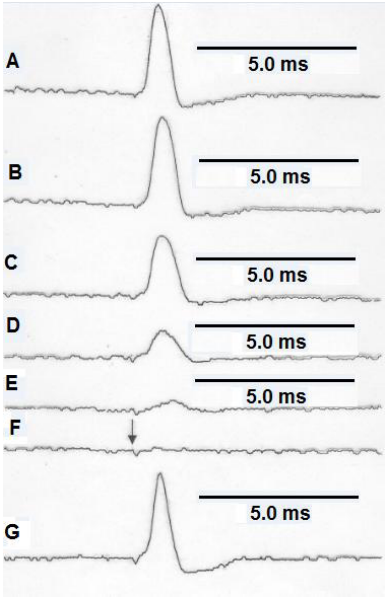

Figure 1: Effect of 2-NP on the nervous conduction: A. CAP obtained before exposing the nerve to 2-NP (control group, previously the nerve was immersed in deionized water to cleanse it of impurities), B-F. Records obtained after exposing the nerve to 2-NP at intervals of 20 s, respectively (before contacting the nerve with the solvent, the nerve was immersed in deionized water to cleanse it of impurities). Arrow in F indicates only stimulus artifact, which is not followed by the appearance of the nerve impulse (total blockade). G. CAP obtained after immersing the nerve in deionized water to remove the solvent (seen the restoration of nerve conduction in its entirety). It shows only one in ten records, the remaining nine had the same pattern.

EXPERIMENT	NCV (m / s)	EXTENT OF THE CAP (%)	DURATION OF THE CAP (m / s)
Control	36.5 ± 1.38	100 ± ----	1.02
Exposure to 2-NP	* 23.59 ± 2.6	* 16 ± 6	* 1.42
After washing with deionized water	30.76 ± 6.76	85 ± 19	1.02

Table 1: Effect of 2-NP on the nervous conduction: This table shows the effects of 2-NP on the NCV, the amplitude of the CAP, and the duration of the CAP (1 min after exposing the nerve to 2-NP). Statistical significance was set when * P < 0.05 versus the Control, and the values are given as the Mean ± Standard Error (SE) to NCV and CAP with n = 10 for each parameter evaluated.

the NCV and the NIC (in the sciatic nerve), administered in its natural form *in vitro*. This suggests that there was no damage or abnormalities in the structure of the nerve during the corresponding exposure, at least in our research protocol. This study demonstrates the occurrence of two events raised by the 2-NP: Our solvent inhibits the NCV (in the sciatic nerve), behavior consistent with information reported in some studies with propanes like 2-BP which causes damage in myelin sheath [18]. Similarly, the long term exposure to TCE at threshold limit values may affect slightly the trigeminal and sural nerve [19]. The 2-NP is able to block the nerve impulse conduction (NIC). Both effects were reversibly. In contrast, the effect found in this study is similar or equal to that which characterizes the local anesthetics because the inhibitory effect provoked by the 2-NP was reversible. In this regard, we recommend constant medical monitoring of people who are at risk of exposure to solvents, and the use of protective equipment indicated in the data sheet for the 2-NP. Additionally, it should be noted that poor workplace conditions can contribute significantly to exposure to solvents, including non-use of personal protective equipment indicated in the data sheet of 2-NP. Finally, we recommend the establishment

of prevention programs and/or monitoring of those people who are at risk of exposure to organic solvents such as the 2-NP. We emphasize the need of research related to the issues raised in the present study to elucidate the mechanisms of action of this solvent in the nerve cells.

Conclusion

The results of this investigation indicate that the conduction velocity of the sciatic nerve exposed to 2-NP significantly decreased and the NIC was blocked, both events occurred in a reversible manner.

Declaration of Interest

All authors read and approved the final manuscript, and report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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