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 ANTIDEPRESSANT DESIPRAMINE ASSESSMENT ON CARDIAC FUNCTION

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ABSTRACT 
Desipramine has been widely used in humans in psychiatric therapy for the last 15 years; changes in the EKG pattern suggest that the drug could alter the electrophysiological properties of cardiac fibers. The purpose of this study was to evaluate the effects of desipramine (DMI) on cardiac tissues using electrophysiological and pharmacological studies. The studies were conducted in male rats of the Wistar strain (W), Wistar Kyoto (WK) and spontaneously hypertensive Wistar Kyoto (SHWK) (n = 6). The heart rate parameters were evaluated (HR), R wave amplitude (RmV) and left ventricular systolic pressure (LVSP). The results show that desipramine induces a depressant effect concentration - dependent in all strains studied, observing from mild to moderate effects on heart rate and, from moderate to severe in R wave amplitude (RmV) and LVSP, more severe in strain predisposed to hypertension (WK) and the spontaneously hypertensive (WKSH).

Keywords: Desipramine, Cardiac Function, Hypertension.

INTRODUCTION 
The mammalian’s heart is an organ with a complex intrinsic nervous system. Numerous studies have shown the presence of different components sympathetic and cholinergic markers such as neurotransmitters and dopamine transporters which support the presence and sympathetic cholinergic nerve cells in the heart. Also, the presence of other neuronal markers have been reported, suggesting the presence of histamine neuromodulation type, nitrergic, peptidergic and serotonergic in the same organ [1]. In previous studies in guinea pig hearts, it was determined that DMI acts in a paradoxical way depressing the myocardial function of concentration-dependent manner, which makes us suspect that possesses other sites of action in addition to the serotonin and noradrenaline transporters [2]. The increase in heart rate may also result from the increase sensitivity of norepinephrine receptors. An elevated heart rate has been observed in depressed patients with and without cardiovascular disease. Depression may be associated with abnormal function of the hypothalamic-pituitary-adrenal and high sympathetic activity, which can lead to cardiovascular irregularities. The role of stress is an important component in the etiology of depression as well as the influence of the depression in cardiovascular regulation. It has been observed that the variation of the heart rate increases in depressed patients after antidepressant treatment and cognitive behavioral therapy. For example, Carney cited by [3]; suggested that heart rate and heart rate variability can improve in depressed patients treated, but it can never return to baseline levels. It has been suggested that the heart rate variability in humans is predominantly due to a reduction in vagal tone. The influence of cholinergic innervation to heart via the vagus nerve in patients with depression, has not received much experimental attention. However, the cholinergic activity in the CNS can increase the depression. Recent pharmacological data suggest that central serotonergic mechanisms can influence heart rate variability in psychiatric patients [3].

The DMI has been widely used in psychiatric therapy for the last 15 years; changes in the EKG pattern suggest that DMI could alter the electrophysiological properties of cardiac fibers. [4]. One of this mechanism could be a muscarinic effect [5, 6]. The ADCs cholinergic effect contributes to the development of sinus bradycardia, hyperthermia, paralytic ileus, urinary retention, pupil dilation and possibly coma. The most importantly the electrophysiological effect on the heart in the full individual is the inhibition of fast sodium channels, producing a retardation of phase 0 depolarization of the His-Purkinje fibers and ventricular myocardium. In the electrocardiogram, this results in a prolongation of the QRS interval, which is characteristic of tricyclic antidepressant overdose (ADC’s). Intracellular sodium motion during phase 0 of the action potential is closely coupled with the release of intracellular stores of calcium. Therefore, may modify myocardial contractile resulting in hypotension [7, 8]. Other effects of the ADC’s on the action potential of...
cardiac cells include a slowing of phase 4 of the depolarization and repolarization, and an inhibition of Ca$$^{2+}$$ channels (channels L-type Ca$$^{2+}$$) and channel inhibition potassium input rectifier activated by G protein cardiac (GIRK ¼). The prolongation of repolarization and QT interval, is characteristic of both therapeutic doses and the poisoning ADC’s, predisposing to QT prolongation and development of “torsade de pointes” (rare and distinctive tachycardia polymorphic ventricular characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line), which have been described even at therapeutic doses [7, 8, 9].

In other studies by Isenberg, Tamargo, Delpo’n, Ogata and Zahradnik cited by [8], showed that the ADC’s including Ca$$^{2+}$$ antagonists inhibit calcium currents in heart’s myocytes and the neurons, affecting membrane receptors and various transport systems as well as many other amphiphilic molecules in a range of high concentration (micromolar). It is believed that the therapeutic effect of these drugs is their action in CNS neurons noradrenergic and serotonergic, which are also involved in cardiovascular regulation.

**MATERIAL AND METHODS**

Experiments were performed in male rats of the Wistar strain, Wistar Kyoto and Wistar Kyoto Spontaneously Hypertensive (n = 6) to which were given heparin and sodium pentobarbital intraperitoneally, half underwent thoracotomy for exposure of the heart, subsequently extracted and channeled in the retrograde perfusion system of Laggendorf and perfused (10ml/min) with Krebs-Henseleit solution aerated with carbogen gas (95% O$$\text{2}$$ -5 % CO$$\text{2}$$) at a temperature of 35 ° -37 ° C. Simultaneously electrodes were placed in the atria and apex of the heart and placed a small latex balloon in the left ventricle to obtain its value contractile, with a stabilization time of 30 minutes to each organ studied, making records and establishing baseline values before to implement the protocols. Heart rate parameters were evaluated (HR), R wave amplitude (RmV) and left ventricular systolic pressure (LVSP).

Then, we proceeded to perfuse different concentrations of DMI ($$1x10^{-9}$$ – $$1x10^{-5}$$ M) over a period of 15 minutes for each solution, making three sets of electrocardiographic recordings one every 5 minutes each of them, using of a electrophysiological data acquisition system BIOPAC MP36 with computer interface. After, we started the washing time with a duration of 30 minutes per heart with three sets of registers, one every 10 minutes in order to remove the drug and see if there were baseline recovery. The results are expressed as the mean percentage values ± standard error of the mean (SEM). The values obtained were administered the test Analysis of Variance (ANOVA) one-way and post ANOVA with Dunnet for checking against their respective baseline; values p < 0.05 were considered as significant.

**RESULTS**

Wistar (W). Baseline values of HR in this strain were within a range of 210-150 beats per minute. During the execution of the experimental protocols using DMI ($$1x10^{-9}$$ – $$1x10^{-5}$$ M) showed a decrease of the FC of 14.3%, concentrations of $$1x10^{-7}$$ M and $$1x10^{-6}$$ M to 41.45% at concentration of $$1x10^{-5}$$ M with respect to the basal (Figure 1).

RmV baseline values were within a range of 1.5-0.6 mV. During the execution of the experimental protocols using DMI ($$1x10^{-9}$$ – $$1x10^{-5}$$ M) had a 31.67 % decrease from the concentration of $$1x10^{-9}$$ M, and up to 48.33 % in concentration of $$1x10^{-5}$$ M with respect to the basal (Figure 1).

LVSP baseline values were within a range of 0.4 to 0.3 Dyn / s. During the execution of the experimental protocols using DMI ($$1x10^{-9}$$ – $$1x10^{-5}$$ M) was presented a depressive effect of 37.5 % from the concentration of $$1x10^{-9}$$ M, and up to 56.25% in the concentration of $$1x10^{-5}$$ M with respect to its basal, presenting a progressive decrease during the administration of the different solutions expressing a depressing effect of the concentration - dependent in the parameters studied in this strain (Figure 1).

Wistar Kyoto (WK). Baseline HR was within a range of 210-150 beats per minute. During the execution of the experimental protocols using DMI ($$1x10^{-9}$$ – $$1x10^{-5}$$ M) it featured a depressant effect of 14.29 % from the concentration of $$1x10^{-6}$$ M with respect to its basal (Figure 2).

RmV baseline values were within a range of 1.1 -0.9 mV / s during the execution of the experimental protocols using DMI ($$1x10^{-9}$$ – $$1x10^{-5}$$ M) was observed a decrease of 20.21 % RmV from concentration of $$1x10^{-7}$$ M, and up to 34.85% in the concentration of $$1x10^{-5}$$ M with respect to the basal (Figure 2).
Baseline values for the LVSP were within a range of 1.0-0.2 Dyn/s. During the execution of the experimental protocols using DMI (1x10^{-9} - 1x10^{-5}M), was observed a decrease of 30% LVSP from 1x10^{-9} M concentration and up to 50% at concentrations 1x10^{-3} M with respect to the basals presenting a progressive decrease during the administration of the different solutions expressing a depressing effect of the concentration-dependent in the parameters studied in this strain (Figure 2).

Wistar Kyoto Spontaneously Hypertensive (WKSH). Baseline HR was within a range of 210-180 beats per minute. During the execution of the experimental protocols using DMI (1x10^{-9} - 1x10^{-5}M), was observed a decrease of 16.67% to FC from 1x10^{-5} M concentration and to a 47.62% by 1x10^{-3}M concentration with respect to the basal (Figure 3).

RmV baseline values were within a range of 1.0-0.4 mV/s. During the execution of the experimental protocols using DMI (1x10^{-9} - 1x10^{-5}M), was observed a decrease of 17.5% RmV from 1x10^{-9} M concentration and even at concentrations of 42.5% 1x10^{-7}M with respect to their baseline (Figure 3).

Baseline values in the LVSP, WKSH strain were within a range of 0.5 to 0.4 Dyn/s. During the execution of the experimental protocols using DMI (1x10^{-9} - 1x10^{-5}M) was a decrease of 77.5% LVSP a concentration from 1x10^{-7} M leading to organ ventricular infarction paralysis higher concentrations regarding their baseline, showing a depressing effect concentration dependent without significantly altering atrial function (Figure 3).

**DISCUSSION**

The results of our studies show that the DMI induced a significant concentration-dependent depressant effect on cardiac tissues, with moderate effects on HR and moderate to severe on R wave amplitude and LVSP in the three test strains (W, WK and WKSH), checking that it affects both normotensive strains (W) as biased and hypertensive (WK and WKH) the latter being the most affected, since the ventricular myocardium is depressed to the loss of function in medium and high concentrations. This is consistent with reports by Grippo and Kim, and Zahradnik et al. [2, 8], who mentioned that antidepressant drugs have many side effects, cardiotoxicity reported as one of the most serious. Moreover Zahradnik et al. [8], indicates that the current ADC’s inhibit Ca^{2+} and heart myocytes in neurons, indicating that antidepressants including calcium antagonists, affect the membrane receptors and various transportation systems, like many other amphiphilic molecules in a range of high concentration (micromolar). This confirms our hypothesis that the DMI in rats produces effects similar to those observed in previous studies in guinea pigs, with the notable difference being more severe strain predisposed to hypertension and the spontaneously hypertensive.

**CONCLUSIONS**

According to our results on the study of the effects of DMI in the isolated rat heart, we can conclude: that the DMI induces a concentration-dependent depressant effect on cardiac tissues, affecting both normotensive strains (W) as predisposed and hypertensive (WK and WKSH) the latter being the most affected. In this work, having established that DMI depressant effect exerted at the electrical and mechanical activity of the heart is a further argument to support that DMI interacts in more than one site of action, so that confirm its effects on the isolated heart rat leads us to introduce ourselves to the search of possible mechanisms of action which will be cause to future research.
GRAPH No. 1. The graph shows the effect of different concentrations of DMI strain used in W (n = 6). Shows that the presence of drug significantly reduced the FC at concentration from $1\times10^{-7}$-$1\times10^{-5}$ M, while the amplitude of the waves R (RmV) LVSP and a depressive effect originated from the concentration $1\times10^{-9}$-$1\times10^{-5}$ M, showing a concentration-dependent effect (* p <0.05).

GRAPH No. 2. The graph shows the effect of different concentrations of DMI WK strain used (n = 6). Shows that the presence of drug significantly reduced the HR from $1\times10^{-6}$ M concentration, while the amplitude of the waves R (RmV) LVSP and originated from a depressive effect of concentration $1\times10^{-9}$-$1\times10^{-5}$ M, showing a concentration-dependent effect (* p <0.05).
The graph shows the effect of different concentrations of DMI in WKSH strain used (n = 6). It can be seen that the presence of the drug significantly decreased HR (bites/min) from 1x10^−8 M, while in R wave amplitude (RmV) showed the effect from 1x10^−9 M and 1x10^−7 M on PSVI showing concentration-dependent effect (* p <0.05), with no recovery by washing and the loss of ventricular contractility from 1x10^−6.5 M concentration.

REFERENCES