Methylmercury Poisoning

Subjects: Pathology

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- MeHg treatment induces cardiac electrical remodeling *in vivo*
- Chronic MeHg prolongs action potential duration and impairs Ca^{2+} and K^{+} currents at the cellular level
- Acute exposure to MeHg modifies human ventricular K^{+} currents *in vitro*
- MeHg induces Early AfterDepolarizations (EADs) and arrhythmia *in silico* at picomolar concentrations

mercury cardiac electrical remodelling ion current arrhythmia

1. Introduction

Thousands of workers from mercury mines and mills were studied along the 20th century in Europe [1]. The study concluded that the mortality was higher among these workers when compared with people with different works in the same countries. The higher mortality in people chronically exposed to Hg was associated with cardiovascular diseases such as hypertension, cardiac ischemia or cardiac stroke [1][2]. In addition to the chronic effects, acute Hg exposure has been directly related to sudden death, in some cases from unknown origin and others from cardiac arrest [3][4].

2. Development

In the present work, chronic MeHg exposure reduced the cardiac rhythm, prolonged the rate corrected ventricular repolarization time (QTc) and increased ventricular repolarization dispersion (T_{peak}–T_{end}), parameters associated with increased risk of cardiac arrhythmia. Despite of the high mortality observed in human populations exposed to Hg, we found no studies regarding the effects of this heavy metal on human cardiac electrophysiology. There are, however, electrocardiographic studies with arsenic, another heavy metal, in leukemic patients treated with As_2O_3 and in general population chronically exposed to arsenic contaminated water [5][6]. Interestingly, these works report similar electrocardiographic abnormalities than those we observe in rats chronically exposed to MeHg.

Since the electrocardiogram is the result of the summation of the action potentials of every cardiac cell, we explored the effects of in vivo chronic MeHg exposure on the AP characteristics on ventricular strips from treated and untreated rats. As expected, in cardiac strips from hearts isolated from animals with prolonged QTc, the ventricular repolarization was also prolonged at the cellular level. The APD_{90} and the AP triangulation were longer when compared to control animals. The increase in cardiac AP duration could be due to an increase of the depolarizing Ca^{2+} current $I_{Ca\text{-}L}$, a decrease of the repolarizing K^{+} currents or both. In the present work, both $I_{Ca\text{-}L}$,

and I_{to} were reduced after chronic in vivo exposure to MeHg. This reduction in the two currents at the same time can explain the absence of effect on APD_{30}, since this parameter reflects the duration of the plateau phase of the AP. During this phase, these two currents balance one to each other and the reduction in both of them at the same time maintains the equilibrium. Since $I_{Ca\text{-}L}$ is predominant in the initial phase of the plateau, a decrease in the plateau duration could be expected. However, the great reduction in I_{to} is not able to rapidly repolarize the cell even in the condition of reduced $I_{Ca\text{-}L}$. Overall, as reflected in the APD_{30}, at the initial phase of the plateau there is neither a prolongation nor a shortening. At the end of the plateau, $I_{Ca\text{-}L}$ is inactivated, and I_{to} is the predominating current, resulting in a prolongation of the APD_{90}. There are no studies in the literature about the effects of in vivo MeHg exposure on cardiac Ca^{2+} or K^+ currents, but similar reductions were observed in calcium and potassium currents of rat dorsal root ganglion neurons [7][8].

Next, we wanted to explore whether the effect observed in rat I_{to} could also be reflected on the main I_{to} alpha subunit in human, Kv4.3. Acute in vitro exposure to MeHg of cells expressing the hKv4.3 channels induced a concentration dependent reduction of the $I_{hKv4.3}$ with no effect on the biophysical properties of the current. In contrast, chronic in vivo treatment with MeHg reduced the I_{to} current, but also shifted both activation and inactivation half voltages and slowed the current recovery from inactivation. These differences between in vivo and in vitro effects could be due to an effect of MeHg on the channel regulation. One limitation of the study is that in cardiac myocytes I_{to} carries through Kv4.3 channels associated with auxiliary subunits such as KChIP2, whereas in HEK293 cells the current was carried out only through Kv4.3 channels. MeHg in vivo could affect the association of the channel with accessory proteins or their intracellular signaling pathway regulation. Thus, MeHg decreases I_{to} current and thus prolongs repolarization providing a cellular substrate for arrhythmia. Additionally, the results obtained in the human Kv4.3 alpha subunit strongly suggest that MeHg exerts a direct modulation of the channel.

The main repolarizing current in the human ventricle is the rapid delayed rectifier potassium current I_{Kr}. This current is carried through the Kv11.1 or hERG channel. The data showed a concentration dependent reduction of the I_{hERG} in the subnanomolar range. This result is similar to that found after exposure of these channels to other heavy metals such as cobalt or arsenic [9][10].

The slow delayed rectifier K^+ current, I_{Ks}, is responsible for the adaptation of the AP duration to different heart rates and adrenergic stimulation. This current is carried through a channel formed by the Kv7.1 alpha subunit with the regulatory protein KCNE1. In vitro exposure induced a concentration dependent reduction of I_{Ks} and a positive shift in the voltage dependence of activation. These results also are in agreement with those obtained after Kv7.1/KCNE1 exposure to arsenic [10].

Finally, in order to translate the experimental data obtained on human K^+ channels regarding the susceptibility to trigger arrhythmia to human hearts, we used computer simulations of human cardiac action potentials. When the effect of 0.01 nM MeHg on each current was introduced in the models, the action potential duration increased in resting conditions, in accordance with the prolongation of the QT interval and APD_{90} observed in treated rats and consistent with the reduction of the amplitude of the repolarizing K^+ currents. It is important to note that in the AP

models, EADs and arrhythmias emerged only under β-adrenergic stimulation, also consistent with the reduction observed in I_{Ks}.

In conclusion, MeHg induces ventricular electrical remodeling prone to cardiac arrhythmias. MeHg can exert its high toxicity either after chronic or acute exposure to concentrations as low as the picomolar range.

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