EFFECT OF RACEMIC AND LEVO-METHADONE ON ACTION POTENTIAL PROFILE OF HUMAN CARDIOMYOCYTES: IMPLICATIONS FOR CARDIAC SAFETY

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Patients on chronic methadone treatment for pain or addiction are recommended for a periodic cardiologic check-up because of increased risk of QT-prolongation and development of Torsade de Pointes. Methadone is mainly administered as racemic mixture, but the □-opioid receptor activation is mostly due to levo (R)-methadone. Following experimental observation in recombinant systems, the effect of methadone is attributed to the blockade of the repolarizing rapid delayed rectifier potassium current IKr/hERG, that is targeted more potently by (S)- than (R)-methadone. At cardiac level, such an effect is expected to prolong ventricular repolarization; however, no information are available on the direct effects of racemic or levo-methadone on repolarization of cardiac myocyte from animal or human samples. Interestingly, recent data in neuronal cells and recombinant systems suggest that methadone also affects other ion currents, such as the depolarizing cardiac sodium current INa/Nav1.5.

The aim of this study was to characterize the effect of racemic and levo-methadone on the action potential (AP) profile detected in single human cardiomyocytes obtained from ventricular and atrial samples of patients undergoing septal myectomy, heart transplantation or corrective cardiac surgery. APs were recorded at different driving rates (0.2, 0.5 and 1 Hz) from cells using the perforated or disrupted patch-clamp technique; duration (APD), amplitude and maximal diastolic potential of AP were measured before and after racemic or levo-methadone exposure.

Results show that racemic methadone reduced (rather than prolonging) APD both in ventricular and atrial cardiac myocytes in a concentration-dependent manner (0.1-10μM). The effect was independent from stimulation rate and it was not prevented by naloxone (1 μM), an opioid receptor antagonist, thus excluding the involvement of cardiac opioid receptors expressed in cardiac myocytes. Similarly to the racemic form, levo-methadone (0.1-10 μM) reduced APD of human ventricular and atrial cardiomyocytes, showing an enhanced potency compared to the racemic form. Other AP parameters, including amplitude and maximal diastolic potential were not modified either by racemic and levo-methadone.

In conclusions, both racemic and levo-methadone caused a decrease, rather than the expected increase, in APD of human ventricular and atrial cardiomyocytes. This result suggests that, beyond hERG/Ikr, other channels, such as INa/Nav1.5 or ICa/Cav1.2 are likely to be reduced by methadone, an effect that may counterbalance the reduction of repolarization due to IKr/hERG channel blockade. Whether and how the shortening of APD promotes an increased propensity to develop arrhythmias remains an opened issue. Finally, the more pronounced effect of levo-methadone on cardiac repolarization may implicate the preferential use of a single enantiomer.