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## **Calciseptine isolated from the black mamba toxin selectively blocks cardiac Cav1.2 (alpha1C) versus Cav1.3 (alpha1D) L-type calcium channels**

Pietro Mesirca, Jean Chemin, Christian Barrère, Eleonora Torre, Laura Gallot, Mélanie Faure, Arnaud Monteil, Isabelle Bidaud, Sylvie Diochot, Michel Lazdunski, et al.

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10001

**Calciseptine isolated from the black mamba toxin selectively blocks cardiac Cav1.2 (alpha1C) versus Cav1.3 (alpha1D) L-type calcium channels**Pietro Mesirca<sup>1,2</sup>, Jean Chemin<sup>1,2,#</sup>, Christian Barrère<sup>1,2,#</sup>, Eleonora Torre<sup>1,2</sup>, Laura Gallot<sup>1,2</sup>, Mélanie Faure<sup>1,2</sup>, Arnaud Monteil<sup>1,2,5</sup>, Isabelle Bidaud<sup>1,2</sup>, Sylvie Diochot<sup>2,3</sup>, Michel Lazdunski<sup>2,3</sup>, Tuck Wah Soong<sup>4</sup>, Stéphanie Barrère-Lemaire<sup>1,2</sup>, Matteo E. Mangoni<sup>1,2</sup>, Joël Nargeot<sup>1,2</sup><sup>1</sup>Institut de Génomique Fonctionnelle, Université de Montpellier, CNRS, INSERM, Montpellier, France; <sup>2</sup>LabEx ICST, Université de Nice, Valbonne, France; <sup>3</sup>IPMC, Université de Nice, CNRS, INSERM, Sophia Antipolis, France; <sup>4</sup>Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; <sup>5</sup>Department of Physiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

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**Background:** Selective blockers are important tools for identifying the role of ion channels isoforms. L-type calcium channels (LTCC) are high voltage activated channels sensitive to dihydropyridines (DHP). Two distinct isoforms ( $\alpha 1C$ /Cav1.2 and  $\alpha 1D$ /Cav1.3) mediate calcium entry into cardiac myocytes to trigger respectively cardiac contraction and pacemaker activity. Drugs have been shown to target L-type calcium channels but poor selectivity has been reported between Cav1.2 and Cav1.3. Our goal was to identify a tool able to discriminate between Cav1.2 and Cav1.3 isoforms. We focused on calciseptine (Cas) from mamba venom reported to decrease vascular and cardiac contraction via a L-type calcium channel but without affecting heart rate.**Methods:** Contraction and heart rate were investigated in Langendorff perfused hearts. Patch clamp experiments were used to study the effect of Cas on LTCC in ventricular cells, sino-atrial cells known to express both isoforms and in recombinant Cav1.2 and Cav1.3 currents in HEK cells.**Results:** Calciseptine decreases contraction while no modification of the heart rate is observed up to 1  $\mu$ M Cas. Spontaneous AP frequency recorded from sinus node cells using the patch clamp technique was also unaffected by 100 nM Cas. By contrast, DHPs such as nifedipine or amlodipine decreased both contractility and heart rate and induced arrhythmias. In line with blockade of Cav1.3, DHPs strongly reduced AP frequency in isolated pacemaker myocytes. Voltage-clamp experiments in ventricular and pacemaker myocytes and on recombinant Cav1.2 and Cav1.3 currents confirmed selective inhibition of the Cav 1.2 isoform by Cas and no effect on other calcium channel subtypes (T,N,P/Q) or on hERG potassium current.**Conclusions:** calciseptine is a specific blocker of Cav1.2 L-type calcium current and an interesting tool to study the pathophysiological role of Cav1.2 versus Cav1.3 in heart, or in neuroendocrine and neuronal cells where Cav1.2 and Cav1.3 are co-expressed.

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**Characterising the role of a NOS1AP-C10RF226 intergenic spliced isoform in Cardiomyocytes**Galvin Tang<sup>1,2</sup>, Chang Jie Mick Lee<sup>1,2</sup>, Huang Hua<sup>3,4</sup>, Roger S-Y Foo<sup>1,2</sup><sup>1</sup>Cardiovascular Metabolic Disease Translational Research Programme, NUS Yong Loo Lin School of Medicine, Singapore; <sup>2</sup>Institute of Molecular and Cell Biology, Agency for Science Technology and Research, Singapore; <sup>3</sup>Department of Physiology, NUS Yong Loo Lin School of Medicine; <sup>4</sup>Healthy Longevity Translational Research Programme, NUS Yong Loo Lin School of Medicine**Background:** GWAS studies has linked NOS1AP to the regulation of the QT interval in cardiomyocytes with reports showing have NOS1AP facilitating L-type calcium channels (LTCC) nitrosylation through NOS1. NOS1AP acts as a bridge NOS1 and LTCC via its PDZ and PTB domains respectively. However, overexpression and silencing of NOS1AP both resulted in shorter QT intervals. Our objective was to identify and understand the role of a predominant NOS1AP intergenic-spliced isoform in cardiomyocytes and its potential impact on QT interval regulation.**Methods:** We utilized long-read and short-read RNA sequencing to identify an intergenic-spliced NOS1AP isoform in cardiomyocytes and has shown that this isoform lacks the PDZ domains but retains the PTB domain. Immunofluorescence staining was performed to analyze the subcellular localization of canonical NOS1AP and the intergenic-spliced isoform. Additionally, we knocked out the intergenic-spliced isoform in hESC-derived cardiomyocytes and assessed the effects on QT intervals and calcium dynamics.**Results:** The intergenic-spliced NOS1AP isoform likely competes with canonical NOS1AP for NOS1 binding without recruiting NOS1 to LTCC (due to the lack of PDZ domain), acting as a negative regulator of NOS1AP. Both canonical and intergenic-spliced NOS1AP exhibited similar striation patterns, indicating binding to LTCC at the T-tubules. Knockout of the intergenic-spliced isoform increased QT intervals and promoted calcium overloading in both monolayer cultures and cardiomyocyte cardioids.**Conclusions:** The identified NOS1AP intergenic-spliced isoform is hypothesized to compete with canonical NOS1AP for NOS1 binding, potentially preventing NOS1 recruitment to LTCC and acting as a negative regulator. This finding helps explain inconsistencies observed with NOS1AP manipulation and provides new insights into QT interval regulation in cardiomyocytes. Further investigation into the mechanism of this isoform's action will enhance our understanding of its role in cardiomyocyte function.Journal of Molecular and Cellular Cardiology Plus 10S2 (2024) 100124  
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