Ortner *et al.*: *Intrinsic Activity*, 2014; **2**(Suppl. 1):A1.18
published online: 22 September 2014
http://www.intrinsicactivity.org

20th Scientific Symposium of the Austrian Pharmacological Society APHAR

Innsbruck, Austria, 26–27 September 2014

MEETING ABSTRACT

A1.18

Pyrimidine-2,4,6-triones are a new class of voltage-gated L-type Ca^{2+} channel activators

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Background: The motor symptoms of Parkinson's disease, a non-curable neurodegenerative disorder, reflect the specific loss of dopaminergic substantia nigra pars compacta neurons. The cell death of these pacemaker neurons seems to be attributable to $Ca_V1.3$-mediated dendritic Ca^{2+} transients that add to an elevated level of mitochondrial oxidative stress. $Ca_V1.2$ and $Ca_V1.3$, the two main L-type Ca^{2+} channel (LTCC) isoforms found in the brain, cannot be efficiently discriminated in a pharmacological manner. Since $Ca_V1.2$ is also highly expressed in the cardiovascular system, a $Ca_V1.3$-selective blocker could constitute a promising neuro-protective therapy without blood-pressure lowering side effects.
Methods: Using the patch-clamp technique, we investigated the pharmacological modulation by Cp8 (a pyrimidine-2,4,6-trione derivative, recently reported as the first highly selective $Ca_V1.3$ blocker [1]) of I_{Ba} (10 or 15 mM) or I_{Ca} (15 mM) through $Ca_V1.3$ (rat or human long splice variant, $rCa_V1.3_L$, $hCa_V1.3_L$) and $Ca_V1.2$ (rabbit long or short C-terminus, $rbCa_V1.2_L$, $rbCa_V1.2_S$) α_1 subunits expressed together with β3 and α2–δ1 subunits in tsA-201 cells or using mouse chromaffin cells (MCCs; 2 mM Ca^{2+}).
Results: Unexpectedly, a change in gating kinetics of I_{Ba} and I_{Ca} through different $Ca_V1.2$ and $Ca_V1.3$ channel constructs, closely resembling the activity of known LTCC activators such as FPL 64176, was observed using 50 µM of Cp8. This modulation was characterized by a slowing of activation and inactivation as well as a profound enhancement of tail currents. However, in a minority of cells using Ba^{2+} as charge carrier no change in gating kinetics but a weak and non-selective inhibition of both channel isoforms could be observed. Furthermore, the activating properties of Cp8 could be confirmed on native LTCCs in mouse chromaffin cells (MCCs; 2 mM Ca^{2+}) where non-L-type currents were spared. Additionally, 50 µM Cp8 also increased the spontaneous firing frequency of MCCs and the total Ca^{2+} load during action potentials.
Discussion: Apart from a weak inhibition of both, $Ca_V1.2$ and $Ca_V1.3$, in a minority of cells using Ba^{2+} as charge carrier, neither a potent nor a $Ca_V1.3$-selective (reported IC_{50} 24.3 ± 0.7 µM [1]) inhibition by Cp8 was observed. Moreover, Cp8 induced an LTCC activator-like change in current gating kinetics in all Ca^{2+} and the majority of Ba^{2+} recordings, therefore suggesting that pyrimidine-2,4,6-triones can act as a new class of Ca^{2+} channel activators.
Acknowledgements: This work was supported by the Austrian Science Fund FWF (F44020, W11).

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Reference

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