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MEETING ABSTRACT

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Derivatives of the class I antiarrhythmic agent sparteine act as irreversible Na^+ channel blockers

Vaibhavkumar S. GAWALI[1], Ulla HOCHENEGG[1], Martina DRESCHER[2], Nuno MAULIDE[2] and Hannes TODT[1,*]

[1]Department of Neurophysiology and Neuropharmacology, Center for Physiology and Pharmacology, Medical University of Vienna, Austria; [2]Institute of Organic Chemistry, University of Vienna, Austria

Background: Blockers of voltage-gated Na^+ channels are in clinical use mainly as antiepileptics, antiarrhythmics and as local anesthetic agents (LAs). The use of these drugs as LAs is frequently limited by short duration of action and systemic toxicity. Such limitations could be overcome by agents that give rise to irreversible block of neuronal Na^+ channels. Here we show that attachment of aromatic residues at position 2 of the class I antiarrhythmic agent sparteine (Fig. 1) gives rise to long-lasting inhibition of Na^+ currents.

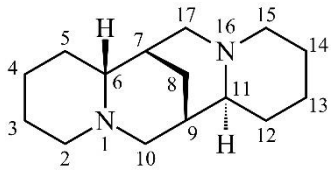

Figure 1: Sparteine

Methods: The compounds were tested by means of whole-cell patch clamp technique (manually as well as using an automated device, Cytopatch™) on tsA201 and HEK 293 cells, transfected with cardiac, neuronal, skeletal-muscle and brain isoforms of voltage-gated Na^+ channels. Na^+ currents were evoked by 20 ms depolarizations to −20 mV at 2 Hz from a holding potential of −140 mV.

Results: At a concentration of 300 µM, sparteine reduced currents through $Na_V1.4$ channels by ~20%. Block developed over 20 s and was completely reversible upon washout. By contrast, with all tested sparteine derivatives block developed over several minutes. With aliphatic substitutions at position 2, application of 10 µM produced a slowly reversible current reduction of ~10%. However, with aromatic substitutions at position 2, application of 10 µM gave rise to complete current reduction which could not be removed by a 20 min washout phase. No obvious isoform preference of the tested compounds could be detected.

Discussion: We conclude that attachment of aromatic residues as position 2 of sparteine produces irreversible blockers of voltage-gated Na^+ channels. Clinically, such agents could be used as long-lasting LAs.

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*Corresponding author e-mail: *hannes.todt@meduniwien.ac.at*