Selective SSTR4 agonists mediate membrane hyperpolarization and reduced intrinsic firing in CA1 pyramidal neurons from humanized SSTR4 rats and human

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INTRODUCTON

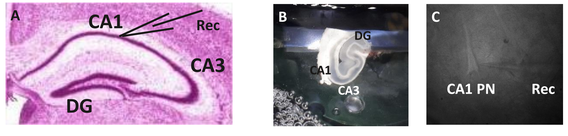
Human studies suggest that aberrant overactivation of the hippocampal network exacerbates neurodegeneration in Alzheimer's Disease (AD). Somatostatin receptor subtype 4 ($SSTR_4$) is highly expressed in the hippocampus and may play an anti-convulsant role by downregulating CA1 pyramidal cell intrinsic excitability through coupling to Kv7 channels (responsible for the M-current). In addition, $SSTR_4$ has been shown to promote amyloid-beta (Aβ) phagocytosis and clearance, and thus $SSTR_4$ agonists have been proposed for the treatment of AD.

Using whole-cell current-clamp recordings in acute hippocampal slices, we examined the effects of novel selective $SSTR_4$ agonists (TAKEDA proprietary compounds A and B, cpA, cpB) and an antagonist (compound C, cpC) on membrane and firing properties of CA1 pyramidal cells from 6-15-week-old male Sprague-Dawley rats of wildtype (WT) and $SSTR_4$ humanized knock-in (hSSTR4) genotypes.

METHODS

Acute hippocampal slice preparations:

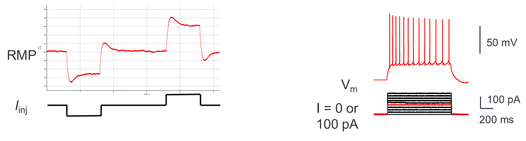
WT and hSSTR4 rats | **Human epileptic patients**



A. Recording configuration in WT and hSSTR4 rats (5x). **B.** Human acute hippocampal slice during the slicing procedure on a conventional vibratome. **C.** Human CA1 pyramidal neuron (PN; 60x). Rec: recording pipette.

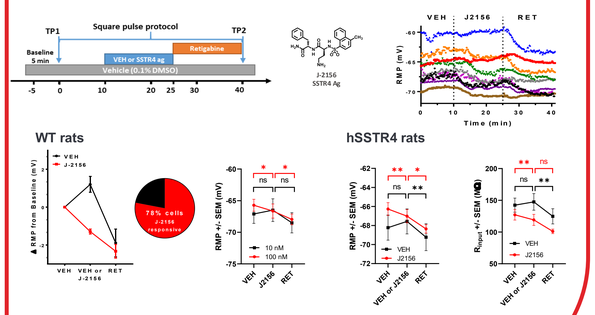
Whole-cell current-clamp recordings:

Square pulse protocol | **Rheobase & firing protocol from RMP & subthreshold V_m**

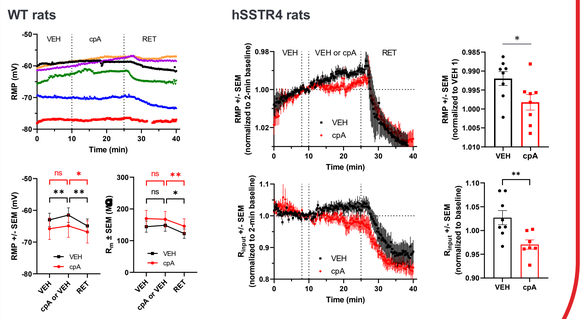


RESULTS

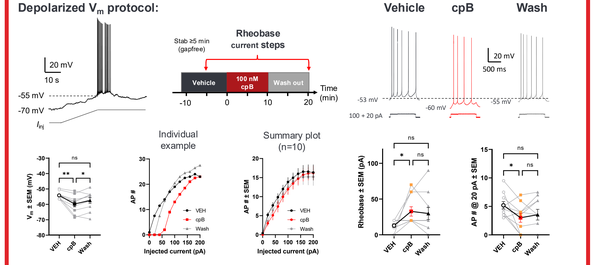
SSTR4 agonist J2156 (100 nM) decreases RMP and input resistance ex vivo in both WT and hSSTR4 rats



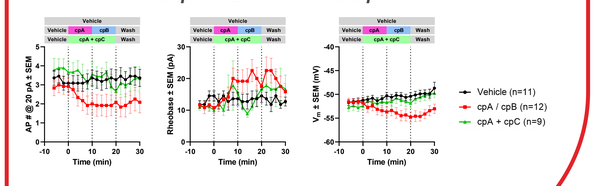
SSTR4 agonist CpA (1 µM) mildly decreases RMP and input resistance ex vivo in hSSTR4 but not WT rats



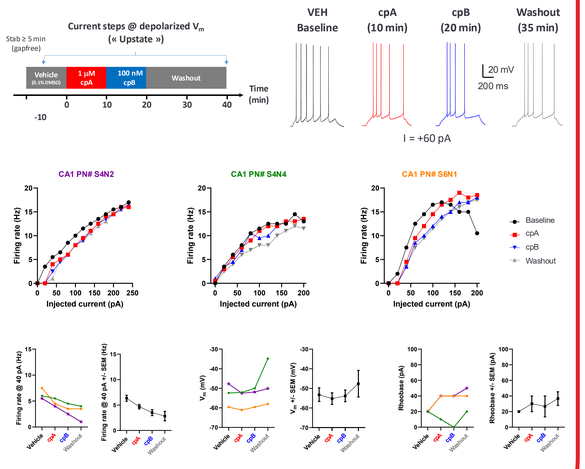
SSTR4 agonist CpB (100 nM) decreases intrinsic excitability in WT rats at depolarized membrane potentials



SSTR4 agonist CpA (1 µM) decreases intrinsic excitability in hSSTR4 rats at depolarized membrane potentials



Preliminary SYR134 and SYR765 human data suggests marginal inhibitory effect



CONCLUSION

- $SSTR_4$ agonists J2156 (100 nM) and Takeda proprietary CpA modestly decreased membrane excitability in hSSTR4 rats at RMP.
- $SSTR_4$ agonists CpA and CpB altered those membrane properties at depolarized potentials more efficiently.
- $SSTR_4$ agonists CpA and CpB similarly dampened CA1 pyramidal neurons intrinsic excitability at depolarized membrane potentials by decreasing V_m and firing levels and by elevating the rheobase.
- This voltage-dependent effect could reflect a possible functional coupling between $SSTR_4$ and Kv7 channels, which would confer them the property to selectively affect the hyperexcitable neurons.
- Concomitant application of the $SSTR_4$ antagonist cpC prevented the effect of the agonist cpA, indicating a specific role of $SSTR_4$.
- Preliminary results showed a modest right shift of the input-output curves, indicating a marginal inhibitory effect on human CA1 pyramidal neurons intrinsic firing.

REFERENCES

ACKNOWLEDGMENT

Neuroscience