(R)-Isometheptene* (IMH) Binds to the Imidazoline-1 Receptor and (S)-IMH increases Blood Pressure: Potentially Superior Benefit-to-Risk Ratio for (R)-IMH as an Analgesic for Headache

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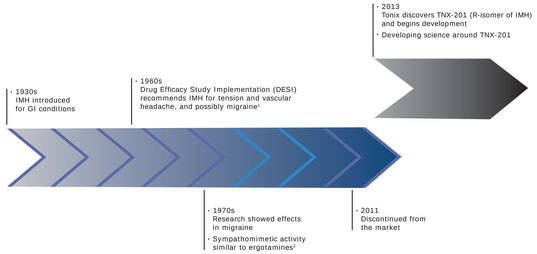
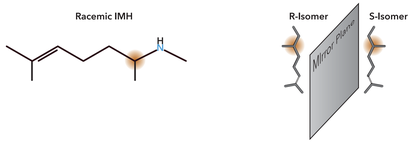
Introduction

- Isometheptene (IMH) is a racemic drug that has been used clinically in the US for more than 70 years primarily as a treatment for headache. Yet its mechanism of action remains unknown.
- Racemic IMH has sympathomimetic effects that have been linked to cardiovascular effects reported in the product labeling.
- To elucidate the mechanism of action of IMH, we separated IMH into the individual isomers, (R)-IMH and (S)-IMH and studied their molecular and cardiovascular effects.

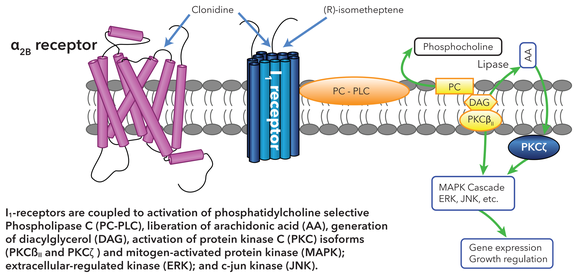
Racemic isometheptene (IMH) has a long track record of use



Previously marketed isometheptene drugs were a mixture containing equal amounts of two chemically distinct, mirror-image isomers



Model of I_1-imidazoline receptor signalling pathways



I_1-receptors are coupled to activation of phosphatidylcholine selective Phospholipase C (PC-PLC), liberation of arachidonic acid (AA), generation of diacylglycerol (DAG), activation of protein kinase C (PKC) isoforms ($PKC\beta_{II}$ and $PKC\zeta$) and mitogen-activated protein kinase (MAPK); extracellular-regulated kinase (ERK); and c-jun kinase (JNK).

Methods

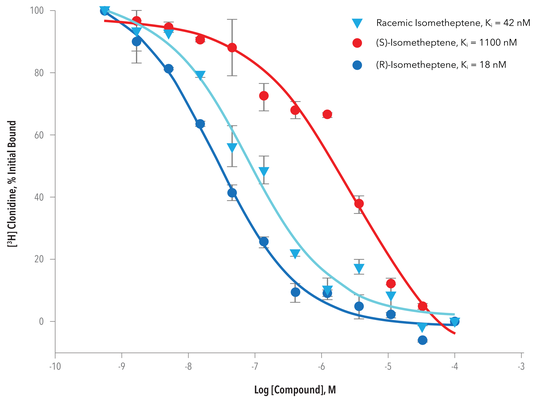
- Racemic IMH was screened on a broad panel of protein targets, which included enzymes, receptors (both GPCR and non-GPCR), ion channels and transporters.
- The effects on arterial blood pressure (BP) and heart rate (HR) of intravenous (IV) racemic IMH mucate, (R)-IMH mucate, and (S)-IMH mucate in anesthetized male Wistar rats were studied (using consecutive doses of 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg IV with 10-minute interdose intervals).
- The pharmacokinetics (PK) of racemic and (R)-IMH were studied in rats using stereospecific liquid chromatography-mass spectrometry.

Results

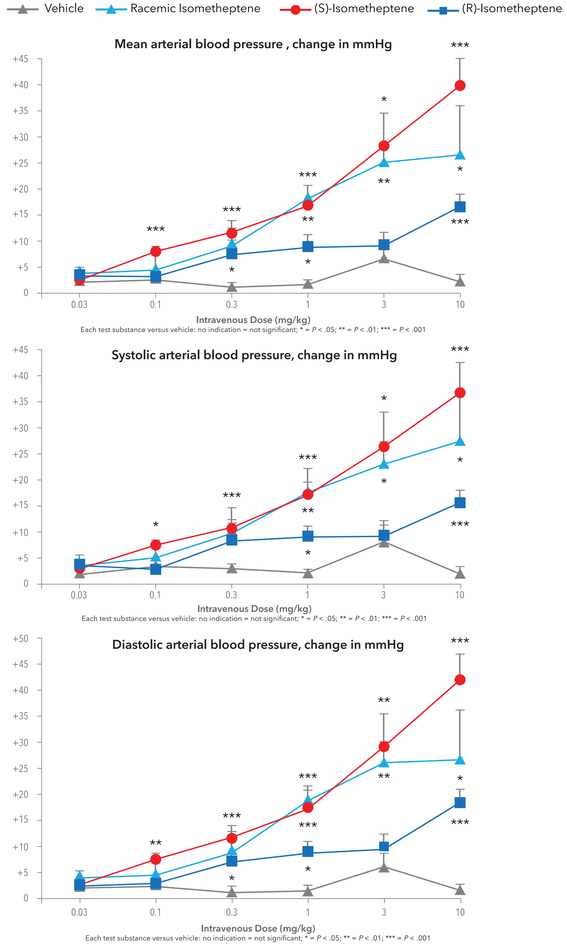
Comparative Binding Affinities of (R)-Isometheptene versus (S)-Isometheptene to Receptors Expressed in the CNS

	K_i(nM)				
Compound	**I_1R**	**I_2R**	**α_{2B}**	**Sigma-1 Receptor**	**Sigma-2 Receptor**
(R)-Isometheptene	18	62	50000	1900	5600
(S)-Isometheptene	1100	180	55000	2100	5200

Equilibrium Binding of (R)-Isometheptene, (S)-Isometheptene and Racemic Isometheptene to I_1-Imidazoline Receptor

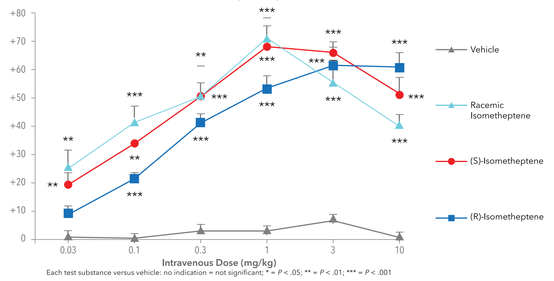


(R)-Isometheptene Has Reduced Effects on Blood Pressure Compared to (S)-Isometheptene and Racemic Isometheptene



Each test substance versus vehicle: no indication = not significant; * = $P < .05$; ** = $P < .01$; *** = $P < .001$

(R)-Isometheptene Has Similar Effects on Heart Rate Compared to (S)-Isometheptene and Racemic Isometheptene



Each test substance versus vehicle: no indication = not significant; * = $P < .05$; ** = $P < .01$; *** = $P < .001$

Pharmacokinetics of Racemic Isometheptene Mucate and (R)-Isometheptene Mucate in Rats

Test Article	Dose, mg/kg	C_{max}, ng/mL		AUC, ng.h/mL		T_{max}, h		$T_{1/2}$, h	
		R-IMH	S-IMH	R-IMH	S-IMH	R-IMH	S-IMH	R-IMH	S-IMH
Racemic IMH	1	165	175	62	66	0.16	0.16	0.37	0.38
(R)-IMH	0.5	198	NC	76	NC	0.16	NC	0.47	NC

Conclusions

R-Isomer
- Analgesic
- Binds to I_1-imidazoline receptor

S-Isomer
- Sympathomimetic

- Our finding that R-IMH binds to I_1R with high affinity suggests that this receptor is the primary site of action for R-IMH's analgesic effects. This is confirmed by recent results in the I_1R knock out mouse in which there is a decreased pain threshold.
- Our finding that S-IMH produces significantly higher increased BP suggest that this isomer is responsible for the cardiovascular liability observed with racemic IMH.
- These findings suggest that R-IMH is an agonist of I_1R, a receptor in the brain that regulates pain perception, and that it may have a superior benefit/risk ratio as an analgesic for headache compared to either the racemic or the (S)-isomer.

References

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3. Zhang L, Zhao TY, Hou N, et al. Generation and primary phenotypes of imidazoline receptor antisera-selected (IRAS) knockout mice. *Cns Neurosci Ther.* 2013;19(12):978-981.

*(R)-IMH mucate is being investigated in the US for tension-type headache as TNX-201 under US Investigational New Drug and it is not approved for any indication.

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