Setbacks in the Clinical Development of TRPV1 Antagonists: What Next?

Narender R. Gavva*

Department of Neuroscience, Amgen, Inc., Thousand Oaks, CA, USA

Abstract: TRPV1 antagonists have been considered as potential treatments for pain associated with inflammatory diseases and cancer. During Phase I clinical trials with AMG 517, a highly selective TRPV1 antagonist, we found that TRPV1 blockade elicits marked, but reversible, and generally plasma concentration-dependent hyperthermia. Furthermore, in a Phase Ib study, AMG 517 administered after molar extraction (a surgical cause of acute pain) elicited long-lasting hyperthermia with maximal body temperature surpassing 40 ºC, suggesting that TRPV1 blockade elicits undesirable hyperthermia in susceptible individuals.

Since TRPV1 blockade elicited hyperthermia is a major hurdle, we investigated the possibility of eliminating hyperthermia while maintaining antihyperalgesia by two approaches: i) peripheral restriction of TRPV1 antagonists, ii) characterization of TRPV1 modulators that exhibit differential pharmacology. Results from the preclinical studies of both approaches will be discussed.

*Address correspondence to this author at the Department of Neuroscience, Amgen Inc., Thousand Oaks, CA, USA; Tel: (805)447-0607; E-mail: ngavva@amgen.com

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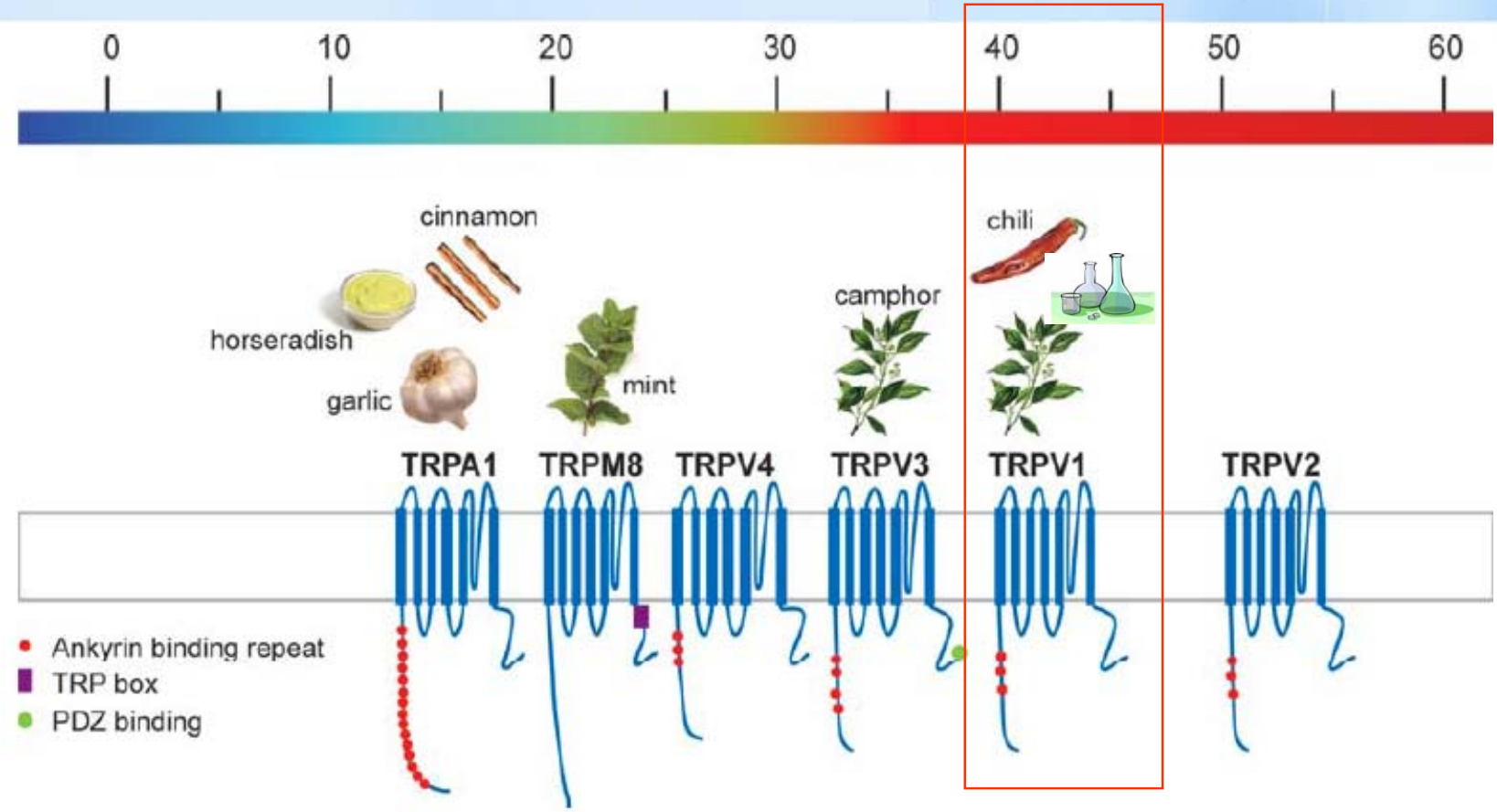
Narender R. Gavva Ph.D.
Department of Neuroscience

AMGEN

Outline

- Introduction
- Functional assays
- AMG 517 preclinical studies
- TRPV1 antagonism - hyperthermia
- Mechanisms of hyperthermia
- AMG 517 clinical trial results
- Peripherally restricted antagonists – hyperthermia
- Differential pharmacology of antagonists – no hyperthermia
- Conclusions

TRP channels are integrators of multiple noxious stimuli

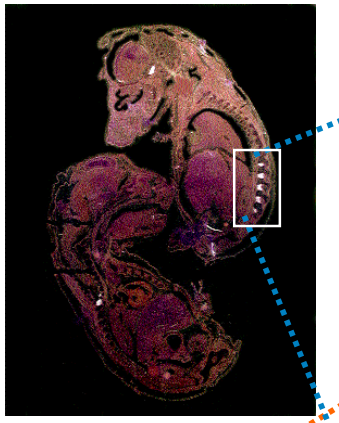


Dhaka et al (2006) *Annu Rev Neurosci.* **29**:135-61

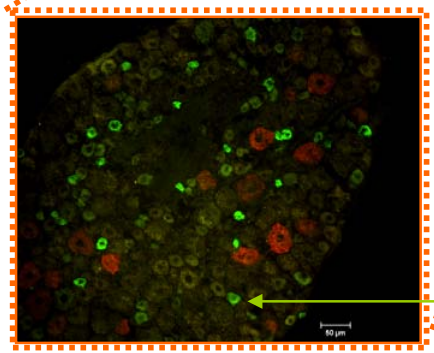
- **Agonists of TRPA1 and TRPV1 cause pain in humans and pain behavior in rodents**

TRPV1: A polymodal detector of painful stimuli

TRPV1 Expression in E19 Rat



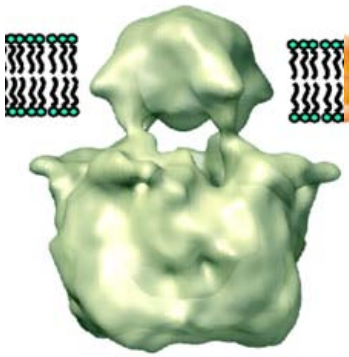
White Areas Show Expression In DRG Neurons in Rats



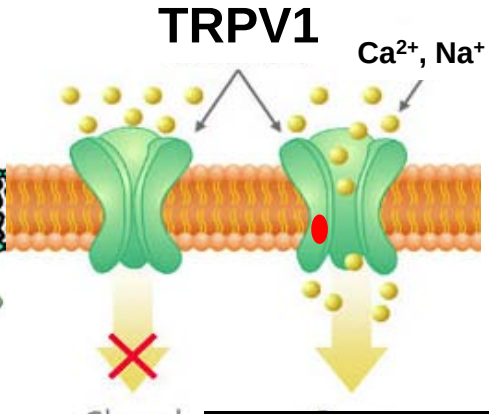
TRPV1 positive DRG neurons

TRPV1 is activated by:

- Chemical ligands (capsaicin, RTX etc)
- Heat
- GPCR signaling
- Phosphorylation
- Low pH



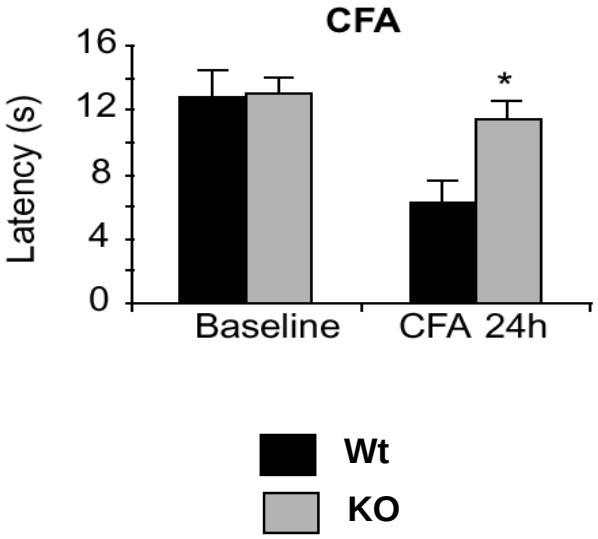
Moiseenkova-Bell et al 2008
PNAS. 105:7451-5

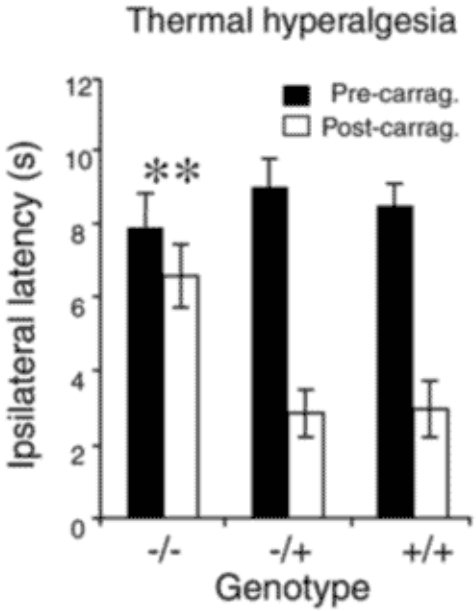


Rat sensory neurons responding to capsaicin (calcium imaging)

TRPV1 – Target validation

TRPV1 knockout mice show reduced thermal hyperalgesia

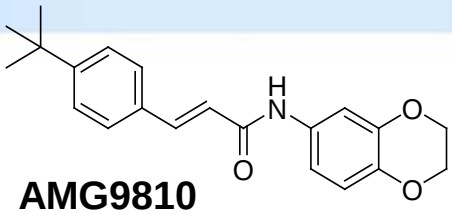




Davis et al (2000) *Nature* 405:183-7; Caterina et al (2000) *Science*, 288, 306-13

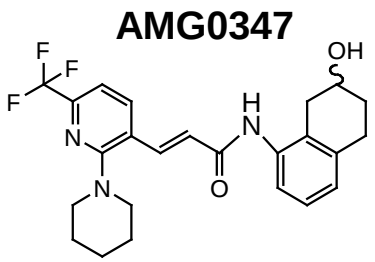
- TRPV1 expression in the spinal cord is up-regulated after SCI – Zhou et al (2002) *J Surg Res.* **107**:140-4
- TRPV1 expression increased in inflamed human oesophagus – Mathews et al (2004) *Eur J Gastroenterol Hepatol.***16**:897-902

Various distinct chemical scaffolds act as TRPV1 antagonists



AMG9810

Gavva *et al 2005 JPET,* **313***:474-484*



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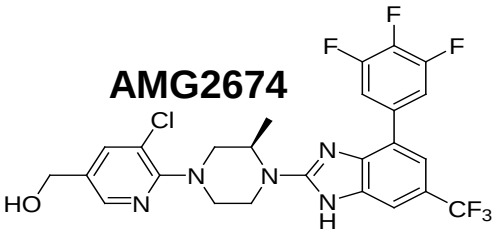
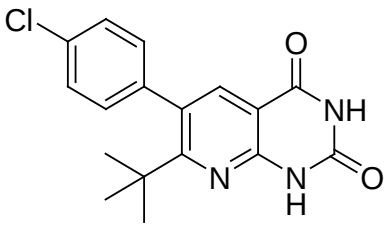
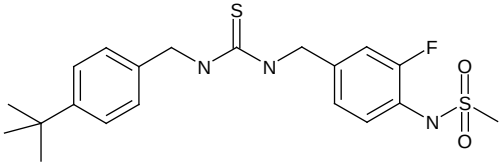


AMG2674



NVS Pyridopyrimidine



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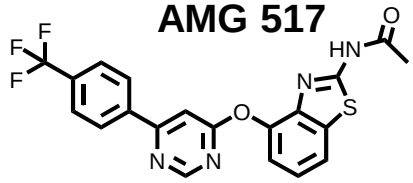
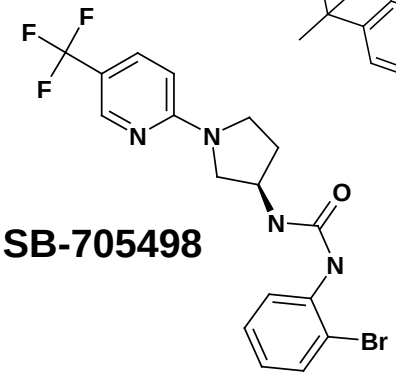


AMG 517

Doherty et al., 2007 JMC **50**:3515-27

Gavva et al., 2007 JPET **323**:128-137



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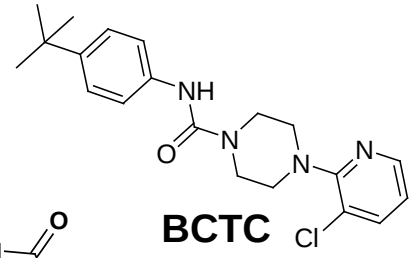
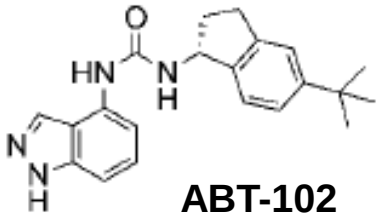


BCTC



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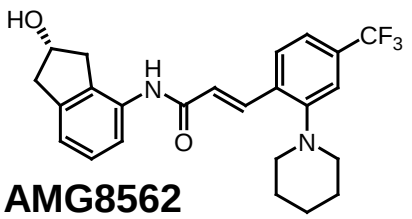
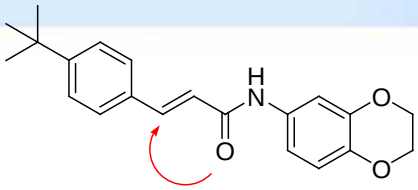
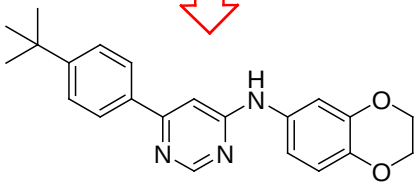


AMG8562

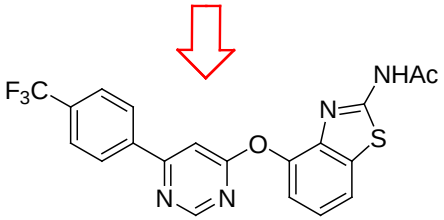
Strategy for SAR development



rTRPV1 (Cap) IC_{50} = 79 nM
rTRPV1 (pH) IC_{50} = 350 nM



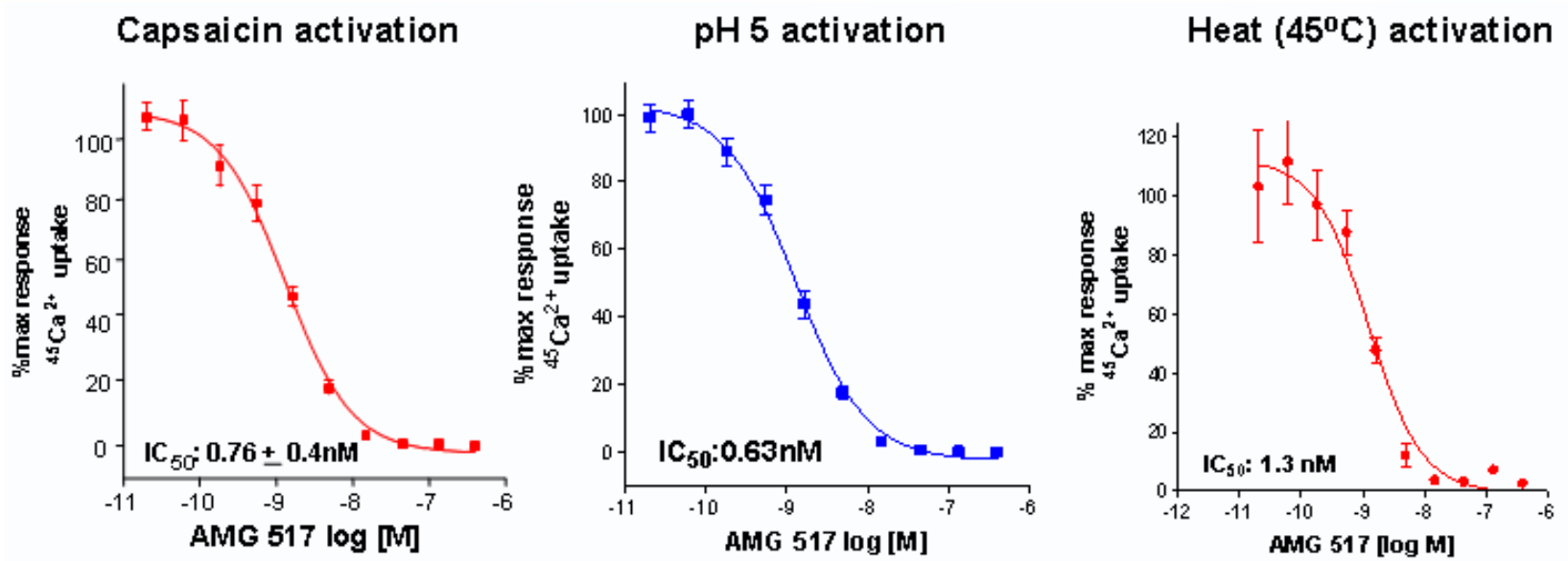
rTRPV1 (Cap) IC_{50} = 120 nM
rTRPV1 (pH) IC_{50} = 680 nM



rTRPV1 (Cap) IC_{50} = 0.9 nM
rTRPV1 (pH) IC_{50} = 0.5 nM

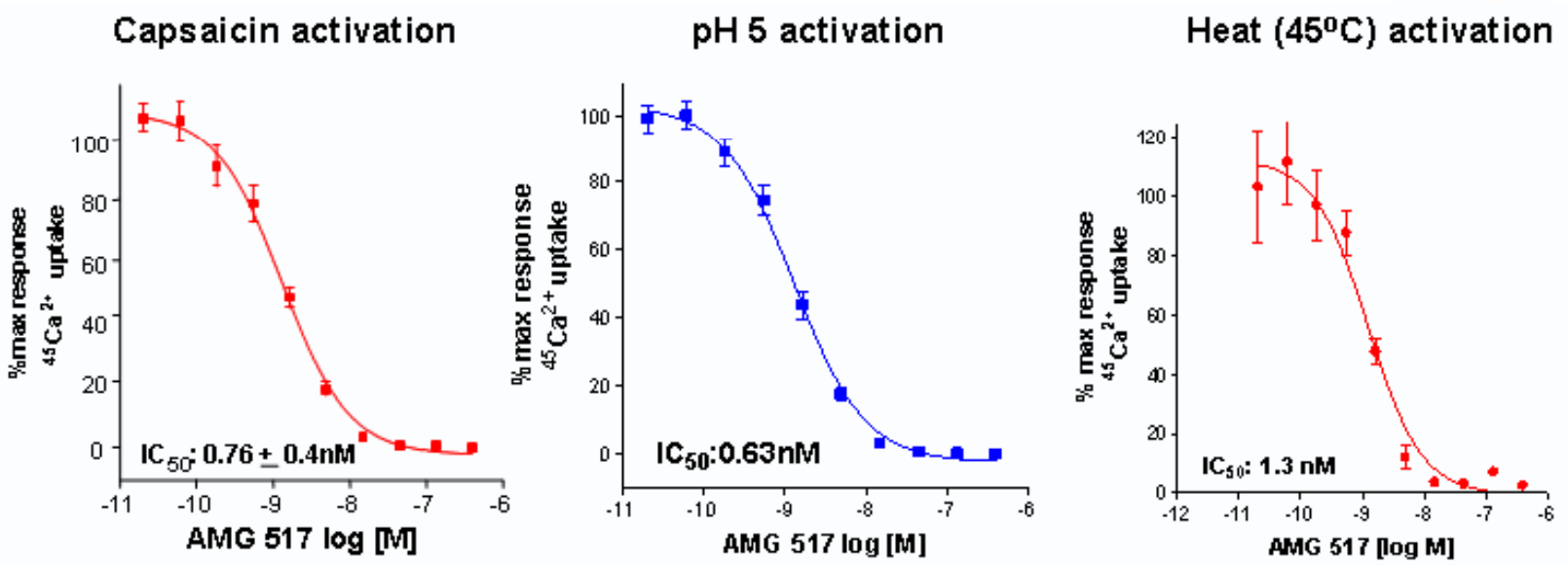
- High-throughput screening of our corporate database identified several *N*-aryl cinnamides as TRPV1 antagonists
- Constrained analogs of *s*-cis cinnamides provided an entry into a novel chemical series of TRPV1 antagonists
- Further optimization lead to the clinical candidate AMG 517

AMG 517 blocks all modes of TRPV1 activation



- AMG 517 is a potent antagonist of rodent, dog, monkey and human TRPV1
- AMG 517 does not block TRPA1, TRPV2, TRPV3, TRPV4, and TRPM8

AMG 517 blocks all modes of TRPV1 activation



- AMG 517 is a potent antagonist of rodent, dog, monkey and human TRPV1
- AMG 517 does not block TRPA1, TRPV2, TRPV3, TRPV4, and TRPM8

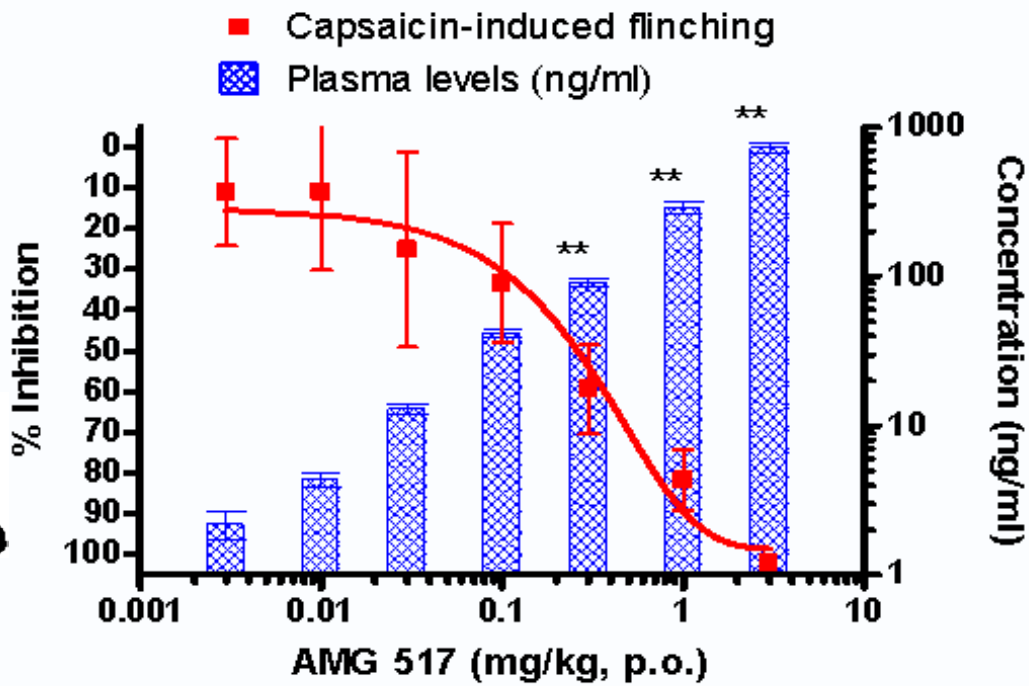
AMG 517 blocks capsaicin-induced flinching in rats

Dose
AMG 517 p.o.

60 min

Inject Capsaicin
Into the Paw

Count # of
Paw Flinches
in 1 min



Gavva et al., *2007* JPET **323**:128-137

AMG 517 blocks inflammation-induced thermal hyperalgesia

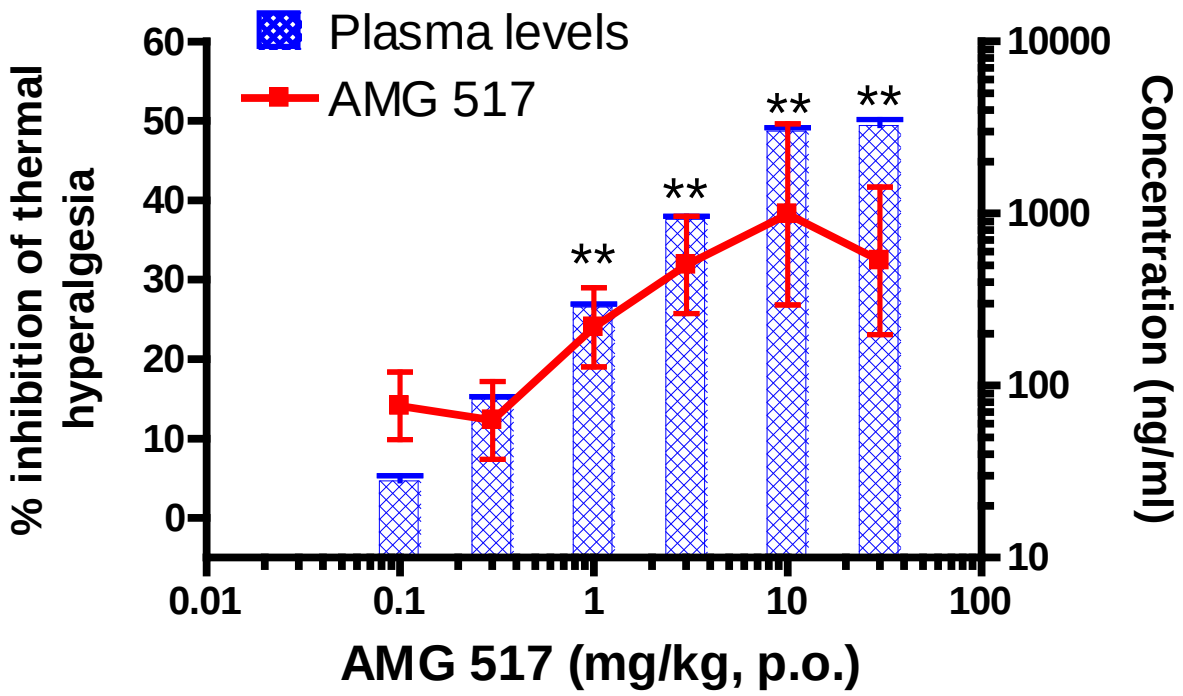
Inject CFA into the paw

22 h

Dose AMG 517, p.o.

2 h

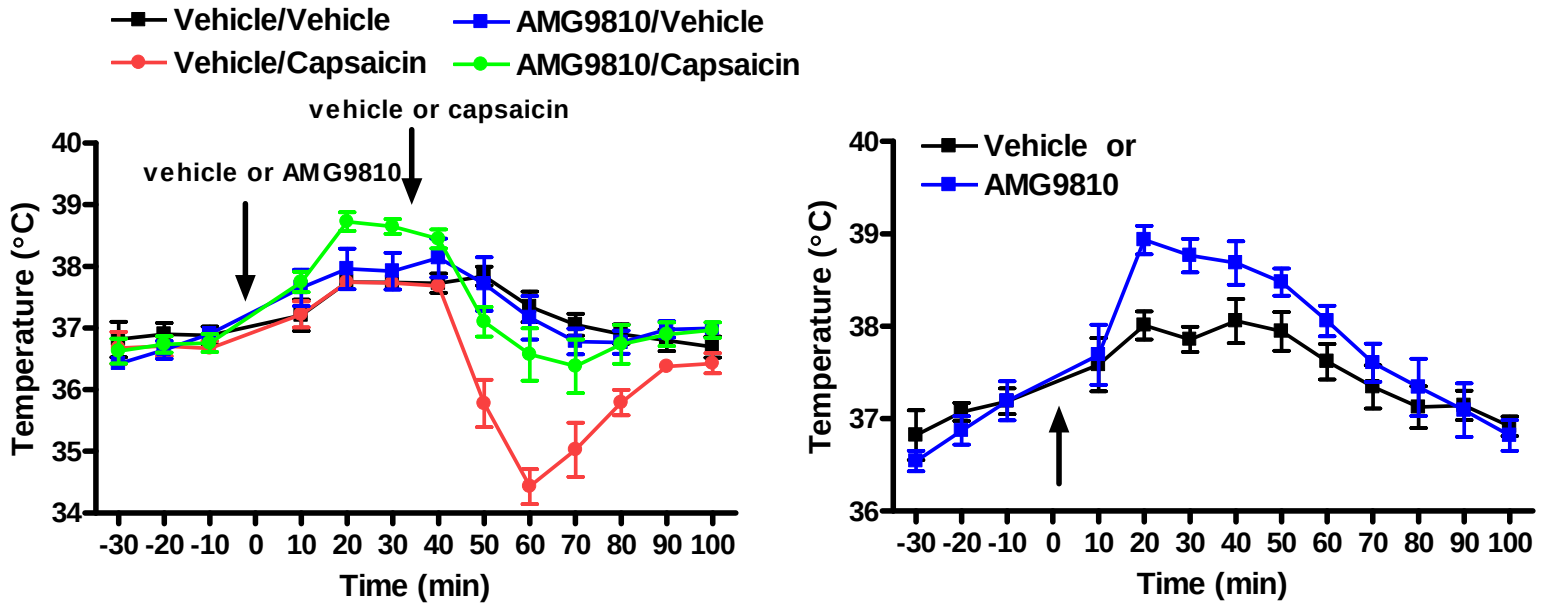
Record thermal sensitivity



Gavva et al., *2007* JPET **323**:128-137

TRPV1 antagonists block capsaicin-induced hypothermia and cause hyperthermia by themselves

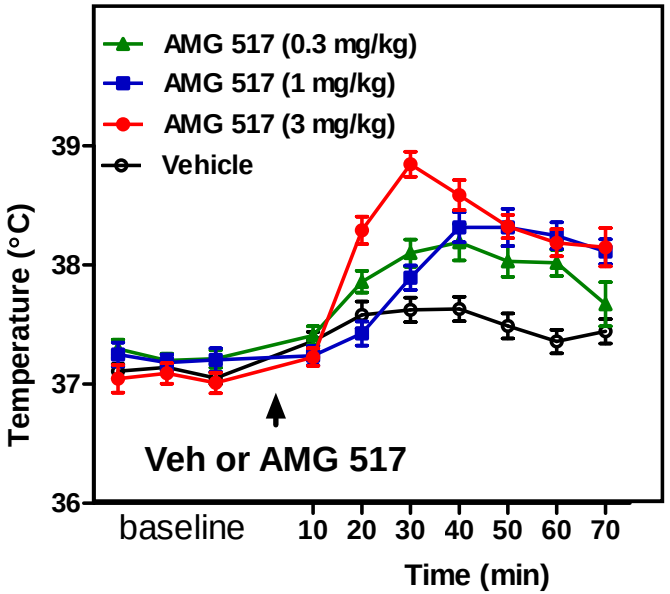
- On-target challenge model
  - Capsaicin, a TRPV1 agonist produces an "on-target" decrease in body temperature
  - Pretreatment with a TRPV1 antagonist should block capsaicin-induced hypothermia



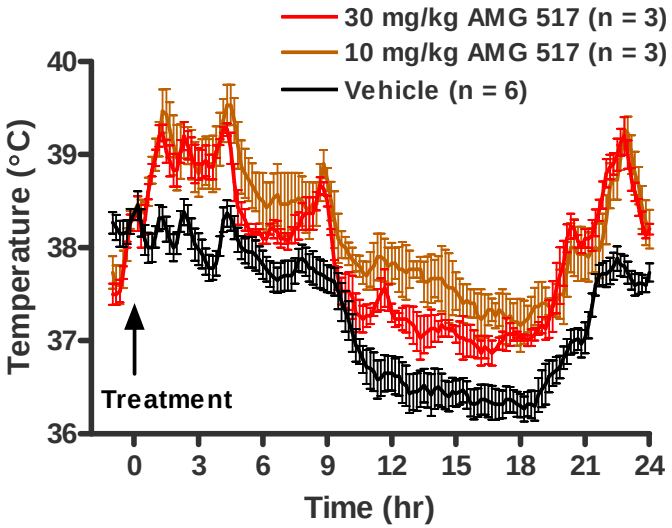
Gavva et al., *J Neurosci*. 2007 Mar 28;27(13):3366-3374

AMG 517 causes hyperthermia in multiple species

Rat radiotelemetry



***Cynomolgus* monkeys**

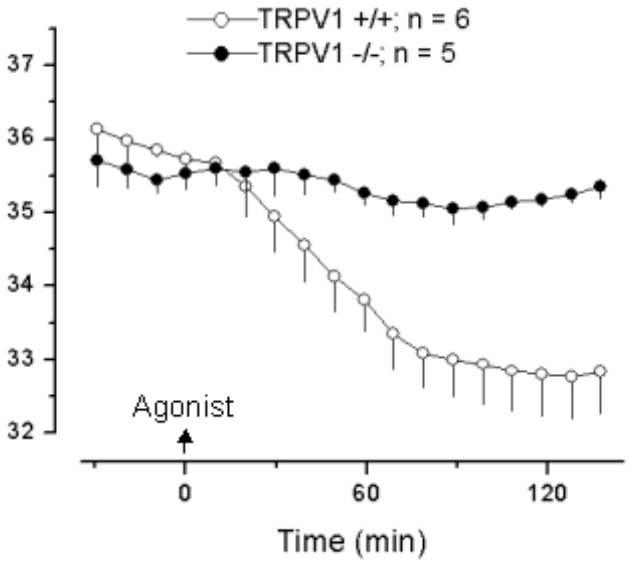


Gavva et al., *JPET* 2007 **323**:128-137

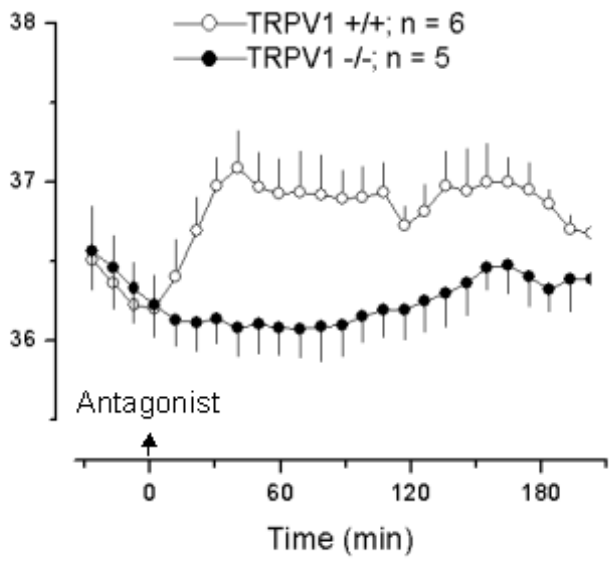
- TRPV1 antagonists caused hyperthermia in rodents, dogs, monkeys

Agonists and antagonists do not cause body temperature changes in TRPV1 knockout mice

Agonist-induced hypothermia



Antagonist-induced hyperthermia



Steiner et al., *J Neurosci*. 2007 Jul 11;27(28):7459-68

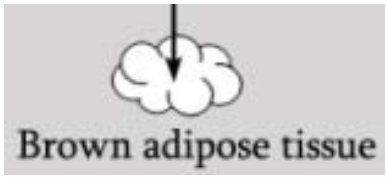
- Agonist-induced hypothermia & antagonist-induced hyperthermia are entirely TRPV1 mediated

AMG 517 causes hyperthermia by vasoconstriction and increased thermogenesis

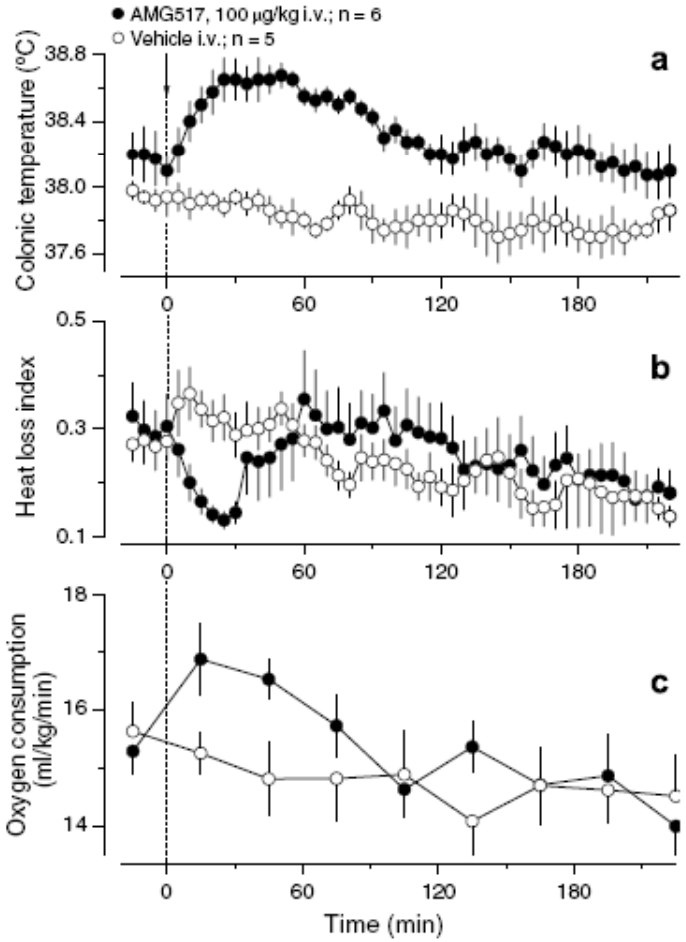
Individual effectors

Skin vasomotor tone

Nonshivering thermogenesis

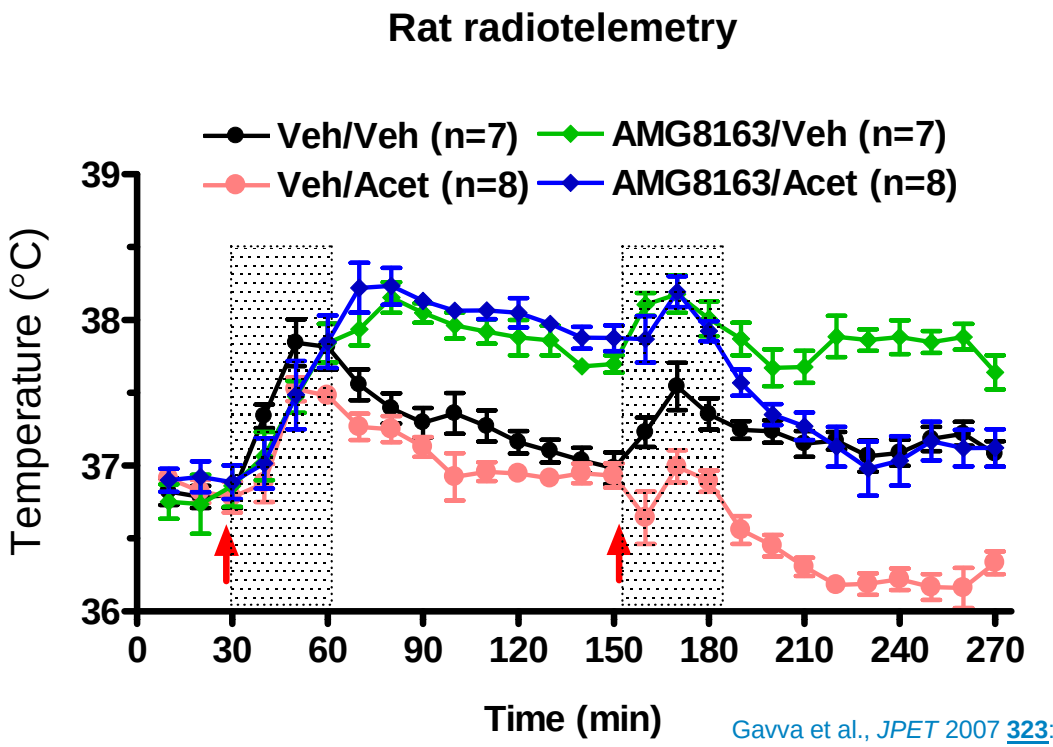


Shivering



Gavva et al., 2008 Pain **136**:202-210

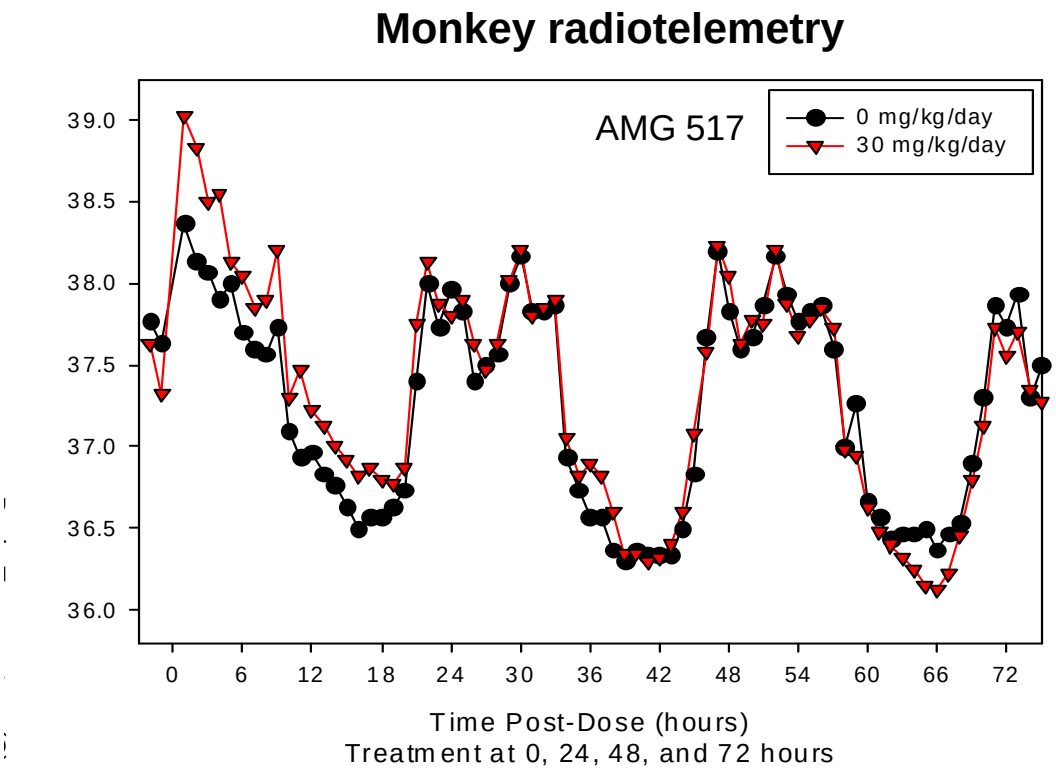
Antipyretic acetaminophen suppresses TRPV1 antagonist-induced hyperthermia



Gavva et al., *JPET* 2007 **323**:128-137

- AMG8163 is a 'boc' analogue of AMG 517
- Similar to AMG 517, AMG8163 blocks all modes of TRPV1 activation

Repeated administration of AMG 517 attenuates hyperthermia



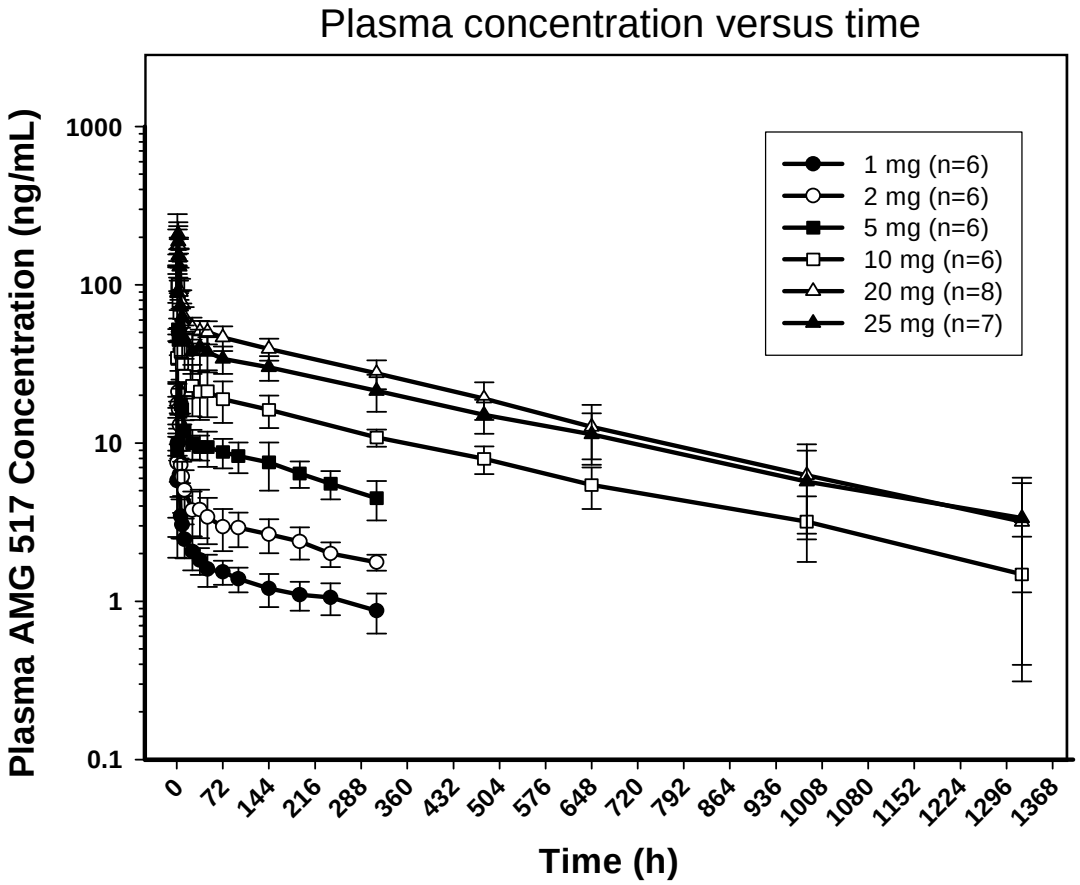
- TRPV1 is tonically activated and plays a role in body temperature regulation
- Role of TRPV1 in thermoregulation can be compensated

Clinical trial design

- **Vehicle of all studies**: A suspension in a 100 ml of 2% Pluronic 108 in OraPlus® followed by two 75 ml water washes
- 1st Phase I – single dose safety & pharmacokinetic study
  - Double-blind, placebo-controlled, randomized, single dose, dose-escalation sequential cohort study
  - Healthy subjects received 1, 2, 5, 10, 20, or 25 mg AMG 517
  - End points: number and incidence of treatment emergent-events, oral and tympanic body temperature measurements
- 2nd Phase I – Repeated dose study
  - Double-blind, placebo-controlled, randomized, single dose, dose-escalation sequential cohort study
  - Placebo, 2, 5, or 10 mg of AMG 517
  - treatment emergent-events, difference in max body temperature on day 1 versus subsequent days, through day 7
- Phase Ib – Dental pain study
  - Double-blind, placebo-controlled, randomized, Parallel group, multi-center study
  - Inclusion criteria: moderate to severe post-operative pain
  - Single doses of placebo, 2, 8, or 15 mg of AMG 517

More details can be found in: Gavva et al., 2008 Pain **136**:202-210

AMG 517 has a long half-life in healthy subjects

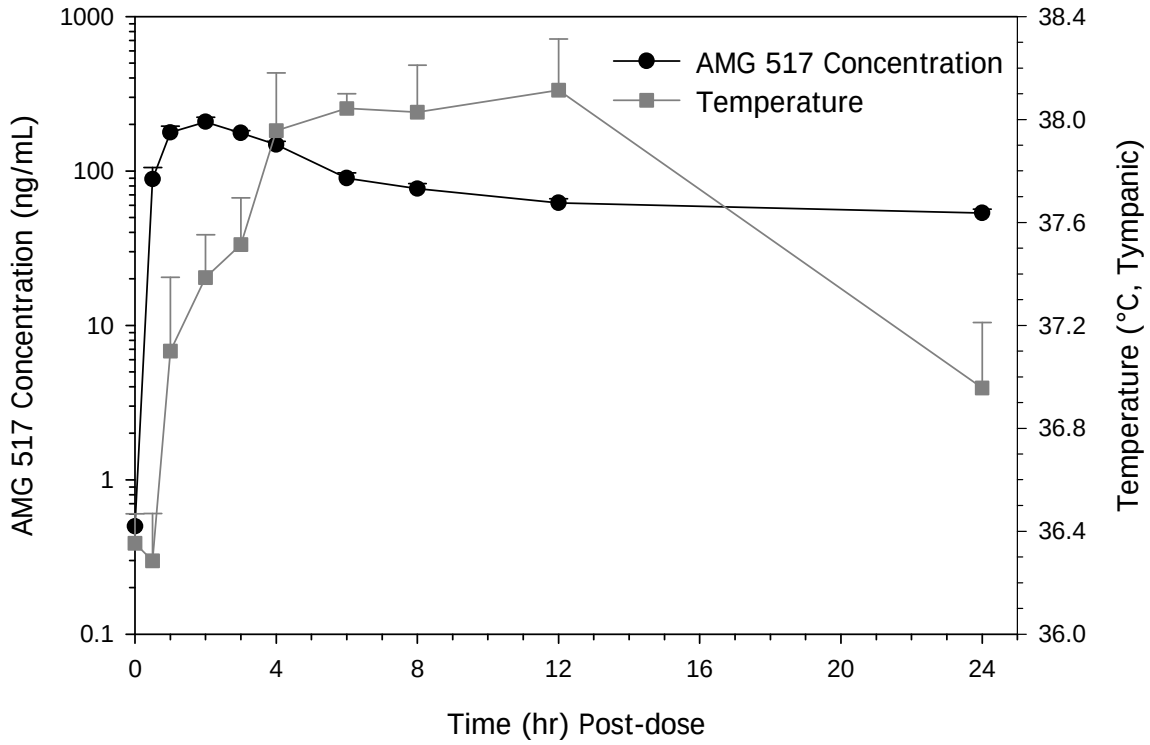


- Plasma half life: ~ 300 hrs

Gavva et al., 2008 Pain **136**:202-210

AMG 517 elicits transient hyperthermia in humans

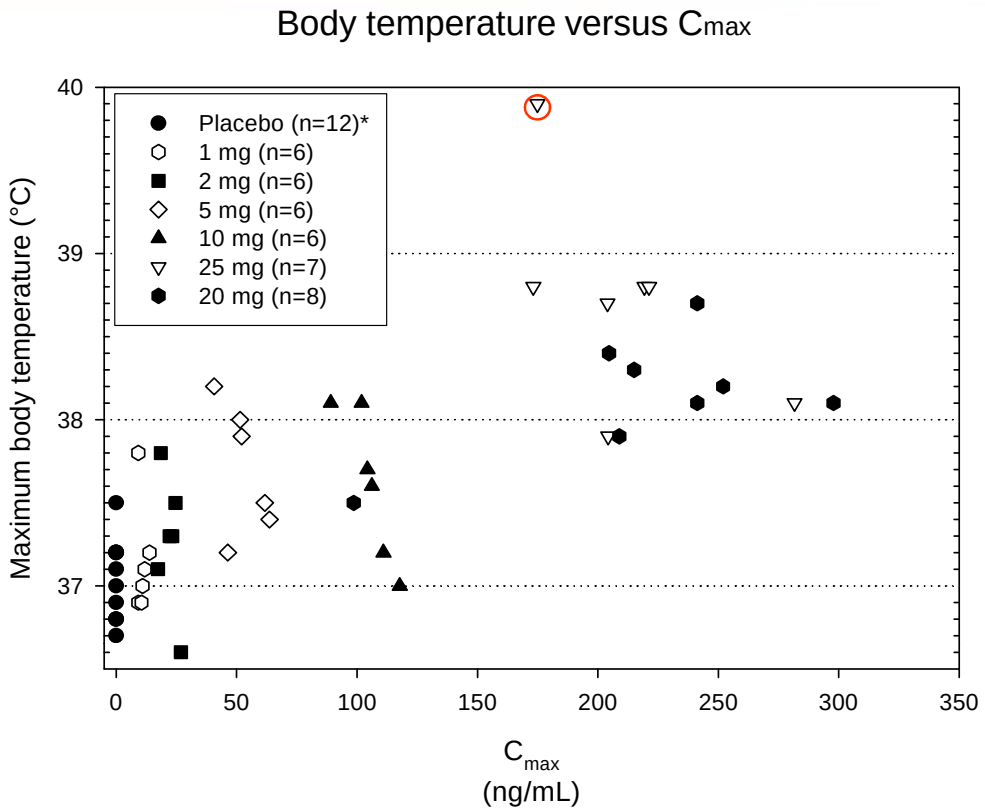
Body temperature & C_{max} versus time



(mean ± SD of the max body temperature [tympanic] presented)

Gavva et al., 2008 Pain **136**:202-210

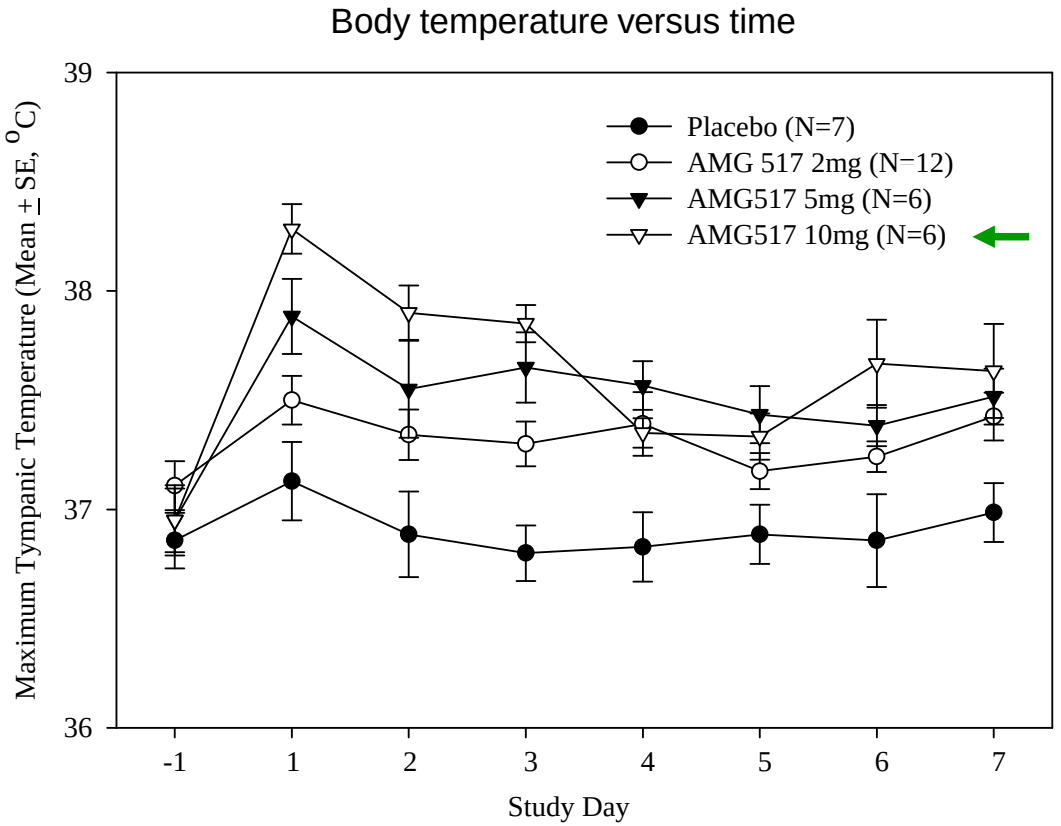
AMG 517 caused plasma concentration-dependent hyperthermia in healthy subjects



Gavva et al., 2008 Pain **136**:202-210

- Single dose, oral suspension in a 100 mL of 2% Pluronic 108 in OraPlus®
- Plasma half life of AMG 517 in humans: ~ 300 hrs

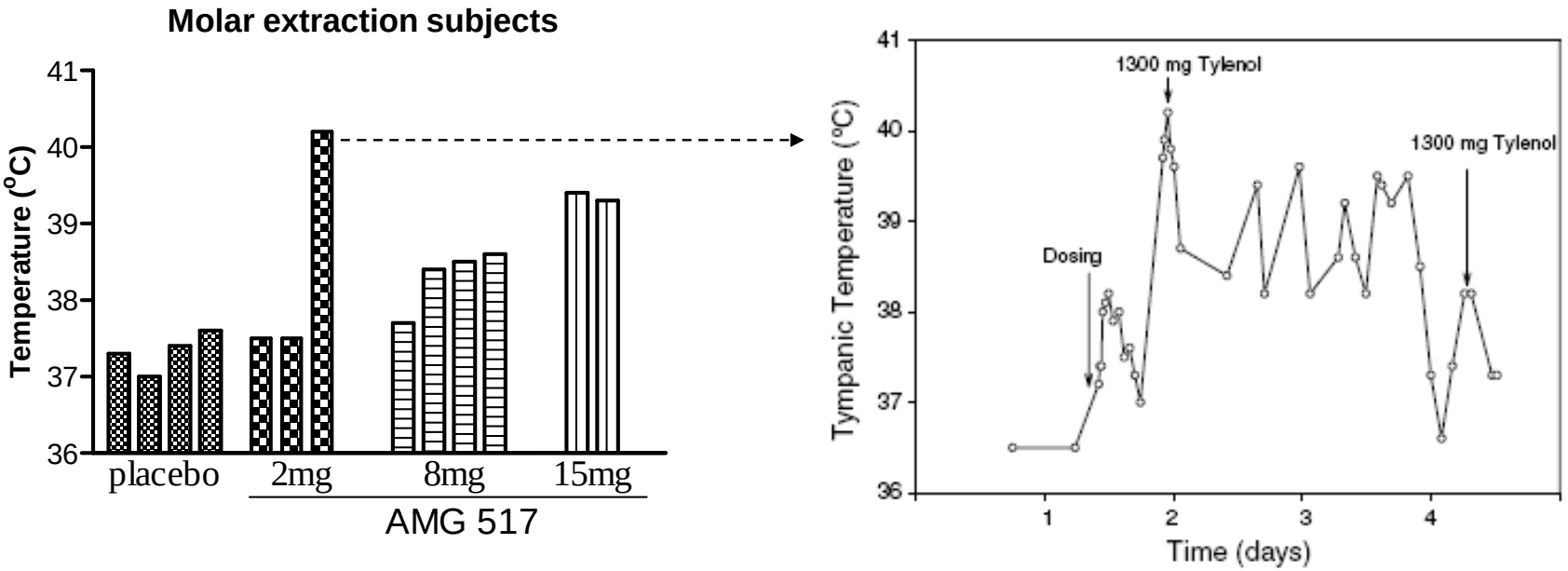
Trend of hyperthermia attenuation after repeated administration of AMG 517



(mean ± SD of the max body temperature [tympanic] presented)

Gavva et al., 2008 Pain **136**:202-210

AMG 517 caused marked hyperthermia in subjects who underwent molar extraction



- TRPV1 antagonists causing hyperthermia in rodents, dogs, monkeys, and humans indicates an evolutionarily conserved role of TRPV1 in thermoregulation

Gavva et al., 2008 Pain **136**:202-210

First approach to address hyperthermia: Peripheral restriction of antagonists

Hypothesis

- Thermoregulation is CNS mediated
- Can we minimize hyperthermia by restricting antagonists to the periphery?

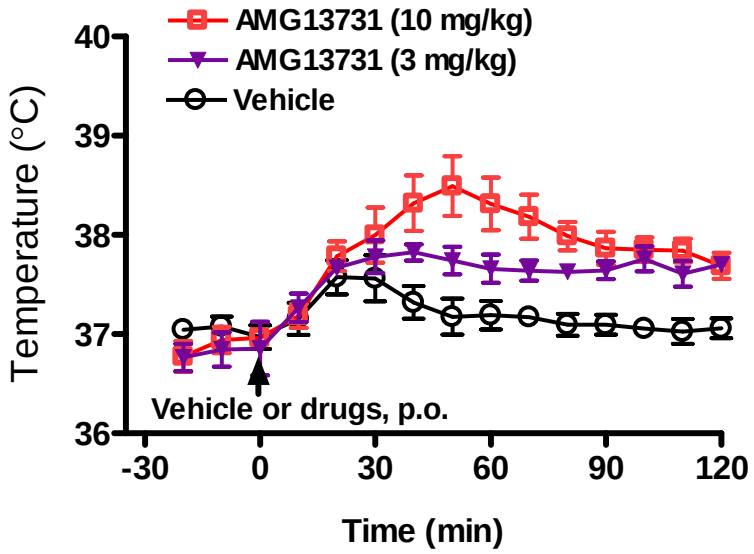
Strategy

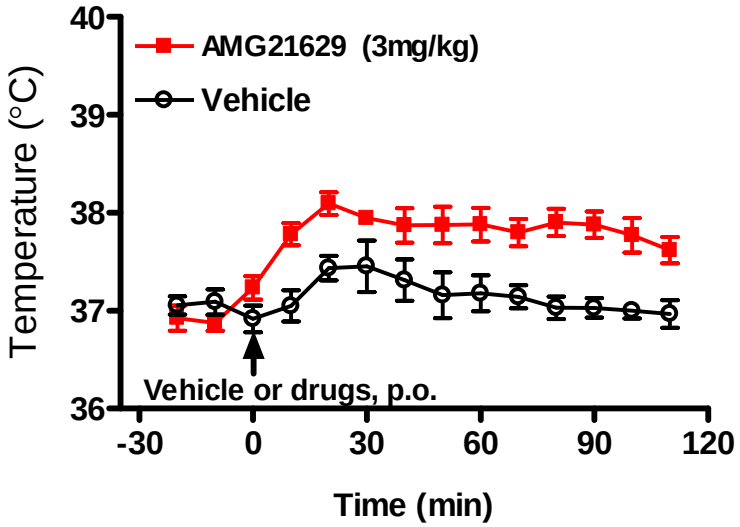
- Reduce brain exposure: peripherally restricted TRPV1 antagonists
  - Increase polar surface area (PSA)
  - Decrease logP
  - Increase number of hydrogen-bond donors

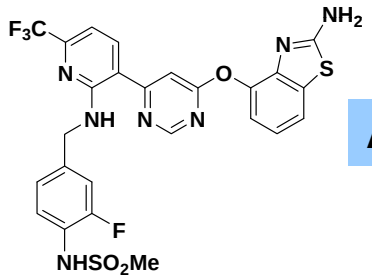
Profiles of peripherally restricted TRPV1 antagonists

Compound	PSA	clogP	Cap IC_{50}	B/P ratio
AMG13731	145	3.9	2.9	0.02
AMG21629	128	3.5	0.5	0.05
AMG32915	141	1.9	0.2	0.04
AMG41394	132	3.9	1.3	0.04

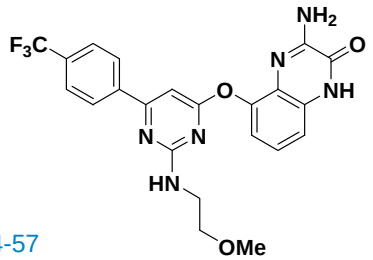
Effect of AMG13731 and AMG21629 on rat body core temperature







AMG13731



AMG21629

Tamayo et al 2008 J Med Chem. 51:2744-57

- Site of action for TRPV1 antagonist-induced hyperthermia is outside the BBB

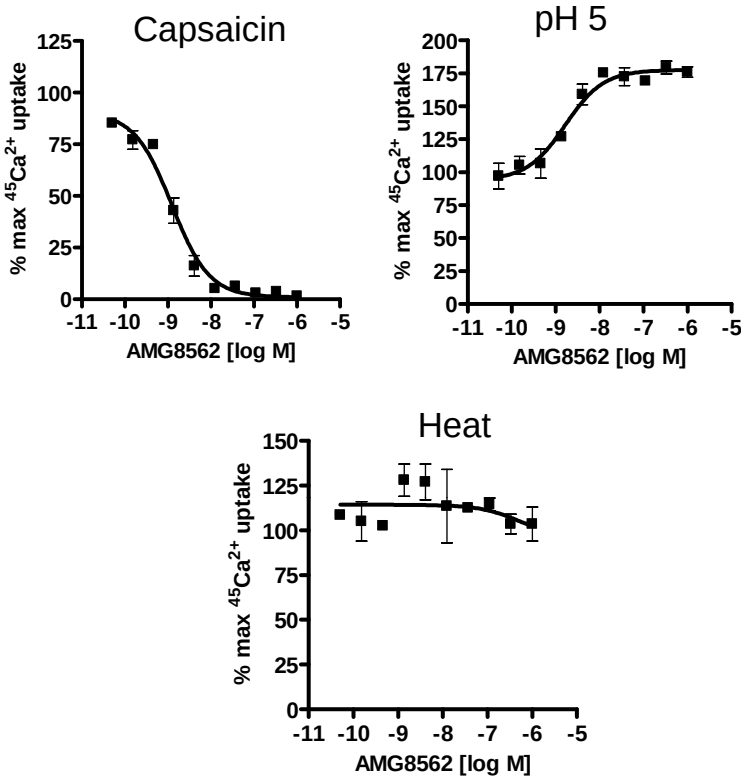
Evaluation of compounds exhibiting differential pharmacology - 2nd Approach

	Capsaicin	pH 5	Heat	Body temp
Profile A	Block	Block	Block	↑
Profile B	Block	Partial block	Block	↑
Profile C	Block	Potentiate	No effect	– ↓
Profile D	Block	Potentiate	Potentiate	↓

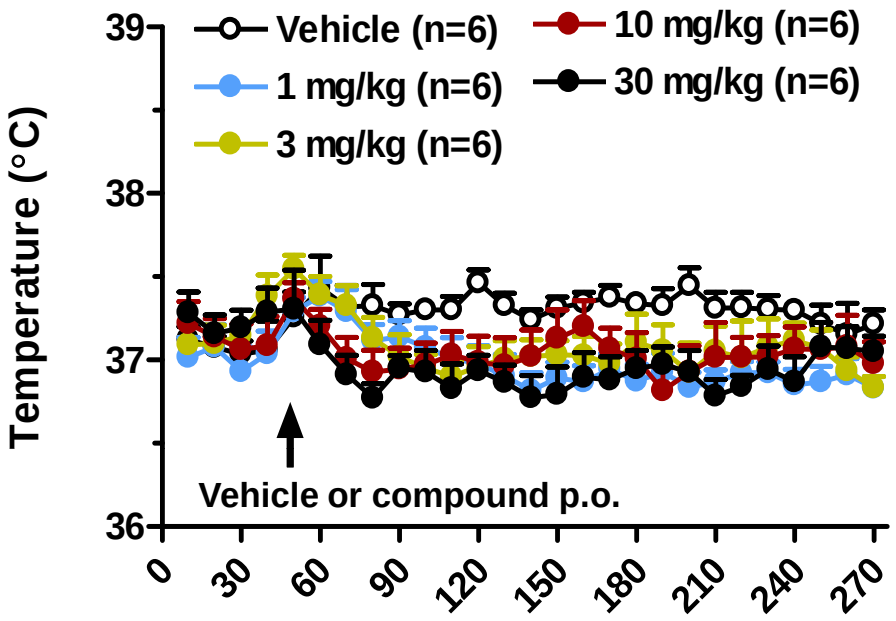
- Profiles defined by agonist-induced $^{45}Ca^{2+}$ uptake assays

AMG8562, a profile C compound that does not cause hyperthermia in rats

In vitro data



Rat radiotelemetry



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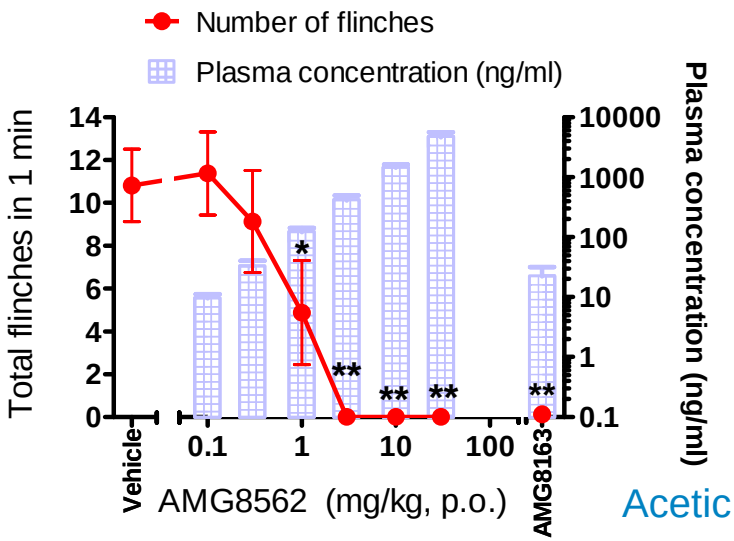
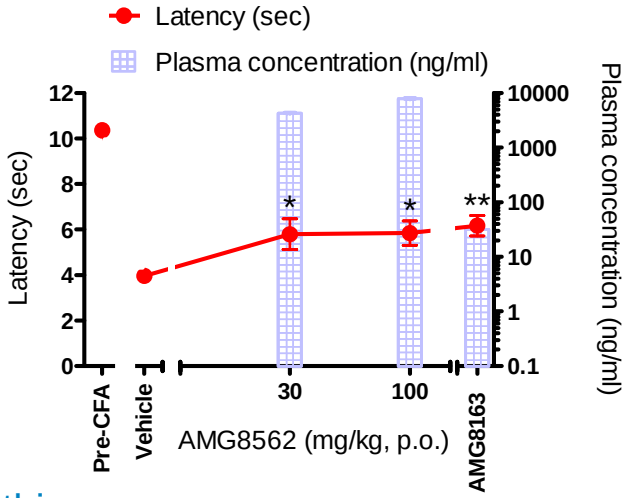
AMG8562 is modestly effective in capsaicin-challenge and pain models

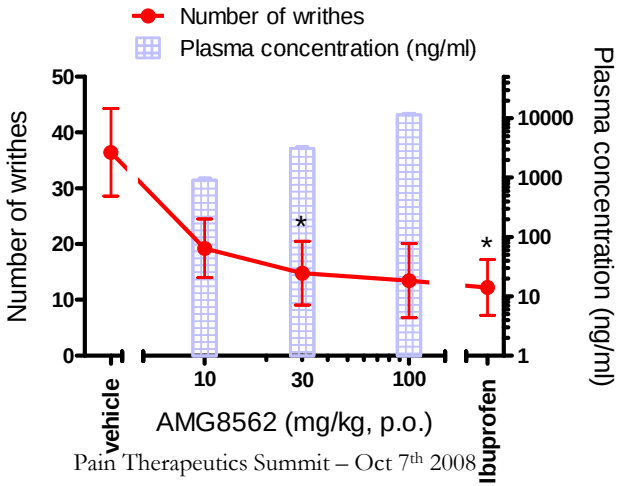
Capsaicin-induced flinch



CFA-induced thermal hyperalgesia



Acetic acid-induced writhing



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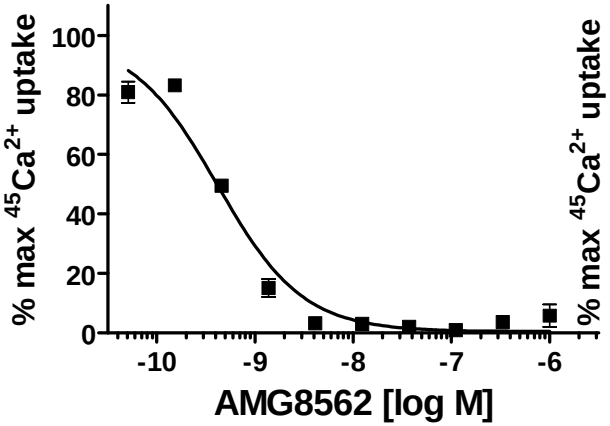
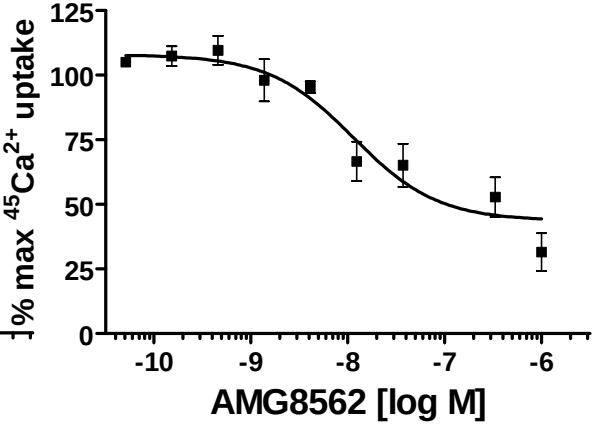
AMG8562, exhibits profile B modulation of human TRPV1

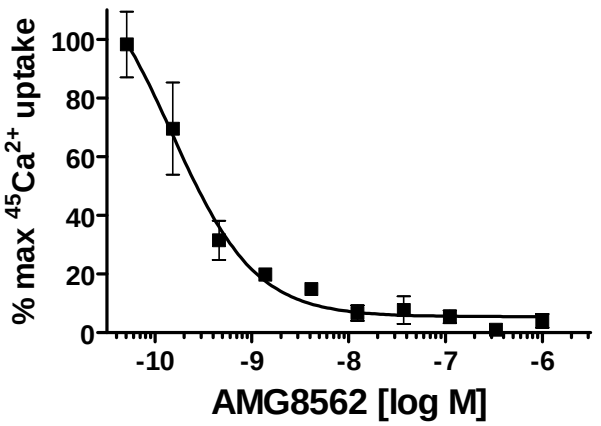
Capsaicin activation



pH 5 activation



Heat activation



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- Profile B modulators cause hyperthermia in rats

Current status of TRPV1 antagonists in the clinic

Compound name	Company	Route of administration	Indication	Stage	Current status
ABT-102	Abbott	Oral		Phase I	Initiated ?
AMG 517	Amgen	Oral	Dental pain	Phase Ib	Terminated
AZD1386	AstraZeneca	Oral	Dental pain	Phase II	Completed
GRC 6211	Lilly/Glenmark	Oral	Dental pain	Phase II	Suspended
JTS-653	Japan Tobacco	Oral	Overactive bladder pain	Phase I	On going
MK 2295	Merck/Neurogen	Oral	Dental pain	Phase II	Completed
SB-705498	GSK	Oral	Migraine	Phase II	Terminated
			Rectal pain	Phase II	Terminated
			Dental pain	Phase II	Completed
PF-4065463	Evotec/Pfizer	unknown	unknown	unknown	unknown

Conclusions

- Genetic and pharmacological evidence suggests that TRPV1 contributes to hyperalgesia
- TRPV1 antagonists block capsaicin-induced flinch (on-target challenge) and act as anti-hyperalgesics
- AMG 517, a selective TRPV1 antagonist caused plasma concentration dependent hyperthermia in humans
- Antagonist-induced hyperthermia showed a complete and clear attenuation after repeated dosing in preclinical species but not in humans
- Mechanisms of hyperthermia include antagonist-induced vasoconstriction and increased thermogenesis
- Peripherally restricted TRPV1 antagonists caused hyperthermia
- Profile C modulators of TRPV1 did not cause hyperthermia and demonstrated modest efficacy in pain models
- Clinical trial results of other TRPV1 antagonists are eagerly awaited

Outstanding questions and next steps

Preclinical

- 'Profile C' modulators of both rodent and human TRPV1
- Efficacy after repeated dosing of TRPV1 antagonists
- TRPV1 function in non-pathophysiological states (e.g., thermosensation)

Clinical

- Development by different routes of administration (e.g., topical application)
- Development of short half-life antagonists
- Development of antipyretic + TRPV1 antagonist combination
- Development of TRPV1 antagonists in primary indications (e.g., Osteoarthritis)

The Team

Departments

Neuroscience
PKDM
Modeling
E-phys
Sample Bank
Regulatory Affairs
Toxicology
Pharmaceutics
Clinical
Analytical
Legal
Project Management
Marketing

Neuroscience

Leyla Arik
Anthony Bannon
James Davis
Narender Gavva
Charles Henley
Gal Hever
Rongzhen Kuang
David Immke
Sonya Lehto
Lana Klionsky
Ella Magal
Licheng Shi
Rami Tamir
Jue Wang
Judy Wang
Weiya Wang
Gary Zajic
Dawn Zhu

Chemistry

Yunxin Bo
Ning Chen
Balan Chenera
Darin D'Amico
Liz Doherty
Lillian Liao
Mark Norman
Nobuko Nishimura
Vassil Ognyanov
Dan Retz
Mark Stec
Nuria Tamayo
Phi Tang
Kevin Yang

Process Chemistry

Charles Bernard
Chris Borths
Tracy Bostick
Margaret Faul
Andrew Hague
Tony King
Bobby Raihi
Thomas Storz
Jason Tedrow
Oliver Thiel

TRPV1 Core Team

Narender Gavva
Christopher Banfield
Anthony Bannon
Gudarz Davar
Celia Dominguez
Margaret Faul
Anu Gore
David Hovland
Pat Kesslak
Sonya Lehto
Jean-Claude Louis
Mark Norman
Sekhar Surapaneni
James Treanor

Collaborators

Andrej Romanovsky, Andras Garami
St. Joseph's Hospital and Medical Center, Phoenix, AZ
Frank Porreca, Todd Vanderah
University of Arizona, Tucson, AZ

Narender Gavva Pain Therapeutics Summit – Oct 7th 2008

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