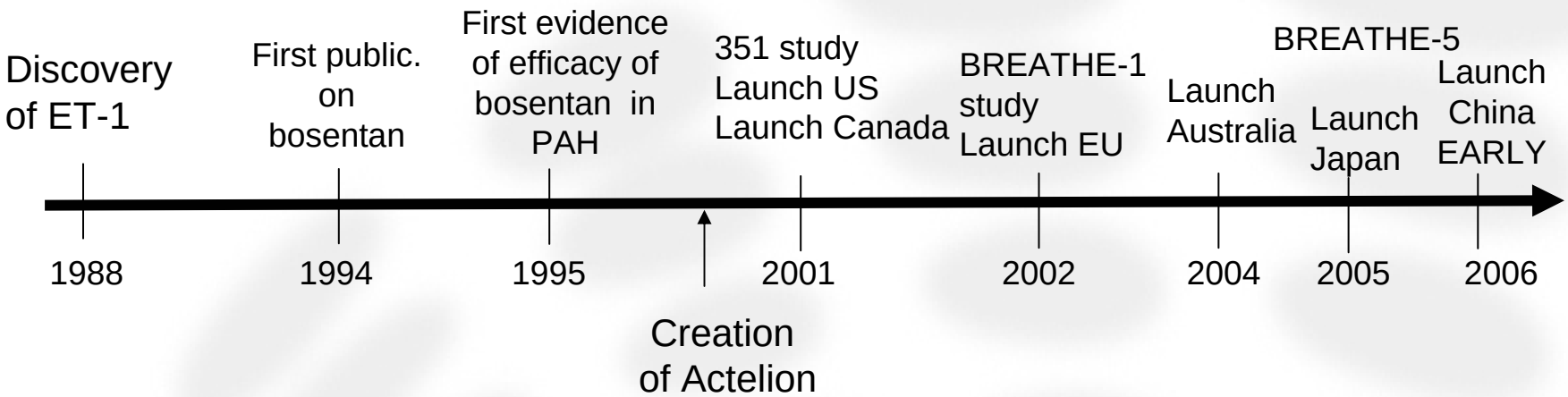
The story of endothelin antagonists

Martine Clozel

Actelion Pharmaceuticals Ltd
Allschwil, Switzerland

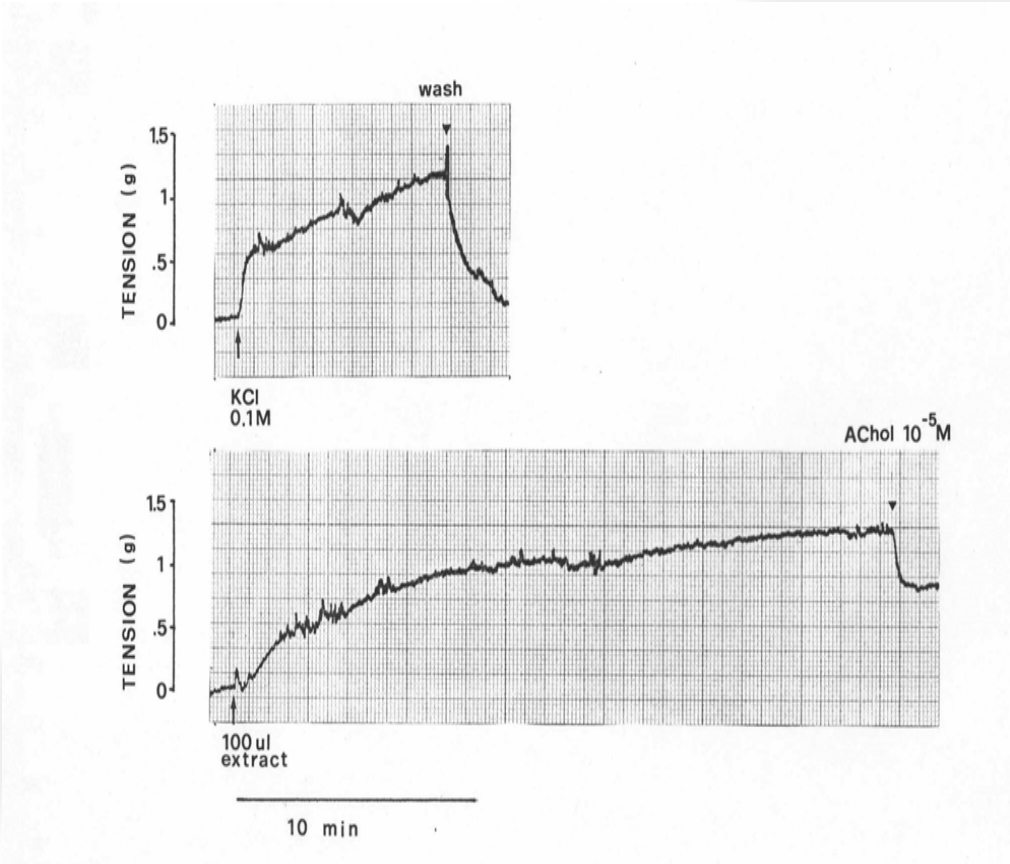
Development of Tracleer® (bosentan)



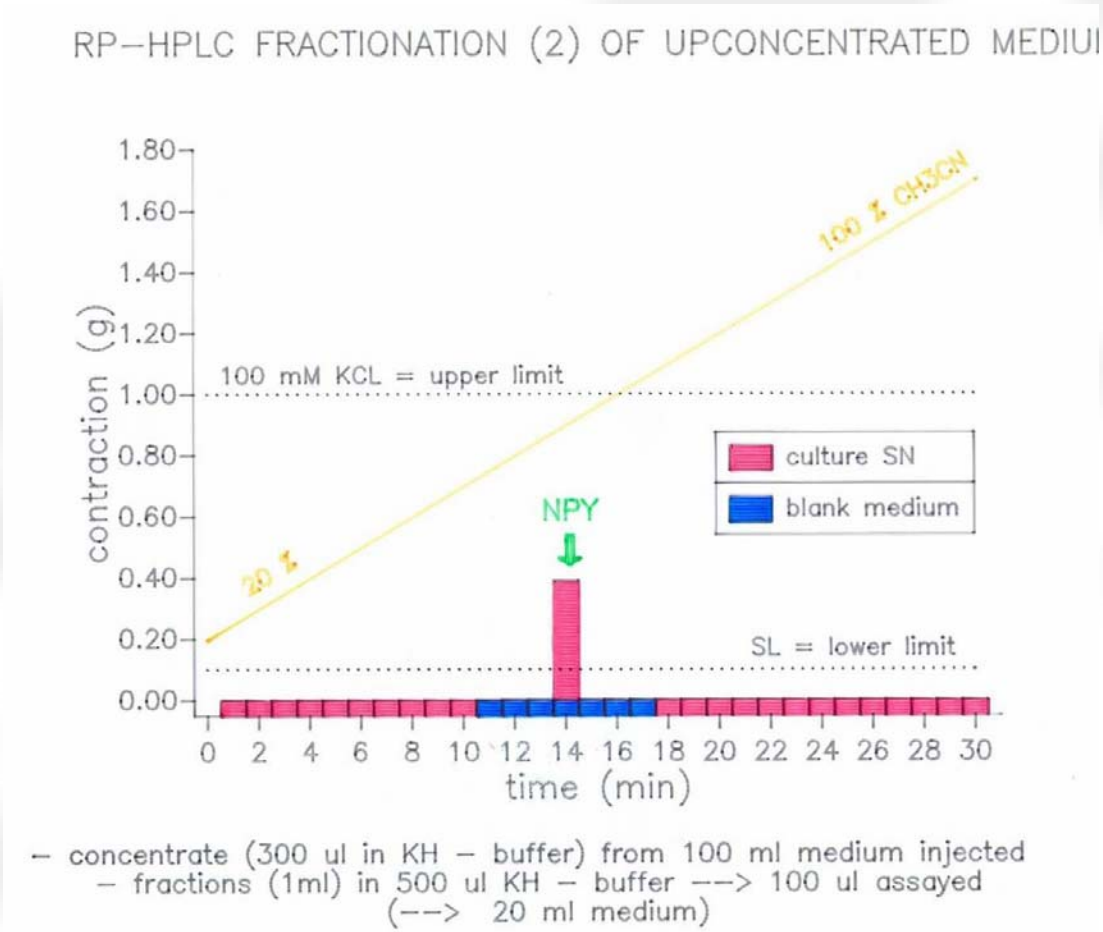
18 years' research in ET and ET receptor antagonists,

more than 130 manuscripts published by our group

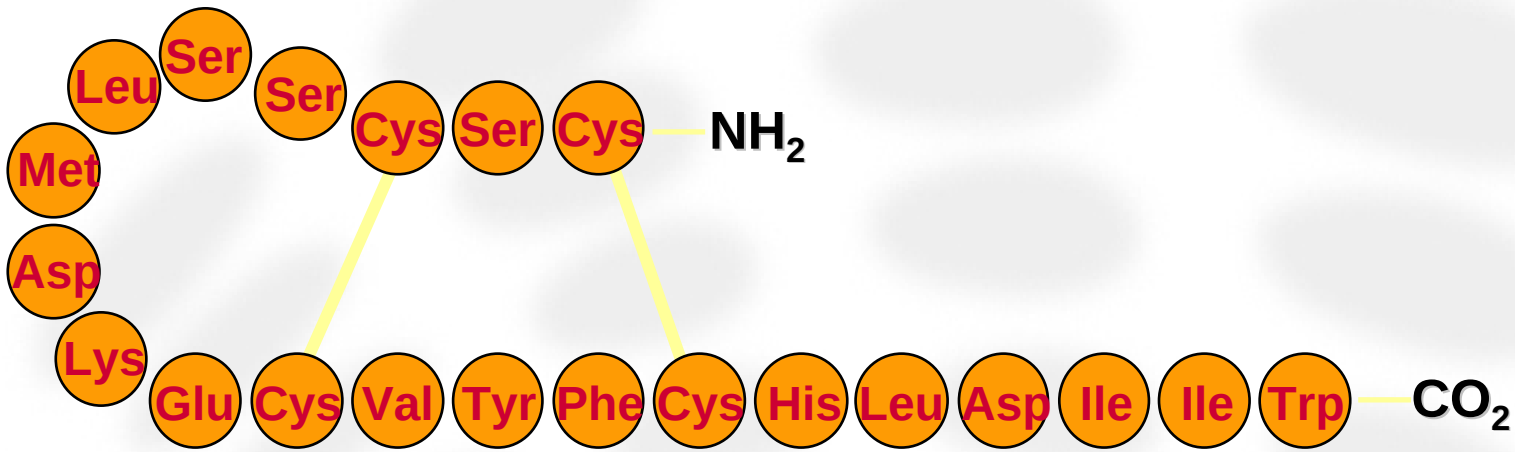
Conditioned Medium from Human Endothelial Cells induces constrictions of rat aorta



HLPC Fractionation of Conditioned Medium from Human Endothelial Cells



Endothelin-1



Yanagisawa M., et al., *Nature*, 1988

Israeli mole viper

(*Atractaspis engaddensis*)

Kloog Y., et al., *Science*, 1988

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The first year after the discovery of ET-1

Human Cultured Endothelial Cells Do Secrete Endothelin-1

Martine Clozel and Walter Fischli

Journal of Cardiovascular Pharmacology
13(Suppl. 5):S229–S231 © 1989 Raven Press, Ltd., New York

SPECIFIC RECEPTORS FOR ENDOTHELIN ON MEMBRANES FROM HUMAN PLACENTA. CHARACTERIZATION AND USE IN A BINDING ASSAY.

Walter Fischli*, Martine Clozel and Claire Guilly**

Life Sciences, Vol. 44, pp. 1429–1436

Specific Binding of Endothelin on Human Vascular Smooth Muscle Cells in Culture

Martine Clozel, Walter Fischli, and Claire Guilly

J. Clin. Invest. Volume 83, May 1989, 1758–1761

Effects of Endothelin on Regional Blood Flows in Squirrel Monkeys

MARTINE CLOZEL and JEAN-PAUL CLOZEL

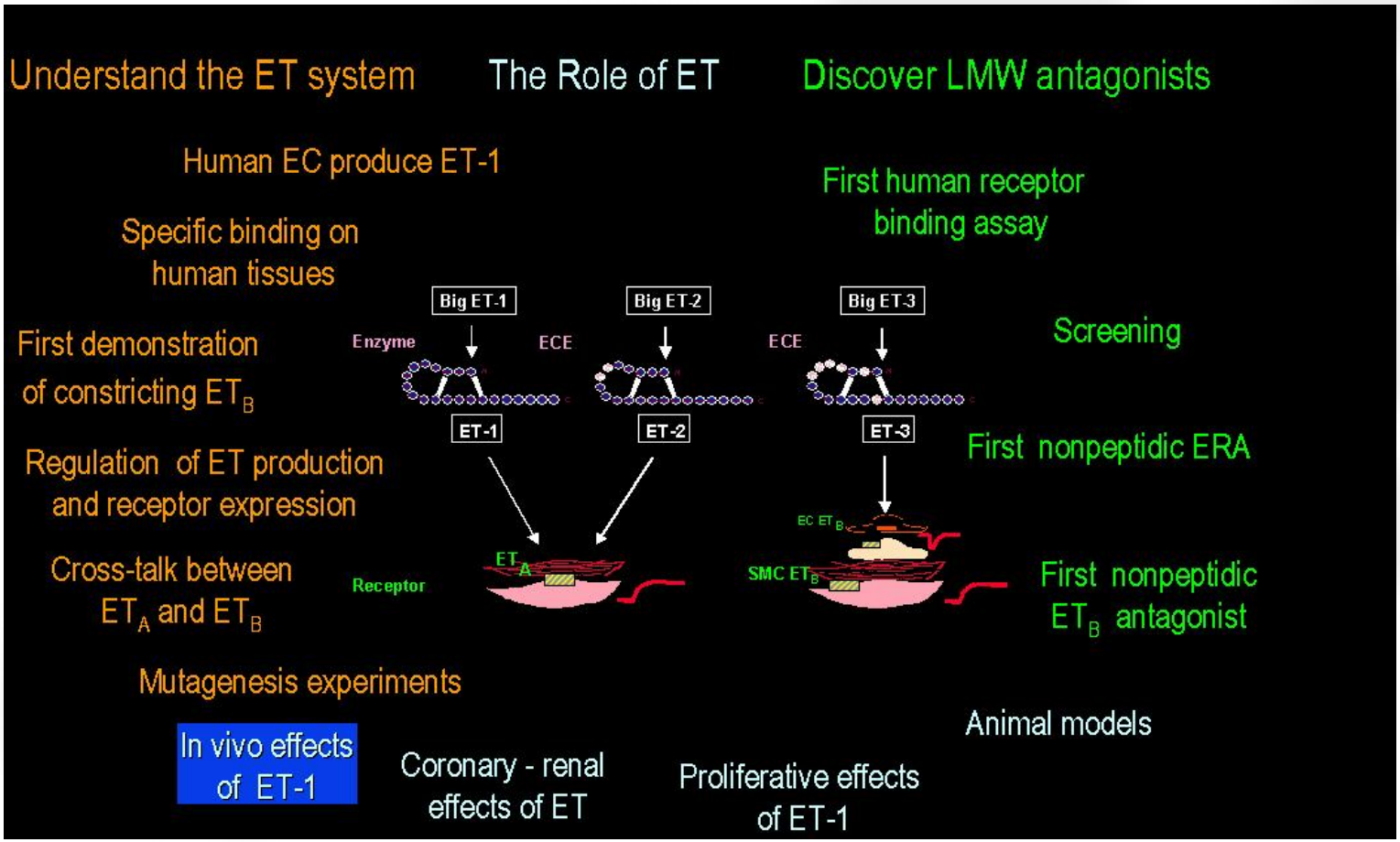
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

Endothelin sensitivity and receptor binding in the aorta of spontaneously hypertensive rats

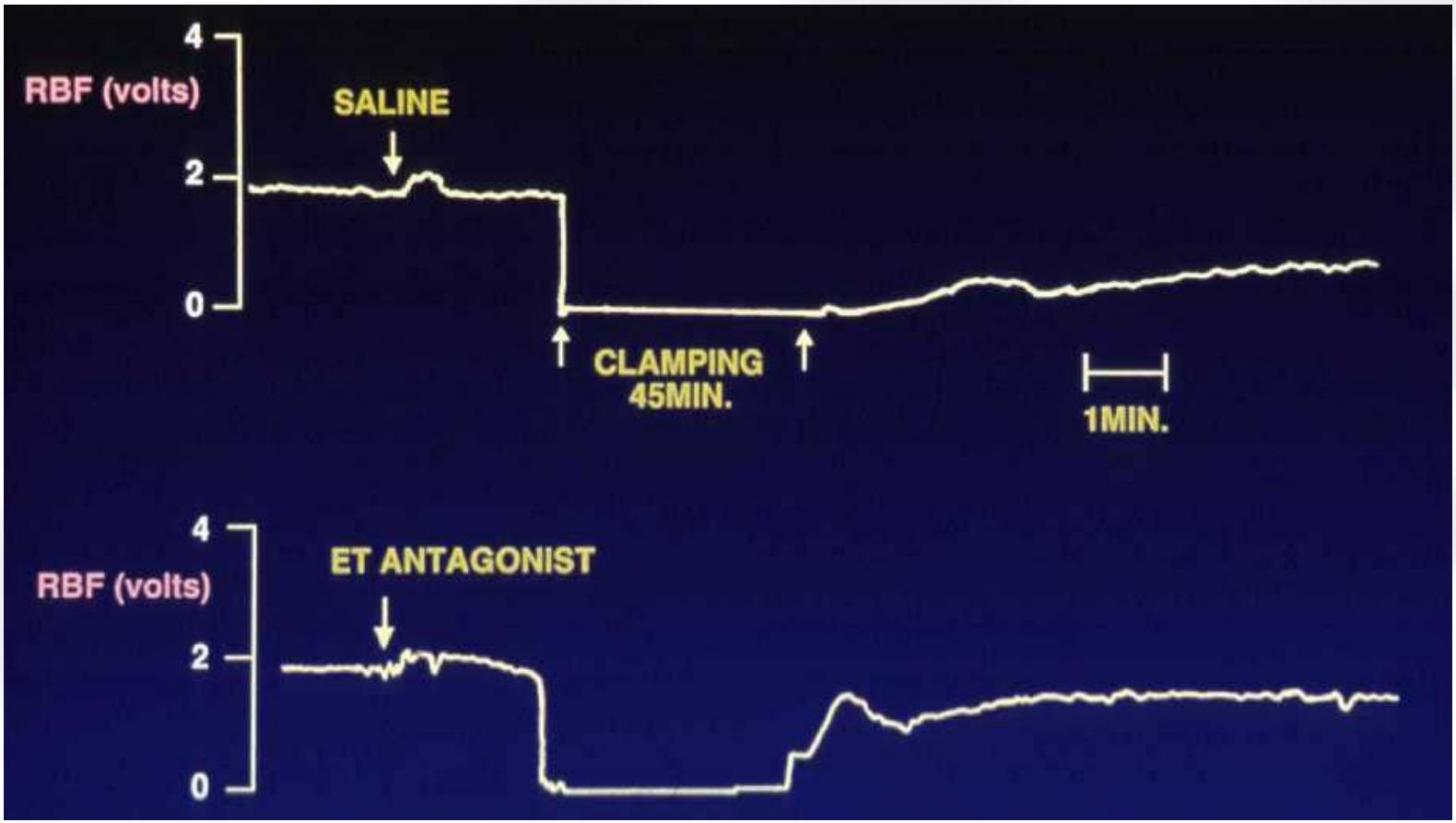
Martine Clozel

Journal of Hypertension 1989, **7**:913–917

Our contribution



Effect of ERA on No-Reflow after Renal Ischemia in Rats



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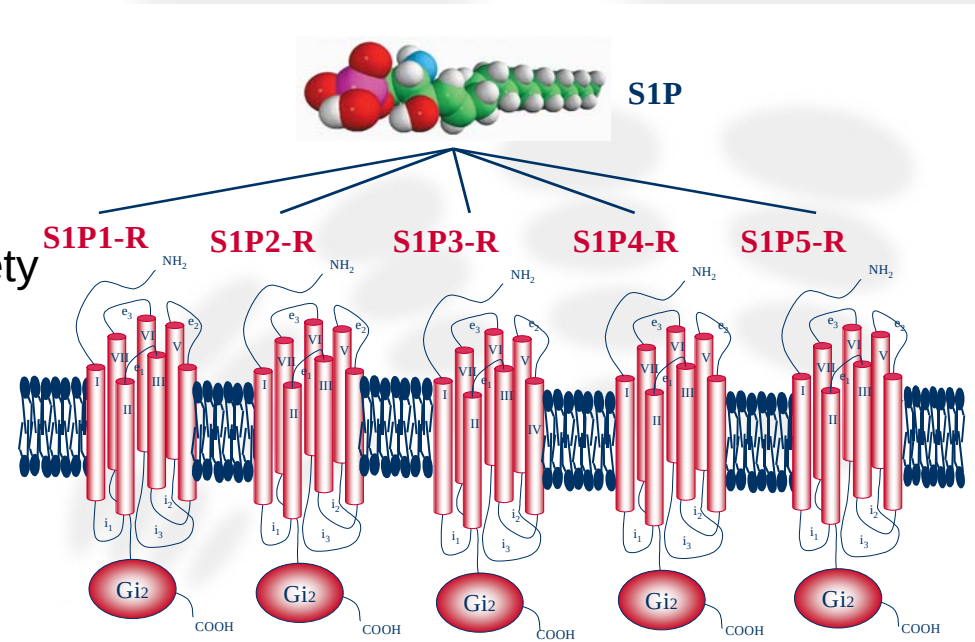
Selective Sphingosine-1 Phosphate Receptor-1 ($S1P_1$) Agonists

Novel cutting-EDG agents for controlled immunomodulation

S1P receptors – A pleiotropic system

- S1P is a phospholipid released by platelets, mast and other cells
- S1P stimulates 5 GPC receptors $S1P_{1,2,3,4,5}$
- The different receptors induce a variety of biological responses



The project at Actelion

- Actelion started in 1999 to work on $S1P_1$ (then called Edg-1) because of its localization on the endothelium
- High-Throughput Screening yielded multiple hits
- Lead optimization program resulted in highly active agonists

Mechanism of FTY720 discovered

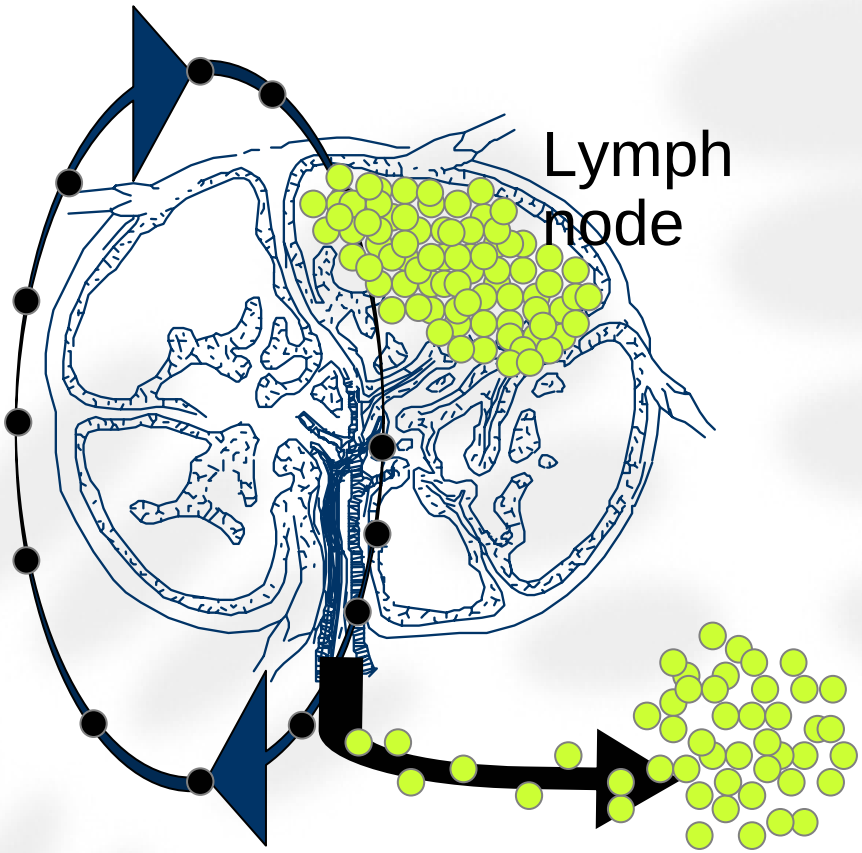
12 APRIL 2002 VOL 296 SCIENCE www.sciencemag.org

Alteration of Lymphocyte Trafficking by Sphingosine-1-Phosphate Receptor Agonists

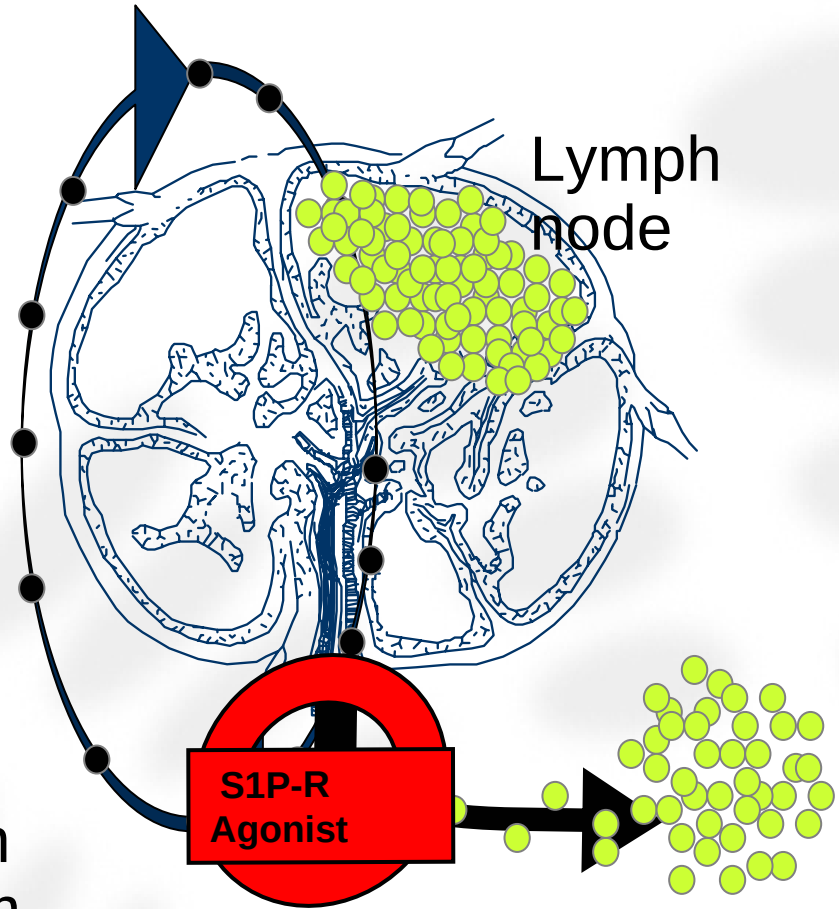
Suzanne Mandala,[1] Richard Hajdu,[1] James Bergstrom,[1] Elizabeth Quackenbush,[2] Jenny Xie,[2] James Milligan,[1] Rosemary Thornton,[1] Gan-Ju Shei,[1] Deborah Card,[1] CarolAnn Keohane,[1] Mark Rosenbach,[1] Jeffrey Hale,[3] Christopher L. Lynch,[3] Kathleen Rupprecht,[3] William Parsons,[3] Hugh Rosen[1]*

Blood lymphocyte numbers, essential for the development of efficient immune responses, are maintained by recirculation through secondary lymphoid organs. We show that lymphocyte trafficking is altered by the lysophospholipid sphingosine-

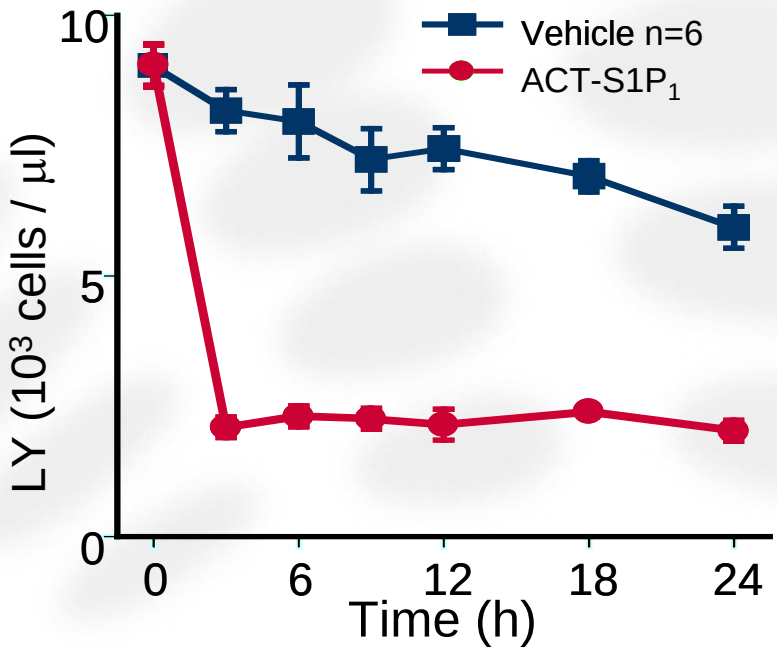
Mechanism of Action



Mechanism of Action



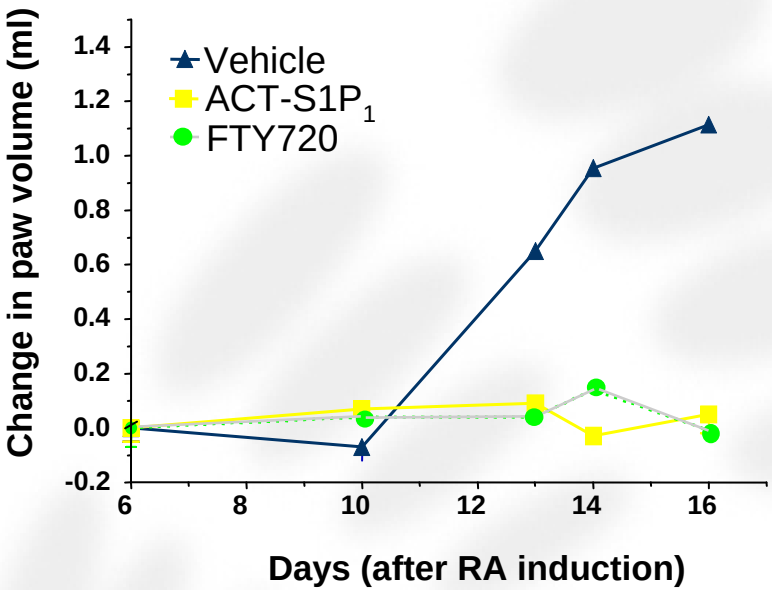
Effect of the selective agonist ACT-S1P$_1$ on lymphocyte count in rats



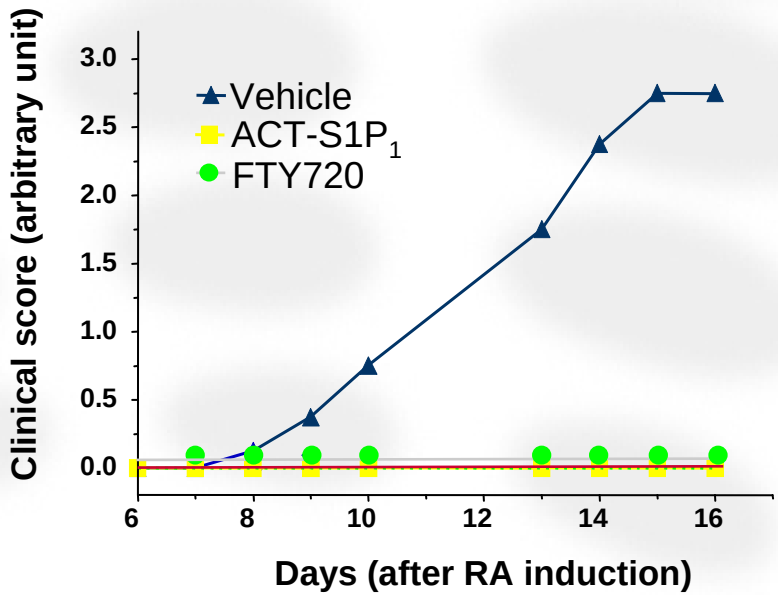
- Substantial decrease of circulating lymphocytes
- Rapid onset of action

The selective agonist ACT-S1P$_1$ is as efficacious as FTY720

Paw volume

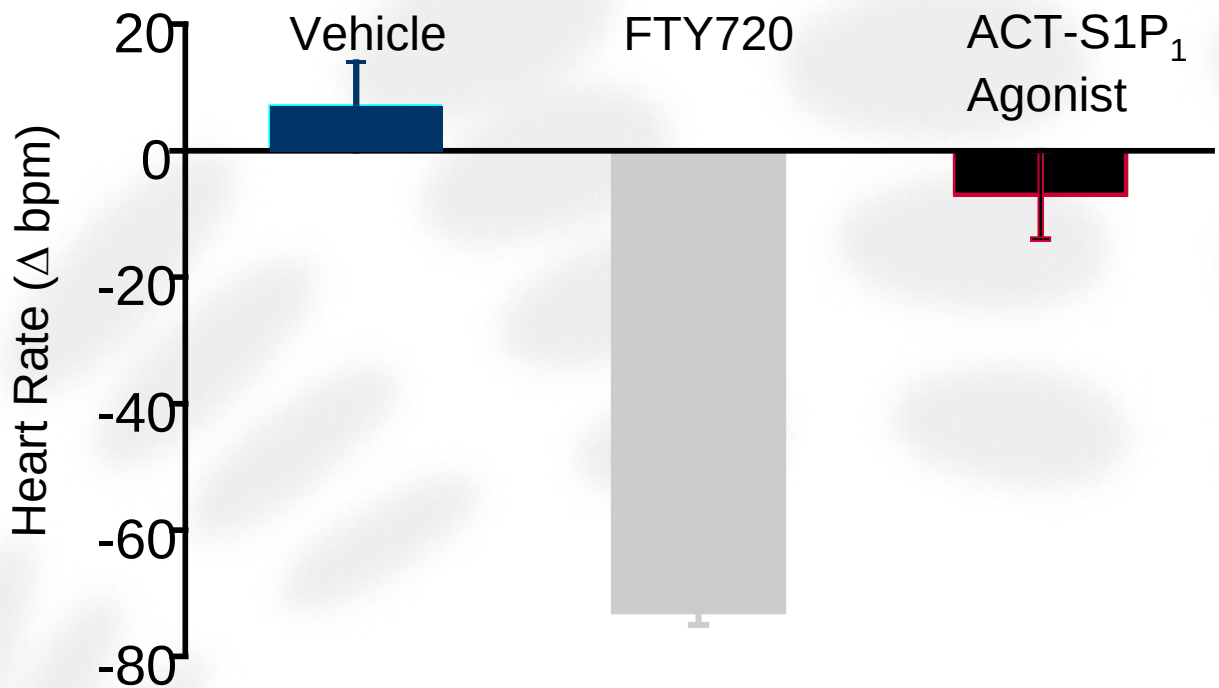


Clinical score



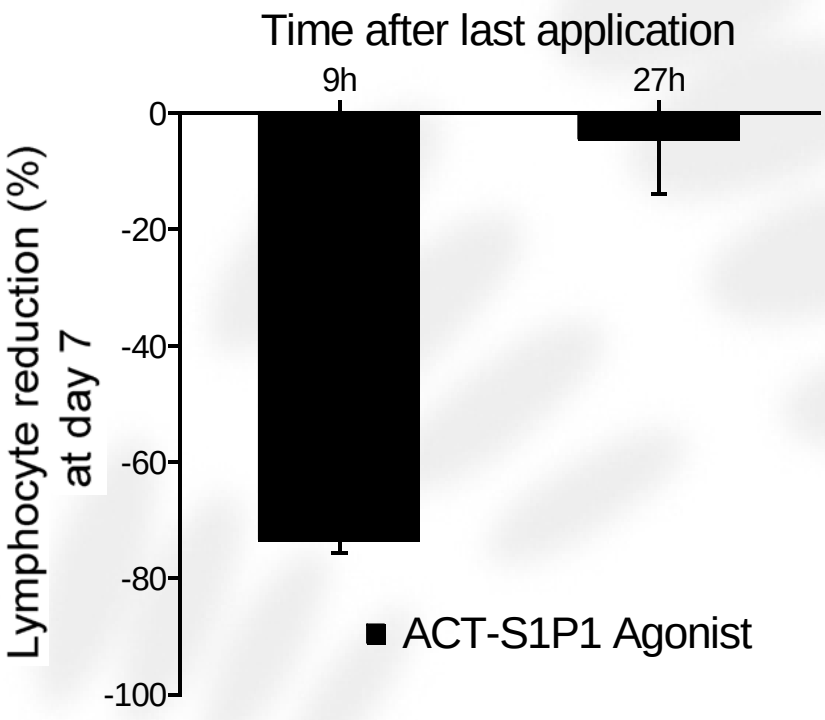
ACT-S1P$_1$ agonist prevents arthritis in rats

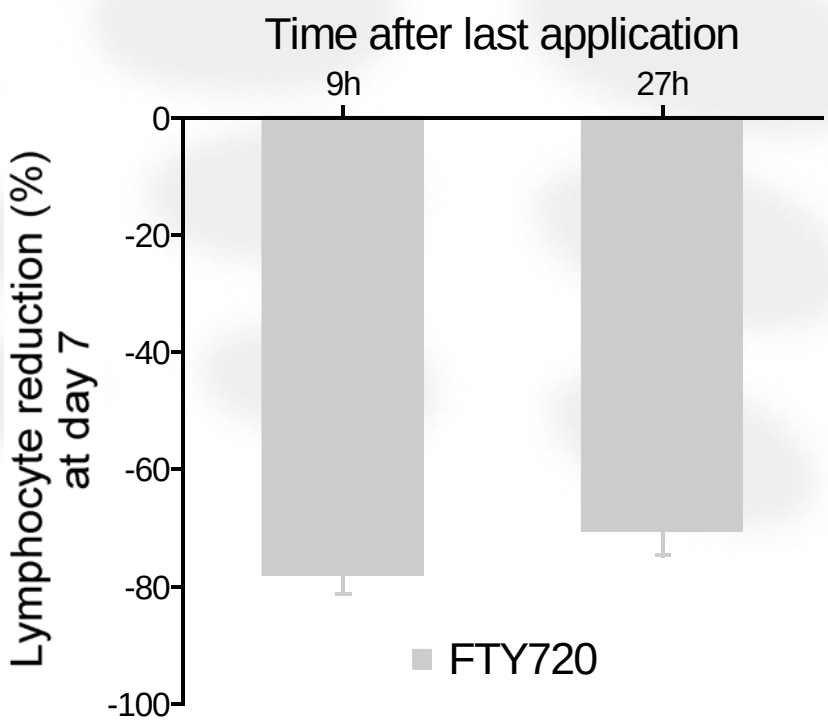
The selective agonist ACT-S1P$_1$ does not induce bradycardia in rats



The effect of ACT-S1P$_1$ is rapidly reversible

7-day study in rat





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The Orexin Receptor Antagonist

Orexin reduces REM (rapid eye movement) sleep

REM sleep is virtually abolished by orexin-A in the rat

	Vehicle	Orexin A (30 μg/rat, i.c.v.)	Change (%)
Time in REM-sleep (% total sleep time)	10.7	1.4	- 87 %

Adapted from *Piper et al., 2000*

Orexins

- Orexins were discovered in 1998

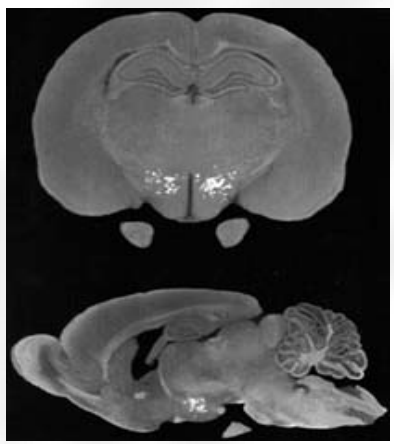
  as peptides of appetite control

  De Lecea et al., 1998, Sakurai et al., 1998

  they are actually peptides of „vigilance“

- Orexin deficiency leads to hypersomnolence

  Lin et al., 1999, Chemelli et al., 1999

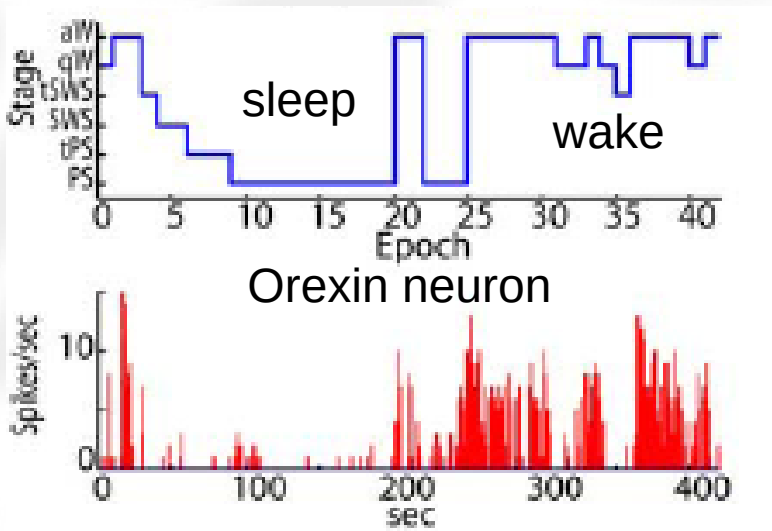


Orexin production in the lateral hypothalamus

Orexin neurons keep us awake and prevent REM sleep

Orexin neurons are

- maximally active during active waking
- virtually silent during sleep and REM sleep



Lee et al., 2005

A specific and potent orexin receptor antagonist

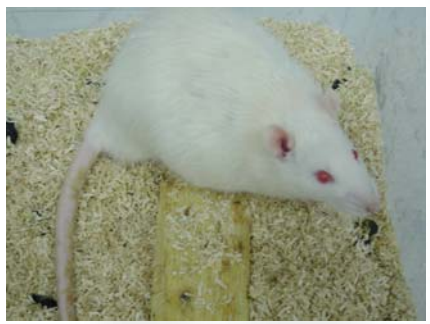
- Selectivity in in-vitro biochemical assays:

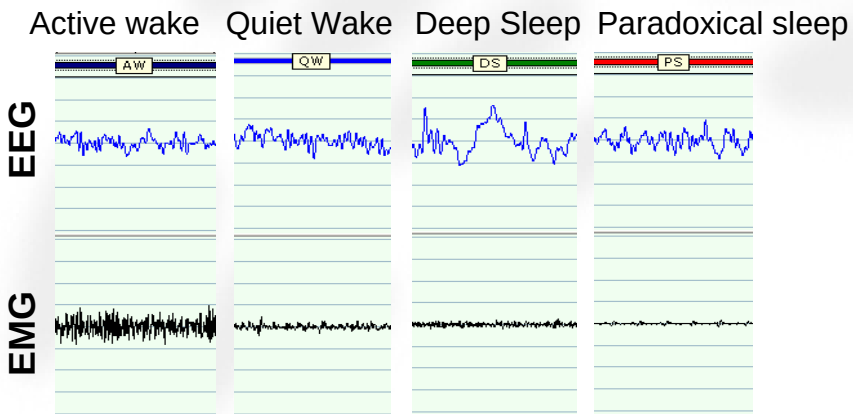
Receptor or enzyme	IC_{50} (nM)
Orexin	**< 10**
Melatonin	> 5‘000
Benzodiazepine	>10‘000
GABA-A, B	>10‘000
Opiate- μ,δ,κ	>10‘000
Histamine-1,2,3	>10‘000
+ 85 other assays	>10000

- Good oral bioavailability
- Excellent brain penetration

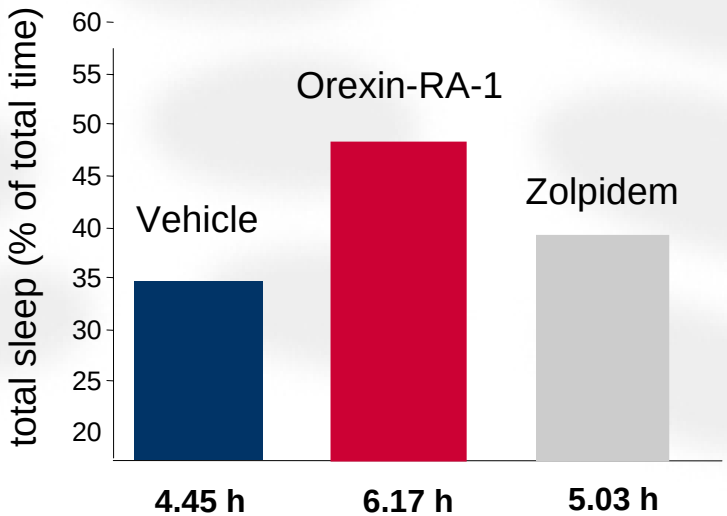
Orexin-RA-1 increases sleeping time

Sleep EEG recorded in the rat using radiotelemetric transmitters

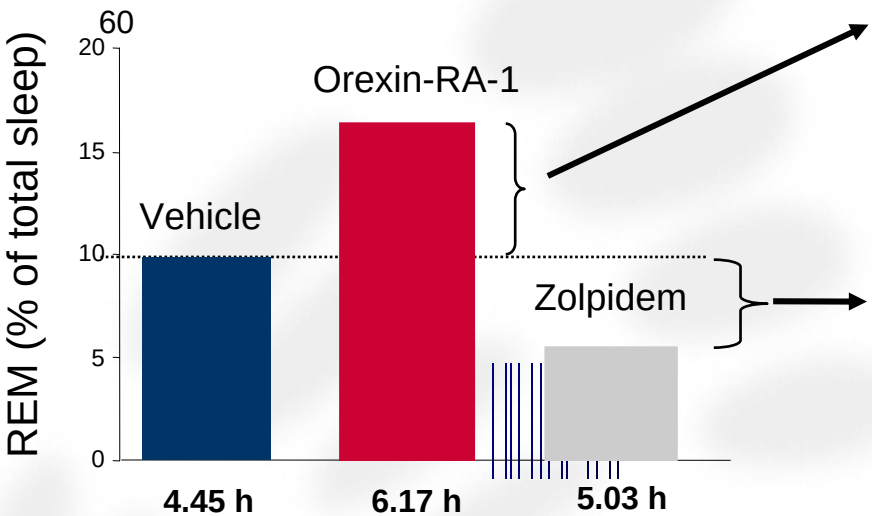




Total sleep time



Orexin-RA-1 increases REM-sleep



Orexin-RA-1:

68% increase in REM-sleep

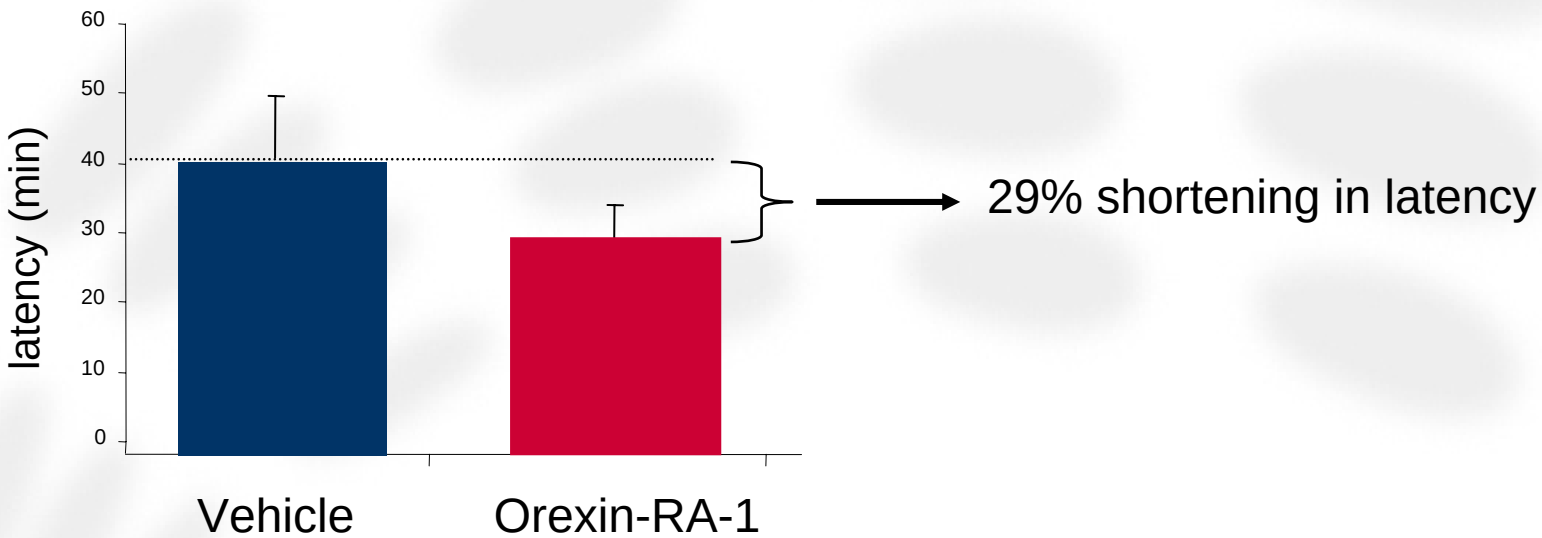
Zolpidem:

43% decrease in REM-sleep

REM stage - and accompanying dream sequences - is linked to memory consolidation

Orexin-RA-1 accelerates time to fall asleep

Latency to first episode of persistent sleep



Orexin-RA-1 does not cause motor impairment