

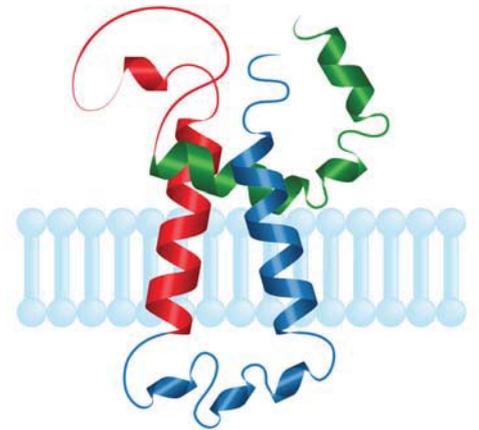
MINI-SYMPOSIUM

Physiopathology of Sigma-1 Receptors

Université Nice Sophia Antipolis
Château de Valrose - Nice, France

Tuesday March 17, 2015

8:30 am > 6:15pm



INVITED SPEAKERS:

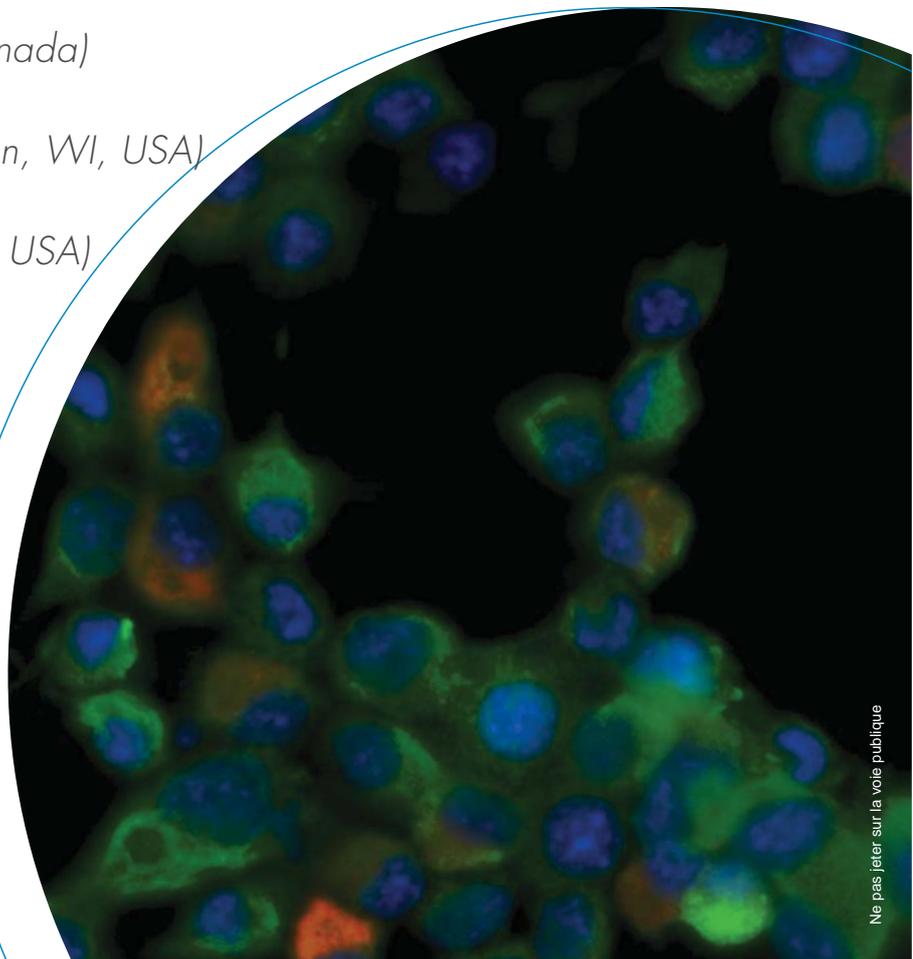
- Richard BERGERON
(OHRI, University of Ottawa, Canada)
- Timur MAVLYUTOV
(University of Wisconsin, Madison, WI, USA)
- Tsung-Ping SU
(IRP, NIDA, NIH, Baltimore, MD, USA)

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*Free of charge
but registration needed.*



Ne pas jeter sur la voie publique

Plenary communications

Tsung-Ping Su, Cellular Pathobiology Section, IRP/NIDA/NIH/DHHS, Baltimore, MD, USA

The molecular basis of the sigma-1 receptor chaperone in neuroprotection

The sigma-1 receptor (Sig-1R) resides specifically at the ER-mitochondrion interface called the MAM where the Sig-1R (1) chaperones the IP3 receptor type 3 to ensure proper Ca²⁺ signaling from the ER into mitochondria; (2) chaperones the ER stress sensor IRE1 to ensure proper ER-nucleus signaling for transcriptional regulation against mitochondria-associated stress; and (3) attenuates free radical formation at the ER. Sig-1Rs can also translocate, upon ligand stimulation or stress, to the plasma membrane to regulate the functions of certain receptors, ion channels, and kinases. In addition, Sig-1Rs also regulate axon extension by facilitating the turnover the cdk5 cofactor p35 to avoid the overproduction of the long-lasting toxic cofactor p25. As the Sig-1R does not belong to any family of the mammalian proteins, the unique action of Sig-1R represents a new mode of action of functional proteins in the biological system. The neuroprotective action of Sig-1Rs and associated ligands may be explained by the novel mode of action of this unique molecular chaperone.

Timur Mavlyutov, Department of Neuroscience, University of Wisconsin Medical School, Madison, WI, USA

Protective role of the Sigma-1 receptor in Amyotrophic Lateral Sclerosis

Sigma-1 receptor was shown to be a target for treatment of a variety of neurodegenerative diseases. In the CNS the highest levels of Sigma-1 receptors are detected in motor neurons in the spinal cord. Not surprisingly, a mutation in the Sigma-1 receptor has been reported to result in ALS, and Sigma-1 receptor specific ligands were shown to prolong the life of mouse models of ALS. In my talk I will summarize advances made over the last five years in understanding how the Sigma-1 receptor can function as a possible therapeutic target for ALS. I will also talk about the identity of the Sigma-2 receptor, its characteristics and applicability for neurodegenerative diseases.

Richard Bergeron, Ottawa Hospital Research Institute, Department of Psychiatry, Univ. of Ottawa, Canada

Modulation of NMDA receptor by Sigma-1 receptor: relevance to Alzheimer's disease

Recently, we showed that Sigma-1 receptor (Sig-1-R) activation increases NMDA receptors at the cell surface, a key receptor in synaptic plasticity and cognition. Sig-1-R is known to regulate calcium homeostasis at the endoplasmic reticulum (ER) / mitochondrial interface. Intriguingly, the Sig-1-R has been implicated in AD disease in a variety of ways. First, Sig-1-R binding sites are decreased in patients suffering from AD. Second, a polymorphism in the Sig-1-R gene, which reduces Sig-1-R expression, is a risk factor for AD. Third, a major drug used in AD treatment, donepezil, targets Sig-1-R. Finally, and most significantly, Sig-1-R agonists are neuroprotective and anti-amnesic in AD mouse models and protect against A β toxicity in vitro. Taken together, this suggests that an animal model based on loss of Sig-1-R could provide an all-encompassing model of AD where drugs targeting calcium homeostasis could be tested. In the last few years, we have undertaken a number of experimental series that suggest a crucial role for Sig-1-R in AD. Wild-type (WT) mice + A β 25-35 and Sig-1-R KO mice + A β 25-35 were infused in order to recapitulate and exacerbate the cellular and physiological phenotypes seen in AD, such as neuronal death (TUNEL staining), A β plaque accumulation (congo red staining), and deficits in synaptic plasticity (basic synaptic physiology, long-term potentiation and long-term depression). We tested whether changes in calcium homeostasis and calcium-induced calcium release could occur in Sig-1-R KO mice + A β 25-35 and whether these occur faster in the mutant mice than in WT mice + A β 25-35. Furthermore, we are currently testing whether restoring calcium homeostasis rescues the behavioral and cellular/physiological changes observed in Sig-1-R KO mice + A β 25-35. In some ways the "sigma enigma" has been clarified and we are in a much better position now than before to tackle more questions that include attempting to link the molecular actions of Sig-1-Rs to AD.

Physiopathology of Sigma-1 Receptor

*Théâtre du Grand Château, Faculté des Sciences
Université Nice Sophia Antipolis*

Mardi 17 mars 2015

Organized by Tangui Maurice, MMDN, Inserm U1198, Montpellier - Olivier Soriani, IBV, Nice

- 8:30 -9:00 *Welcoming*
- 9:00 -9:10 General address
- 9:10 -9:50 Plenary 1 – **Tsung-Ping Su**
"The molecular basis of the Sigma-1 receptor chaperone in neuroprotection"
- 9:50 -10:10 Discussion
- 10:10 -10:50 Plenary 2 – **Timur Mavlyutov**
"Protective role of the σ_1 receptor in Amyotrophic Lateral Sclerosis"
- 10:50 -11:10 Discussion
- 11:10 -11:25 *Coffee Break*
- 11:25 -11:50 Team presentation 1 – Patricia Melnyk
"Design and synthesis of Sigma-1 ligands"
- 11:50 -12:15 Team presentation 2 – Benedicte Oxombre-Vanteghem
"High-affinity Sigma 1 agonist as modulator of experimental neuroinflammation: therapeutical opportunities in Multiple Sclerosis"
- 12:15 -14:00 *Buffet and posters*
- 14:00 -14:40 Plenary 3 – **Richard Bergeron**
"Modulation of NMDA receptor by Sigma-1 receptor: relevance to Alzheimer's disease"
- 14:40 -15:00 Discussion
- 15:00 -15:25 Team presentation 3 – Tangui Maurice
"Development of Sigma-1 protein agonists as neuroprotectants in Alzheimer's disease"
- 15:25 -15:50 Team presentation 4 – Olivier Soriani
"SigmaR1 Drives Cancer Cell Invasiveness by Shaping Membrane Electrical Activity upon Stimulation by Extracellular Matrix"
- 15:50 -16:05 *Coffee Break*
- 16:05 -16:30 Invited presentation 5 – To be announced
- 16:30 -16:55 Invited presentation 6 – Christopher Missling
"Clinical trial design for Sigma1R agonist"
- 16:55 -17:15 General Discussion and Conclusions
- 17:15 -18:15 Club Sigma-1R round table

For lunch organization requirements, please send an email registration to:
michel.bidet@unice.fr



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