

# **ADDRESS COLLOQUIA**

Venue: Medical University Vienna, Center for Physiology and Pharmacology,  
Institute of Pharmacology, Großer Hörsaal  
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**Thursday 17.01.2019**

**17:00 s.t.**

**Host: Harald Sitte**

**Markus Heilig, MD PhD**

Professor of Psychiatry

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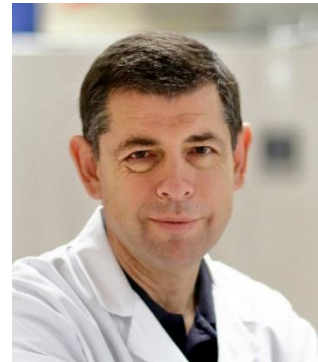
## ***How we got addiction wrong: One lever at a time***

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Neurobiological research on addictive disorders has grown exponentially in the past two decades. It has also become increasingly sophisticated in its ability to identify neural circuits and molecular mechanisms behind drug seeking and taking. These advances have fueled hopes that novel, neuroscience based treatments would emerge and transform treatment of alcohol addiction. That hope has not yet materialized. Existing medications for alcohol addiction provide proof-of-principle for pharmacological treatment of this disorder, but their discovery precedes the neuroscience revolution, and they have not been adopted broadly enough to transform clinical practice. This talk will discuss the limitations of studying drug seeking in isolation. It will introduce the critical importance of studying alcohol seeking in the context of availability of natural rewards, and of individual vulnerability. Implications for medications development will be discussed, focusing in on our recent discoveries implicating GABA-transmission in central amygdala as a key process to target with novel medications.

## **Biography Markus Heilig, MD PhD**

Markus Heilig received his MD and PhD from Lund University, Sweden, 1986 and 1989, resp. He was a post-doc at The Scripps Research Institute, LaJolla, CA 1990 - 1992. Upon returning to Sweden, he completed clinical training in psychiatry, and then served at the Karolinska Institute, Stockholm, Sweden, in various clinical and academic leadership capacities until 2004. At this time, he



became the director of intramural clinical and translational research at the National Inst on Alcohol Abuse and Alcoholism. In 2015, Heilig was recruited back to Sweden and Linköping Univ as professor of psychiatry, and founding director of a new Center on Social and Affective Neuroscience supported by the Swedish Research Council, Linköping University and the region of Östergötland.

Heilig's program currently studies brain processes and long-term neuroadaptations involved in addiction, with the objective to discover novel mechanisms that can be targeted for pharmacotherapies. It uses endophenotype based approaches that span across diagnostic categories. From an initial focus on stress-mediated mechanisms, it has recently expanded the scope of its research to take into account the critical role of choices between drug- and natural rewards, as well as the critical role of social factors in addiction and other psychiatric disorders. Ongoing studies seek to integrate these behavioral processes with an understanding of their neural substrates.

Research strategies in the program span from analysis of gene expression and its epigenetic programming, through behavioral pharmacology in rodent models, to human experimental medicine that utilizes behavioral, neuroendocrine, psychophysiological and functional brain imaging based methods. This research has in total generated some 230 peer-reviewed journal articles, including papers that have appeared in Science, PNAS, Lancet and other high impact journals, yielding >12000 citations, and an h-index of 60.

## Recent key reviews:

1. Heilig M, Barbier E, Johnstone AL, Tapocik J, Meinhardt MW, Pfarr S, Wahlestedt C, Sommer WH. 2017. Reprogramming of mPFC transcriptome and function in alcohol dependence. *Genes Brain and Behavior* 16: 86-100
2. Heilig M, Epstein DH, Nader MA, Shaham Y. 2016. Time to connect: bringing social context into addiction neuroscience. *Nat Rev Neurosci* 17: 592-9
3. Schank JR, Ryabinin AE, Giardino WJ, Ciccocioppo R, Heilig M. 2012. Stress-related neuropeptides and addictive behaviors: beyond the usual suspects. *Neuron* 76: 192-208
4. Heilig M, Goldman D, Berrettini W, O'Brien CP. 2011. Pharmacogenetic approaches to the treatment of alcohol addiction. *Nat Rev Neurosci* 12: 670-84
5. Heilig M, Thorsell A, Sommer WH, Hansson AC, Ramchandani VA, George DT, Hommer D, Barr CS. 2010. Translating the neuroscience of alcoholism into clinical treatments: from blocking the buzz to curing the blues. *Neuroscience and Biobehavioral Reviews* 35: 334-44

## Recent key empirical papers:

1. Augier E, Barbier E, Dulman RS, Licheri V, Augier G, Domi E, Barchiesi R, Farris S, Natt D, Mayfield RD, Adermark L, Heilig M. 2018. A molecular mechanism for choosing alcohol over an alternative reward. *Science* 360: 1321-6
2. Mayo LM, Asratian A, Linde J, Holm L, Natt D, Augier G, Stensson N, Vecchiarelli HA, Balsevich G, Aukema RJ, Ghafouri B, Spagnolo PA, Lee FS, Hill MN, Heilig M. 2018. Protective effects of elevated anandamide on stress and fear-related behaviors: translational evidence from humans and mice. *Mol Psychiatry*, 10.1038/s41380-018-0215-1
3. Barbier E, Johnstone AL, Khomtchouk BB, Tapocik JD, Pitcairn C, Rehman F, Augier E, Borich A, Schank JR, Rienas CA, Van Booven DJ, Sun H, Natt D, Wahlestedt C, Heilig M. 2017. Dependence-induced increase of alcohol self-administration and compulsive drinking mediated by the histone methyltransferase PRDM2. *Molecular Psychiatry* 22: 1746-58
4. Barbier E, Tapocik JD, Juergens N, Pitcairn C, Borich A, Schank JR, Sun H, Schuebel K, Zhou Z, Yuan Q, Vendruscolo LF, Goldman D, Heilig M. 2015. DNA methylation in the medial prefrontal cortex regulates alcohol-induced behavior and plasticity. *J Neurosci* 35: 6153-64
5. Tapocik JD, Barbier E, Flanigan M, Solomon M, Pincus A, Pilling A, Sun H, Schank JR, King C, Heilig M. 2014. microRNA-206 in rat medial prefrontal cortex regulates BDNF expression and alcohol drinking. *Journal of Neuroscience* 34: 4581-8
6. Hirvonen J, Zanotti-Fregonara P, Umhau JC, George DT, Rallis-Frutos D, Lyoo CH, Li CT, Hines CS, Sun H, Terry GE, Morse C, Zoghbi SS, Pike VW, Innis RB, Heilig M. 2013. Reduced cannabinoid CB1 receptor binding in alcohol dependence measured with positron emission tomography. *Molecular Psychiatry* 18: 916-21
7. Schank JR, Tapocik JD, Barbier E, Damadzic R, Eskay RL, Sun H, Rowe KE, King CE, Yao M, Flanigan ME, Solomon MG, Karlsson C, Cheng K, Rice KC, Heilig M. 2013. Tacr1 gene variation and neurokinin 1 receptor expression is associated with antagonist efficacy in genetically selected alcohol-preferring rats. *Biological Psychiatry* 73: 774-81
8. Ramchandani VA, Umhau J, Pavon FJ, Ruiz-Velasco V, Margas W, Sun H, Damadzic R, Eskay R, Schoor M, Thorsell A, Schwandt ML, Sommer WH, George DT, Parsons LH, Herscovitch P, Hommer D, Heilig M. 2011. A genetic determinant of the striatal dopamine response to alcohol in men. *Molecular Psychiatry* 16: 809-17
9. George DT, Gilman J, Hersh J, Thorsell A, Herion D, Geyer C, Peng X, Kielbasa W, Rawlings R, Brandt JE, Gehlert DR, Tauscher JT, Hunt SP, Hommer D, Heilig M. 2008. Neurokinin 1 receptor antagonism as a possible therapy for alcoholism. *Science* 319: 1536-9