

The role of the dopamine system in the ability of (-)-OSU6162 to reduce voluntary alcohol-drinking and binge-eating in the rat



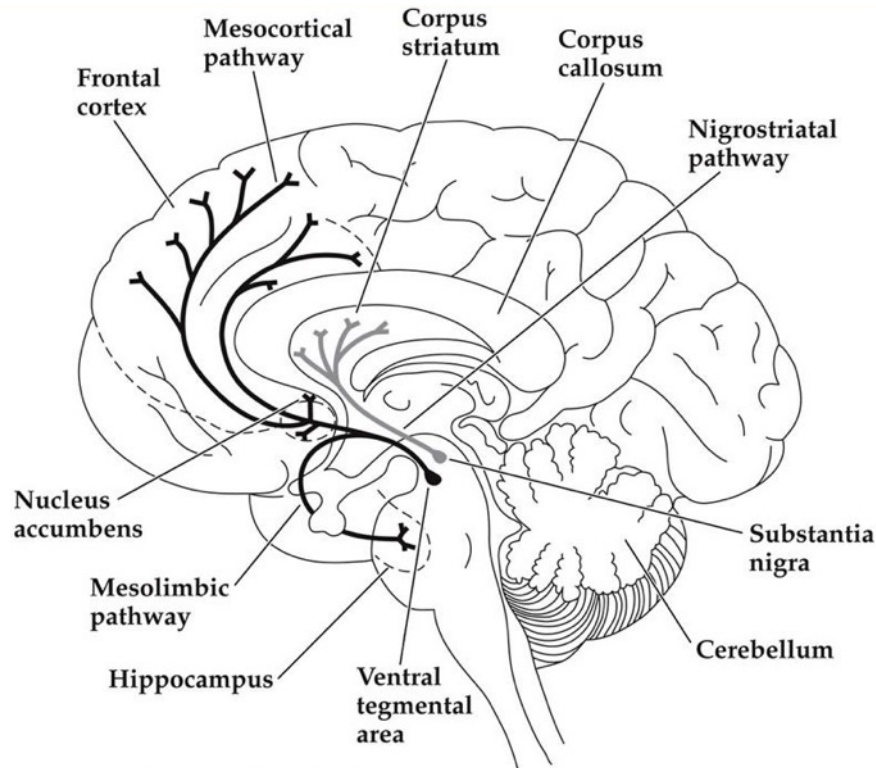
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Kristin Feltmann
SAD Conference
2018



The dopamine system



TUTORIAL ON NEURAL SYSTEMS MODELING, Figure 11.9
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Intoxication

Withdrawal

Craving &
relapse

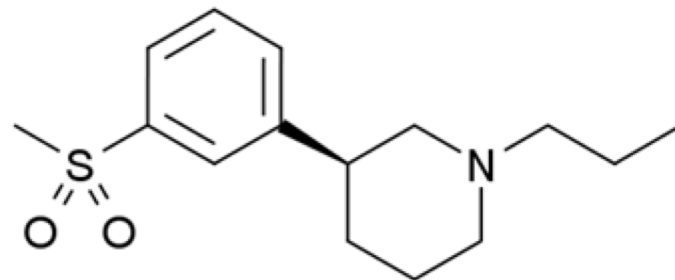
The Monoamine Stabilizer (-)-OSU6162

- Stabilizes dopamine activity depending on prevailing tone
- Non-traditional dopamine D₂-receptor antagonist
- 5-HT_{2A} receptor partial agonist
- clinical well tolerated



Prof. Arvid Carlsson (1923-2018)
Nobel prize 2000

(-)-OSU6162





Biological Psychiatry

Volume 72, Issue 10, 15 November 2012, Pages 823–831

Substance Abuse and Psychosis



Archival Report

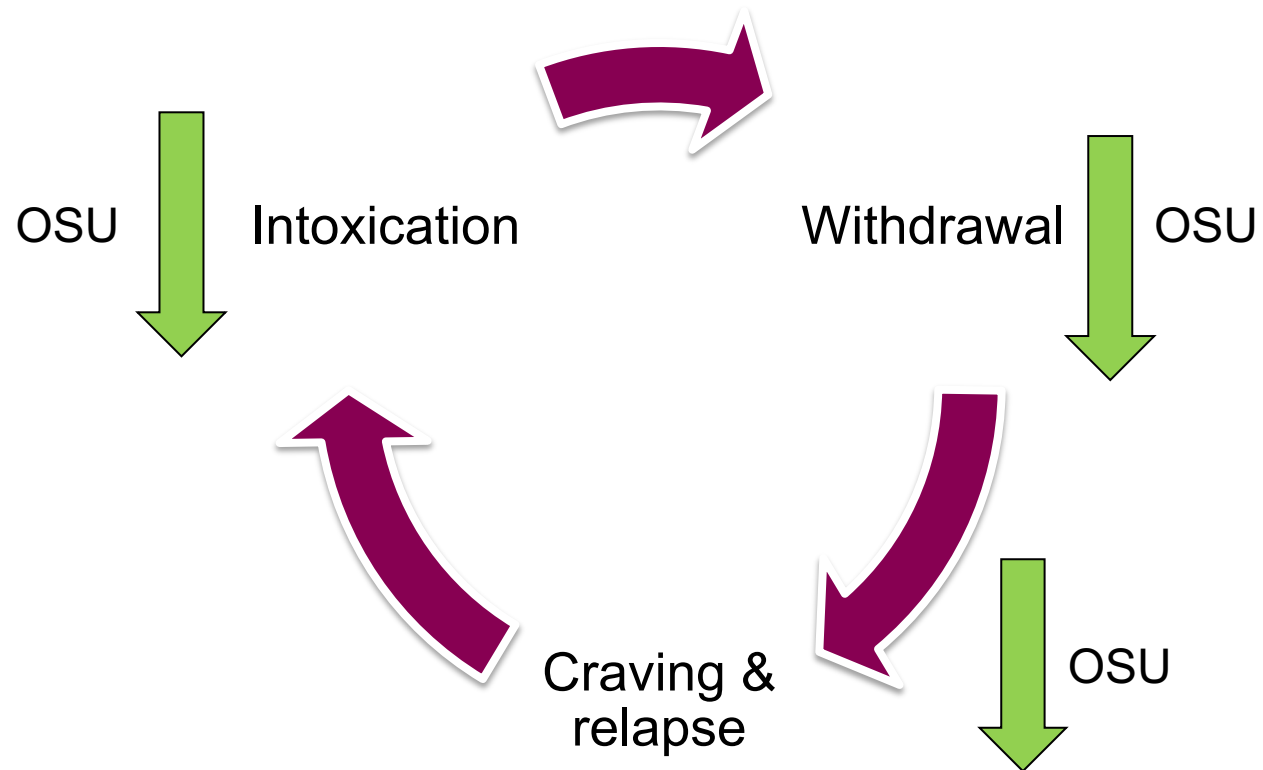
The Monoamine Stabilizer (-)-OSU6162 Attenuates Voluntary Ethanol Intake and Ethanol-Induced Dopamine Output in Nucleus Accumbens

Pia Steensland^a,  , Ida Fredriksson^a, Sarah Holst^a, Kristin Feltmann^a, Johan Franck^a, Björn Schilström^b, Arvid Carlsson^c

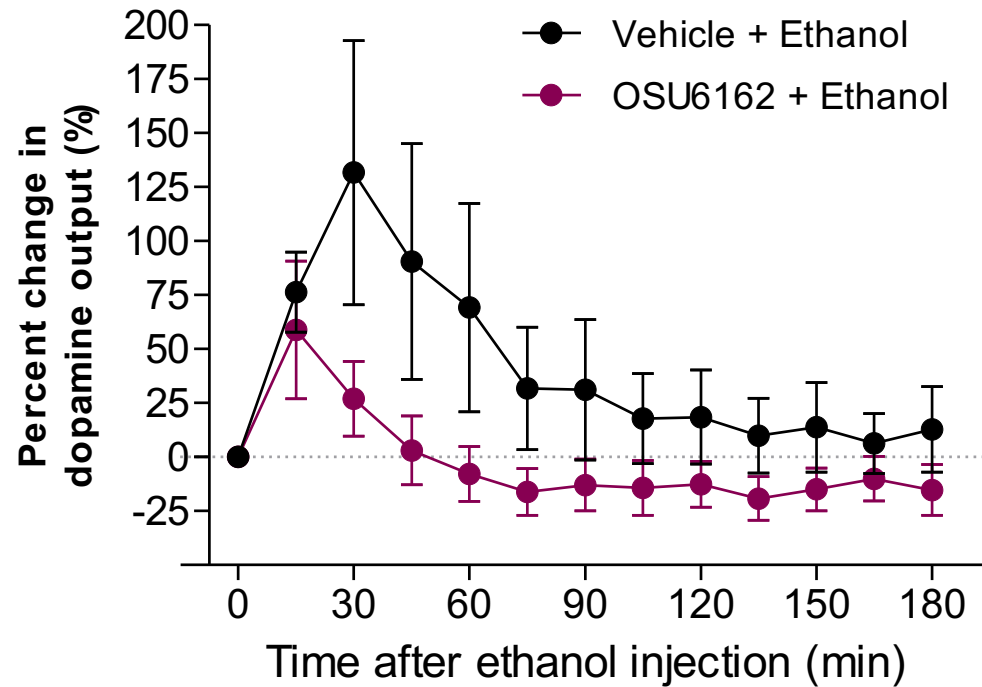
^a Department of Clinical Neuroscience, Karolinska Institutet, Karolinska University Hospital, Solna, Stockholm, Sweden

^b Department of Physiology and Pharmacology, Karolinska Institutet, Solna, Stockholm, Sweden

^c Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden



Alcohol-Naïve Rats



Aims

- Long-term drinking on dopamine system
- Role of DA, D2R and 5-HT₂AR in ability of (-)-OSU6162 to reduce alcohol intake in long-term drinking rats
- Potential of (-)-OSU6162 as a novel treatment for binge-eating disorder



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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 42, No. 2
February 2018

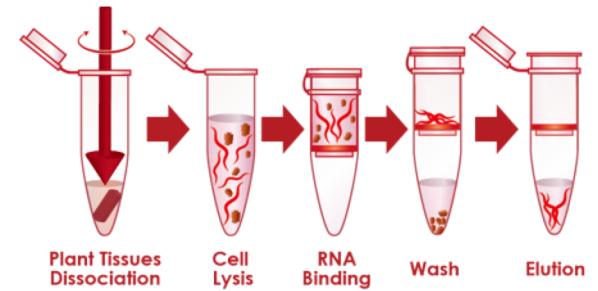
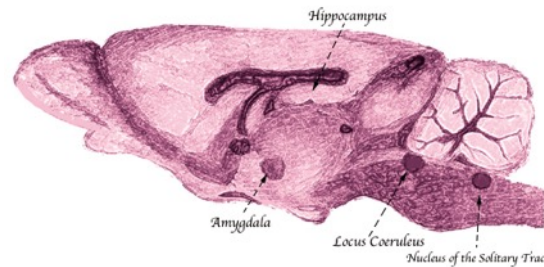
Effects of Long-Term Alcohol Drinking on the Dopamine D2 Receptor: Gene Expression and Heteroreceptor Complexes in the Striatum in Rats

Kristin Feltmann , Dasiel Oscar Borroto-Escuela, Joëlle Rüegg, Luca Pinton, Thatiane de Oliveira Sergio, Manuel Narváez, Antonio Jimenez-Beristain, Tomas J. Ekström, Kjell Fuxe, and Pia Steensland



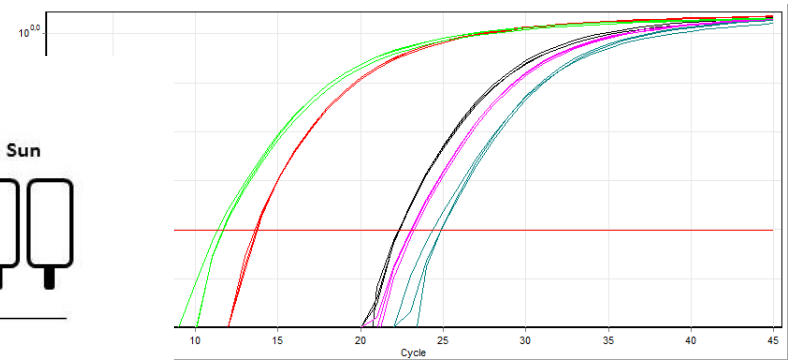
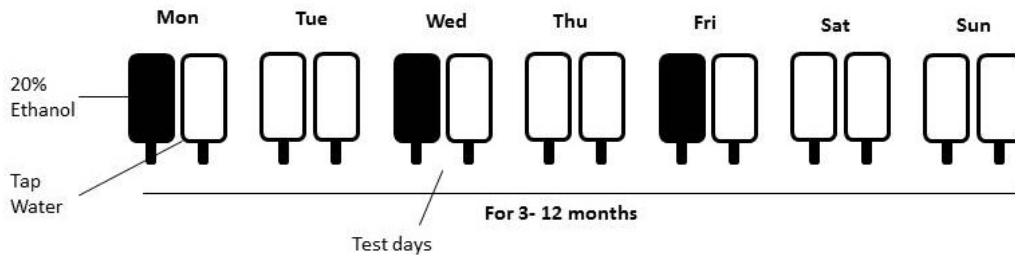
ACH

Long-term drinking on dopamine D2R



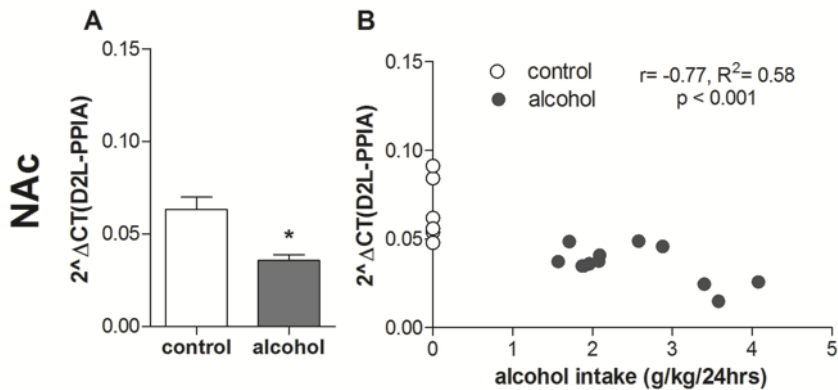
qPCR

IA20E

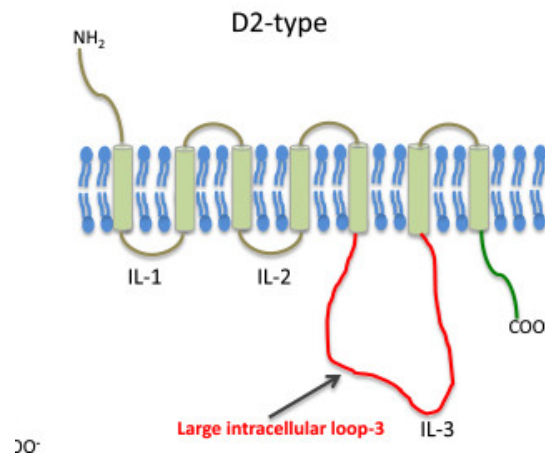
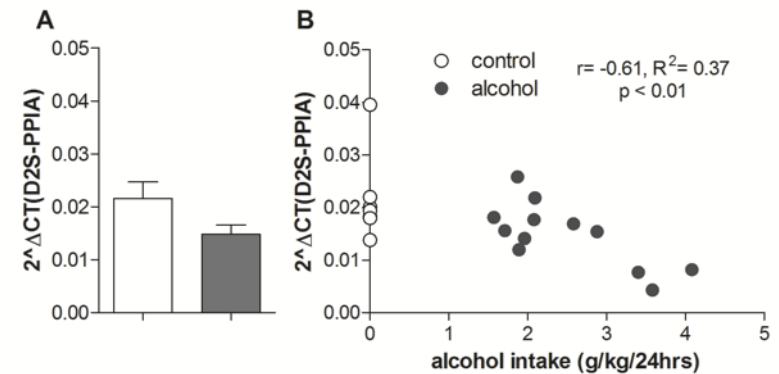


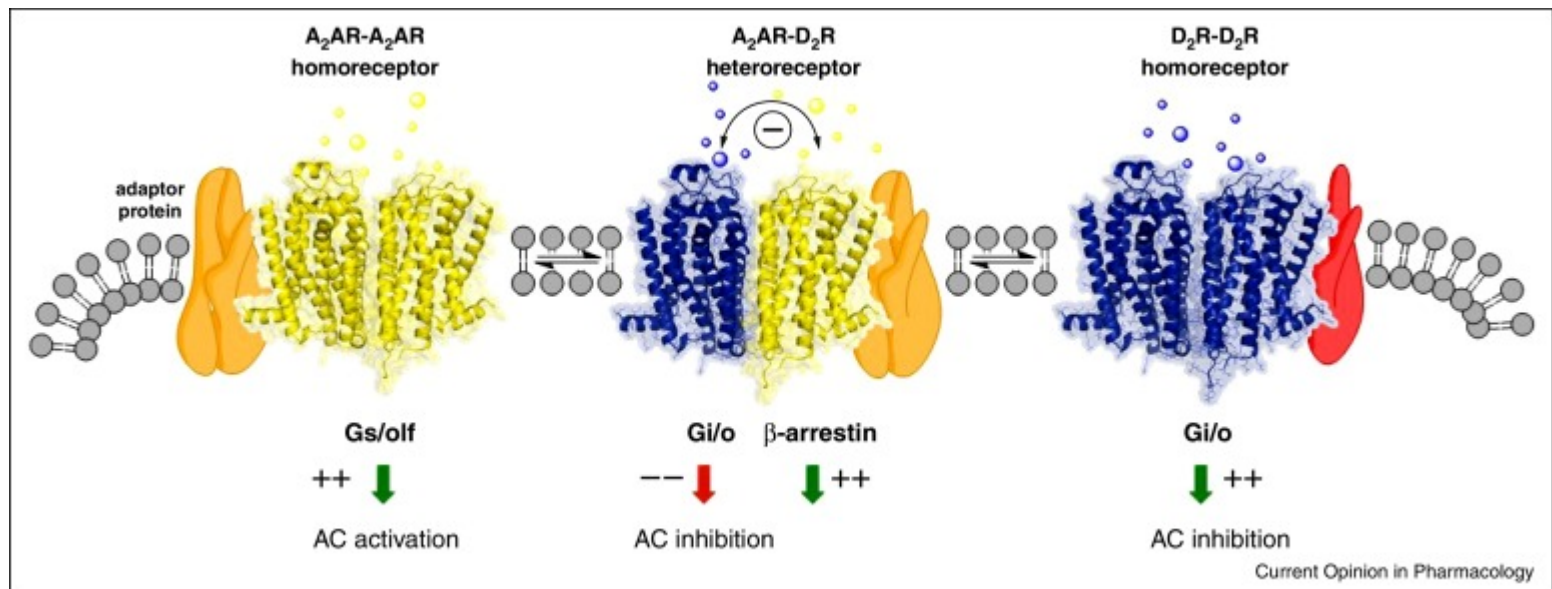
Long-term drinking on dopamine D2R

Long isoform

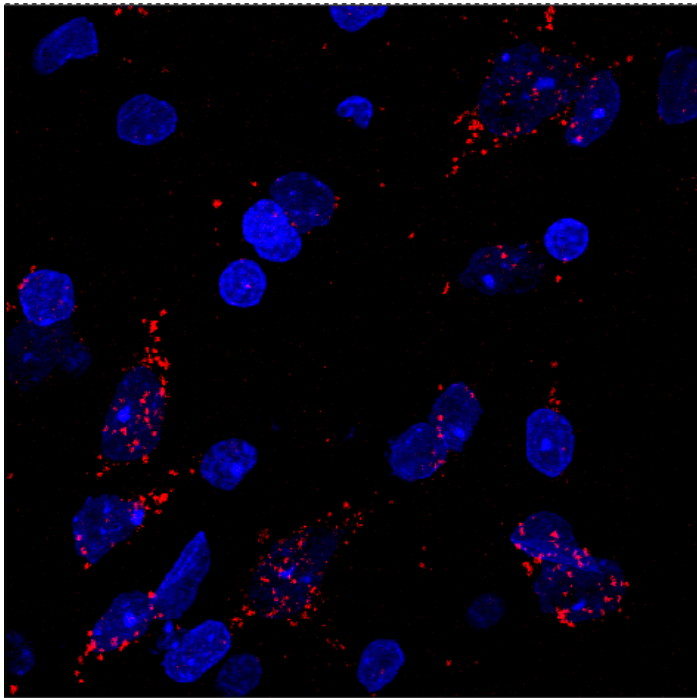
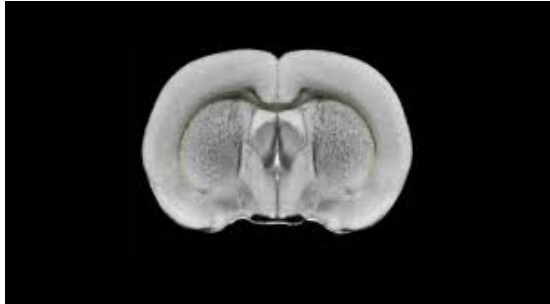


Short isoform

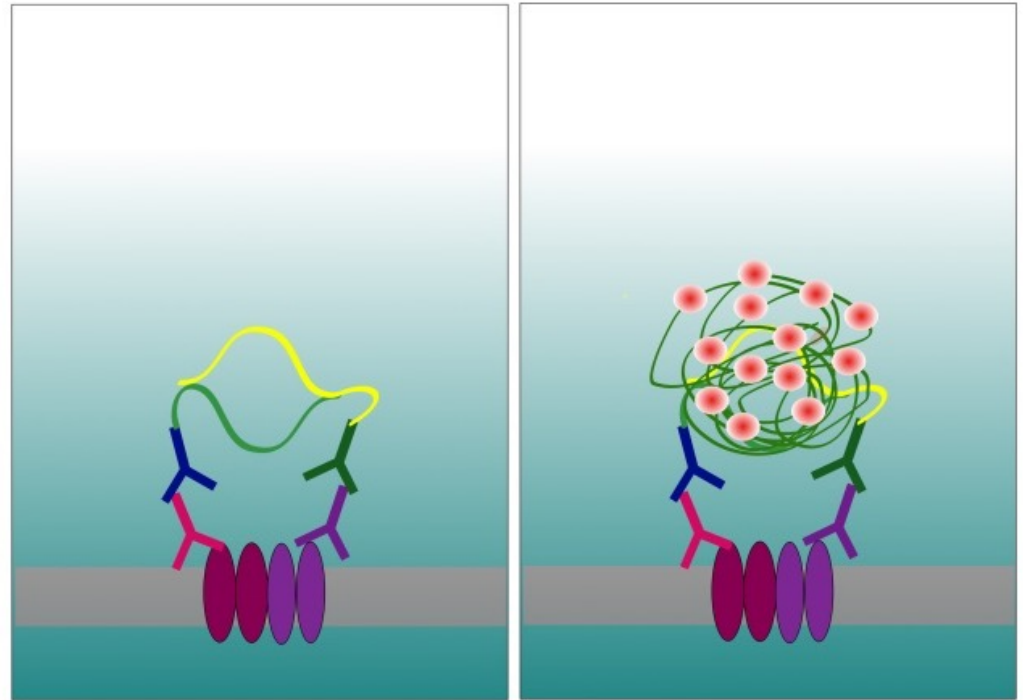




Long-term drinking on dopamine D2R

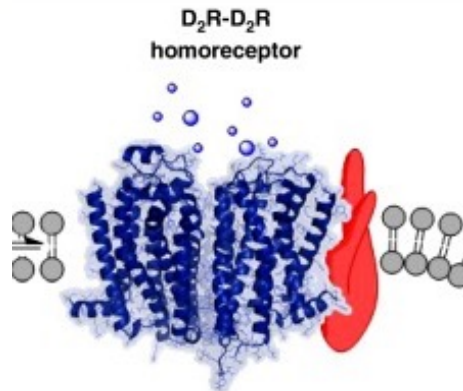
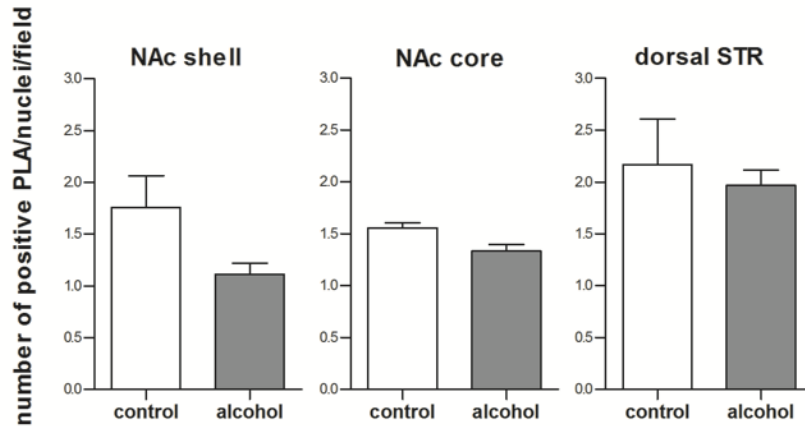


Proximity ligation assay



Long-term drinking on dopamine D2R

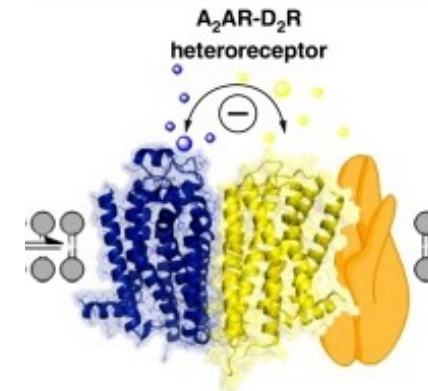
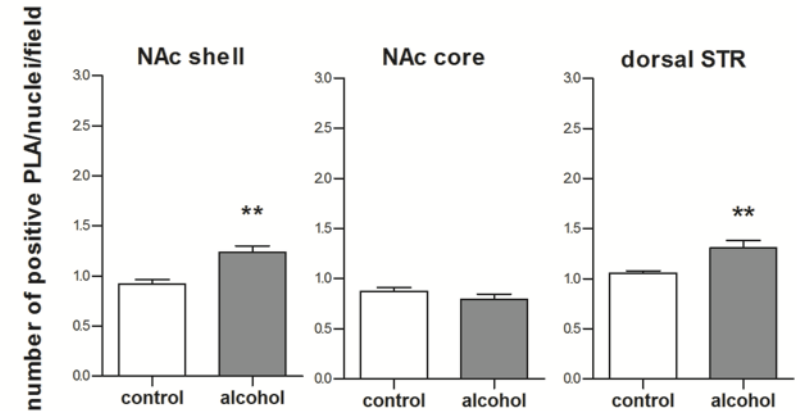
A D2R-D2R homoreceptor complexes



Gi/o
↓ ++
AC inhibition

Current Opinion in Pharmacology

B A2AR-D2R heteroreceptor complexes



Gi/o β-arrestin
-- ↓ ++
AC inhibition

Paper 1:

Long-term drinking reduces the D2R levels in the striatum



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Addiction Biology



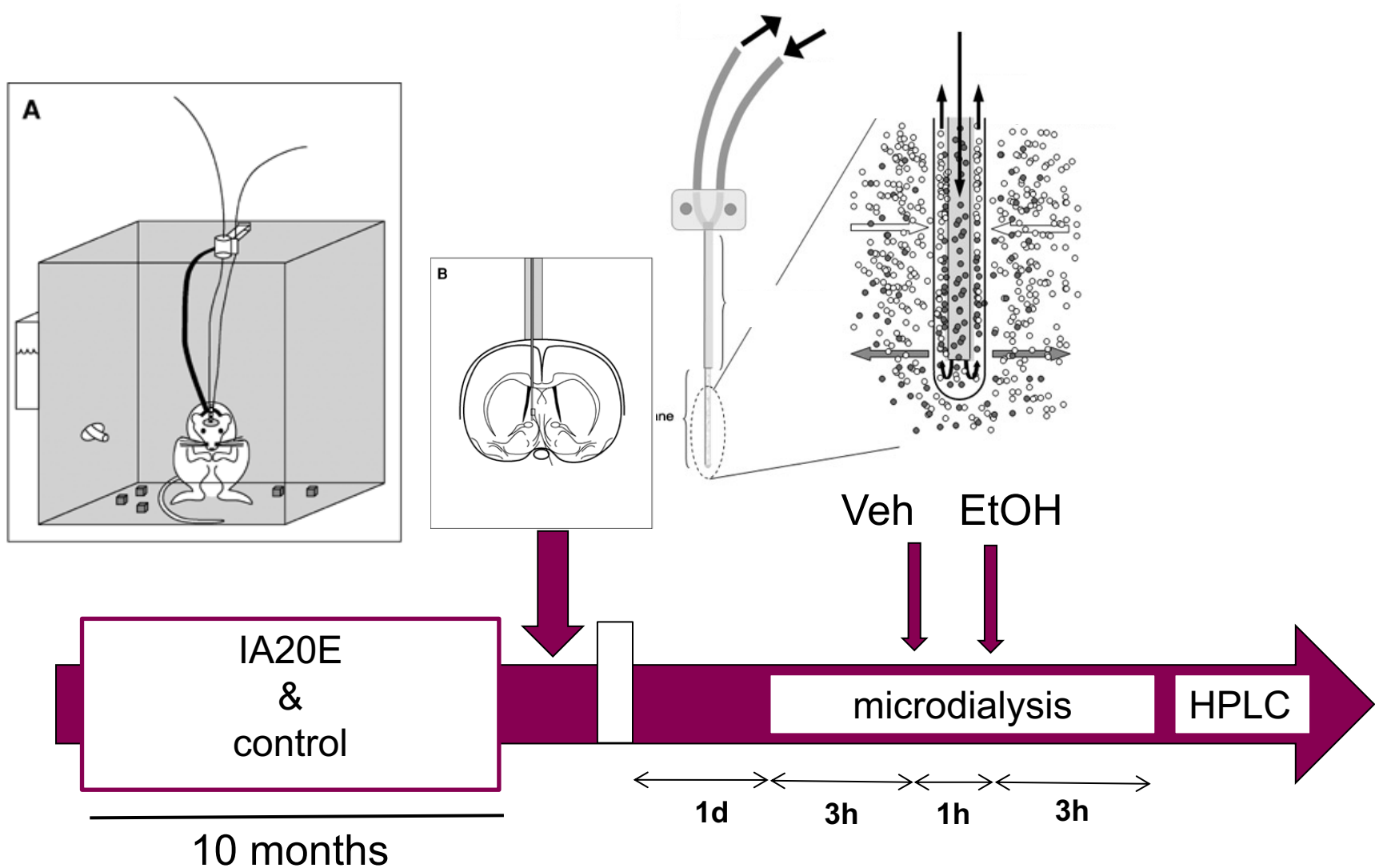
PRECLINICAL STUDY

doi:10.1111/adb.12304

The monoamine stabilizer (–)-OSU6162 counteracts downregulated dopamine output in the nucleus accumbens of long-term drinking Wistar rats

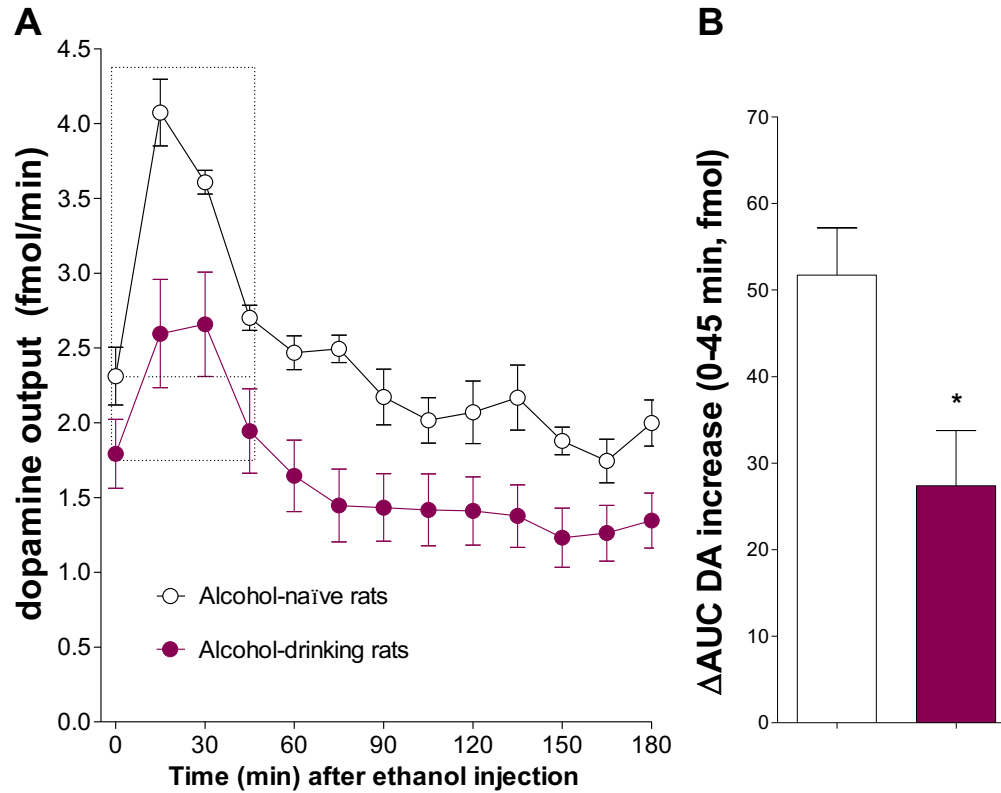
Kristin Feltmann^{1*}, Ida Fredriksson^{1*}, Malin Wirf¹, Björn Schilström^{2,3} & Pia Steensland¹

Long-term drinking on Dopamine in NAc

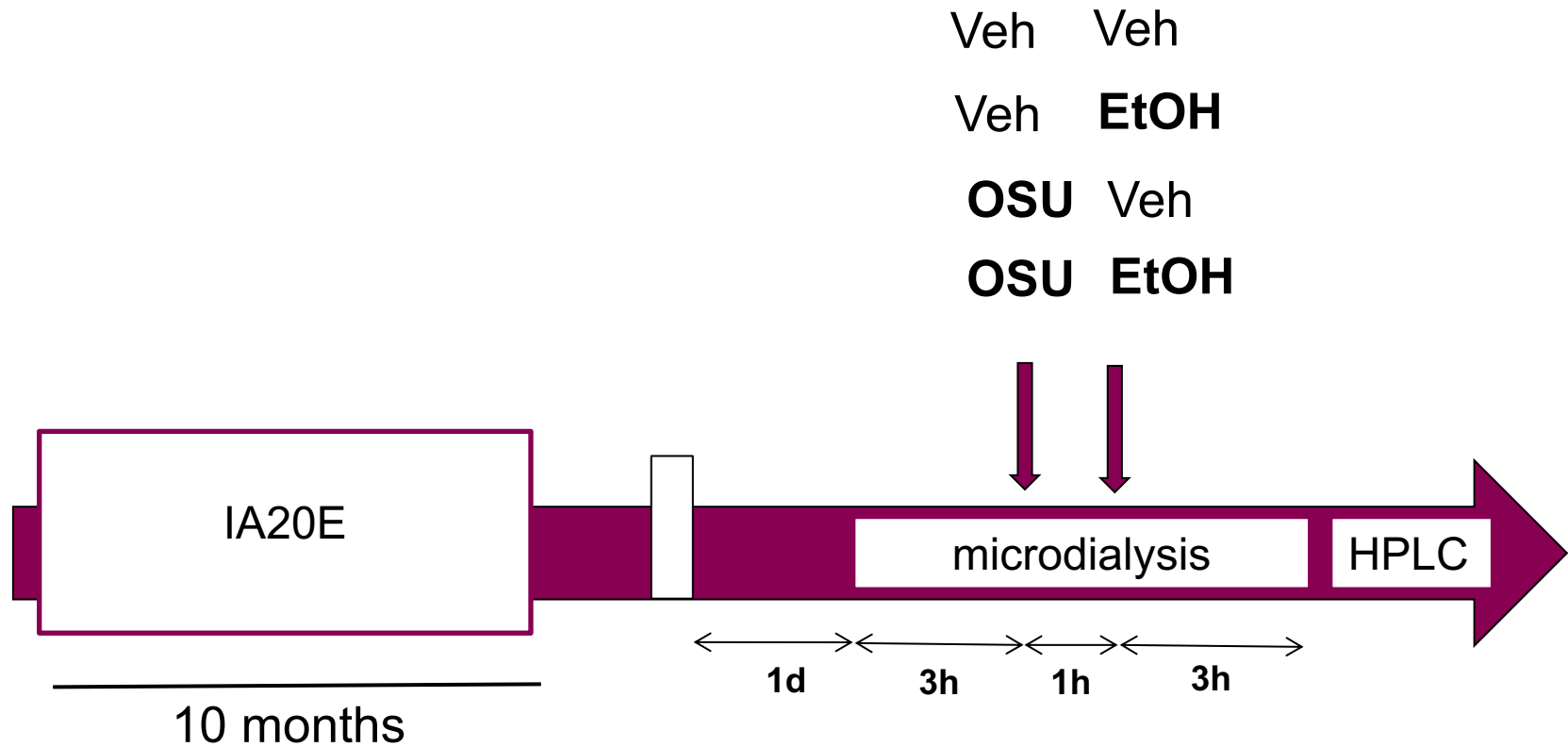


Long-term drinking on Dopamine in NAc

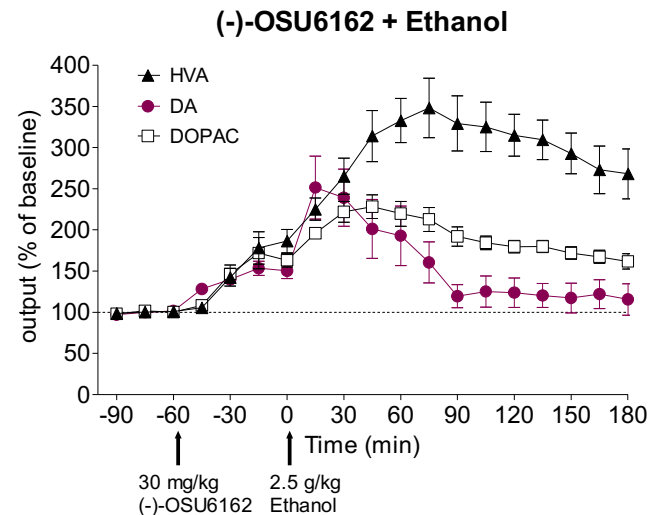
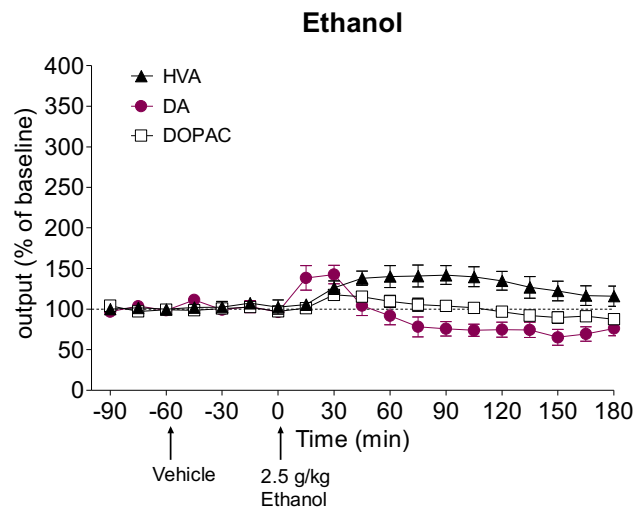
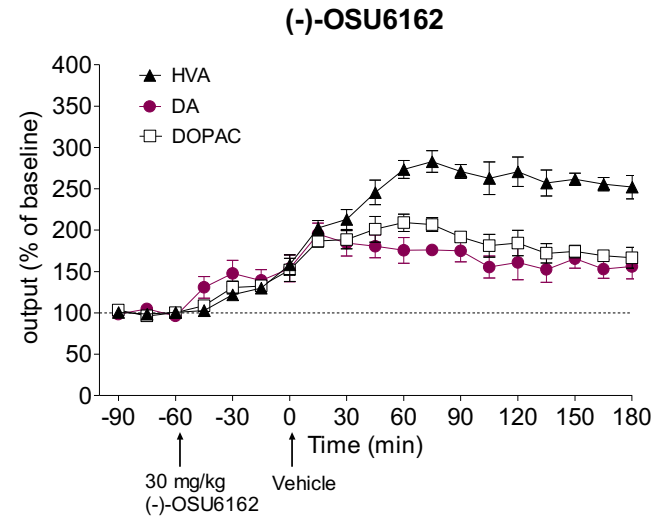
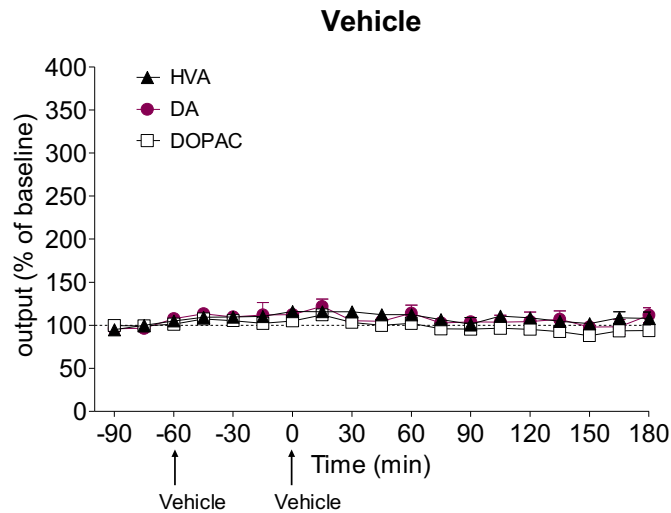
- Alcohol-drinking reduces DA baseline



Effects of (-)-OSU6162 on dopamine in NAc



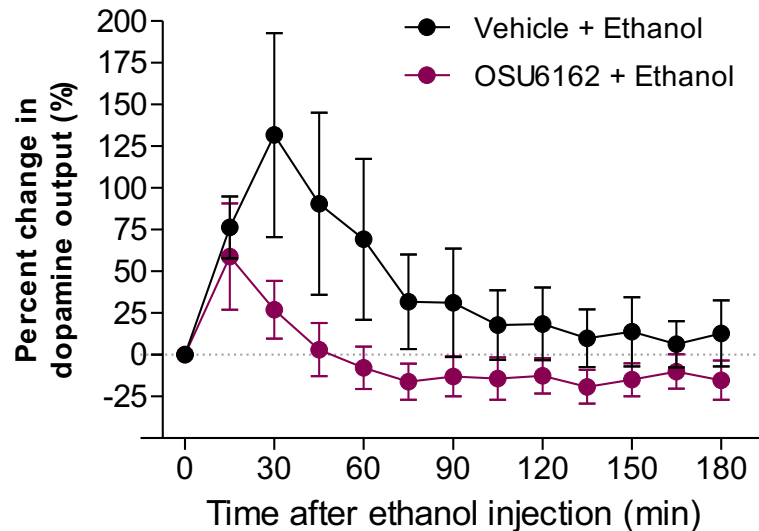
Effects of (-)-OSU6162 on dopamine in NAc



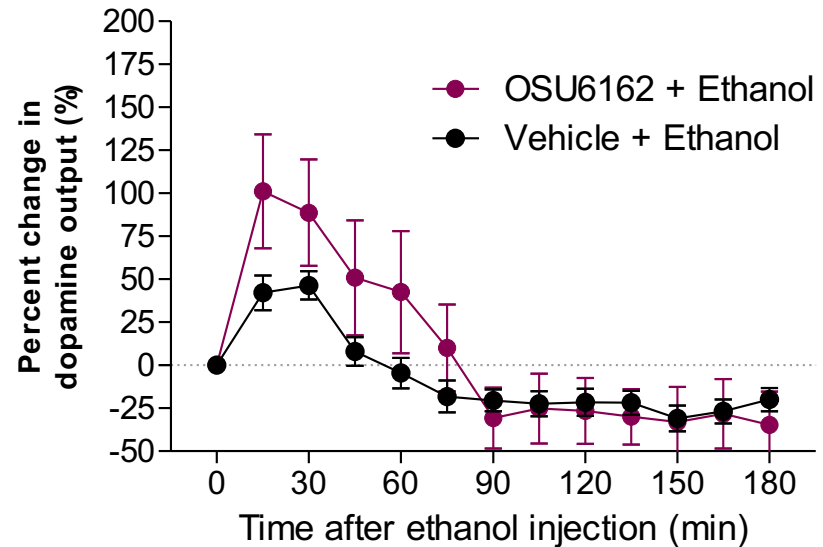
Effects of (-)-OSU6162 on dopamine in NAc

Ethanol-Induced Dopamine Output

Alcohol-Naïve Rats



Alcohol-drinking rats



Paper 2:

Long-term drinking reduces basal and alcohol-induced DA levels & (-)-OSU6162 counteracts these effects



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Paper 3:

Role of the D2R and 5-HT2AR in the ability of (-)-OSU6162 to reduce alcohol-drinking



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OPEN

Neuropsychopharmacology (2017), 1–10

Official journal of the American College of Neuropsychopharmacology

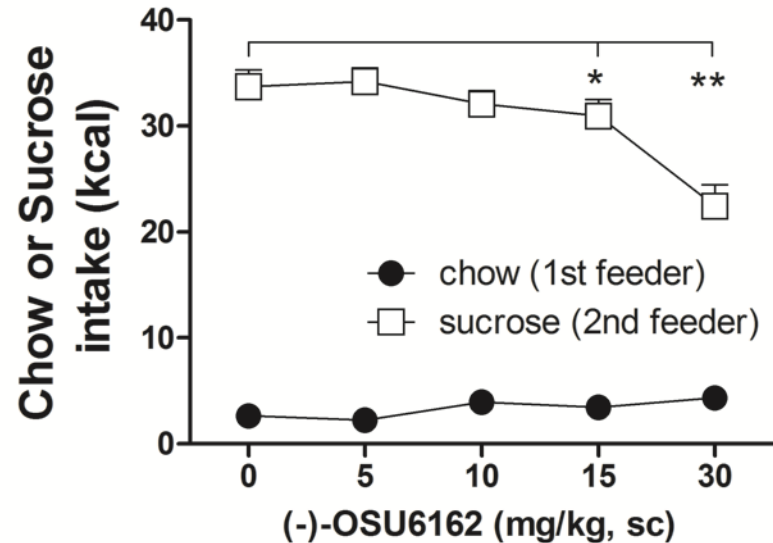
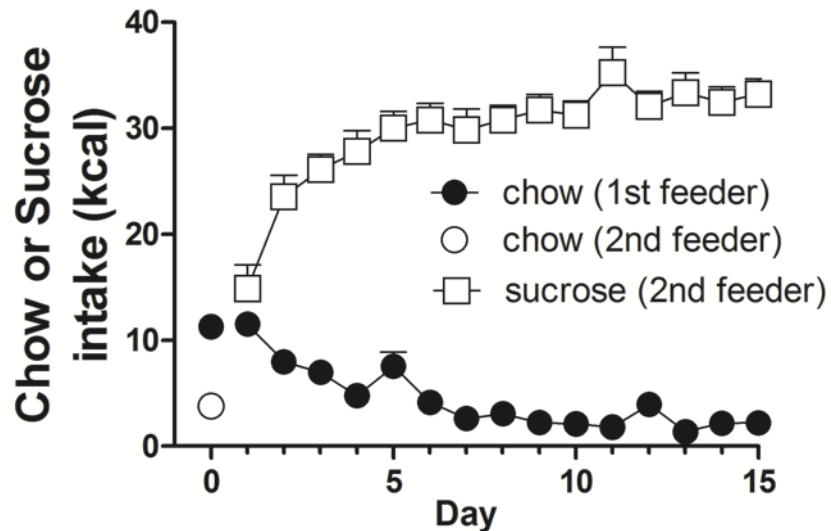
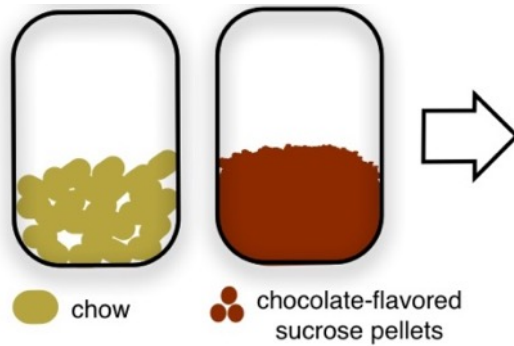
www.neuropsychopharmacology.org

The Effects of the Monoamine Stabilizer (–)-OSU6162 on Binge-Like Eating and Cue-Controlled Food-Seeking Behavior in Rats

Kristin Feltmann^{*,1,4}, Chiara Giuliano^{2,4}, Barry J Everitt², Pia Steensland¹ and Johan Alsiö^{2,3}

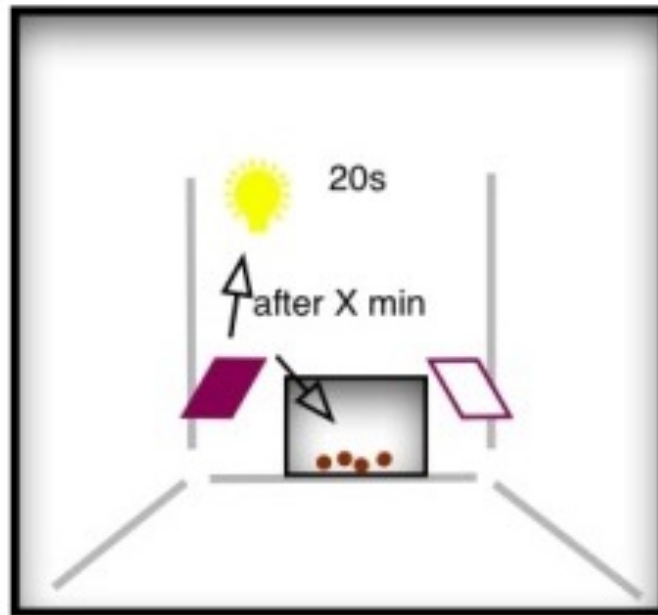
¹Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden; ²Department of Psychology and Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK; ³Department of Neuroscience, Unit of Functional Neurobiology, University of Uppsala, Uppsala, Sweden

Effects of (-)-OSU6162 on binge-eating



Effects of (-)-OSU6162 on food seeking

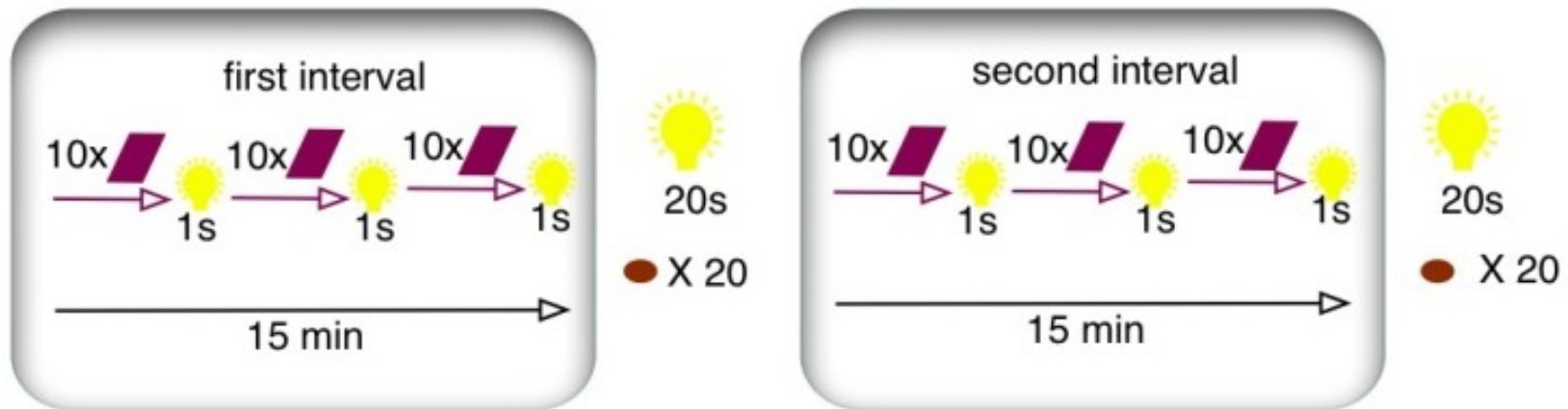
Fixed interval (FI)



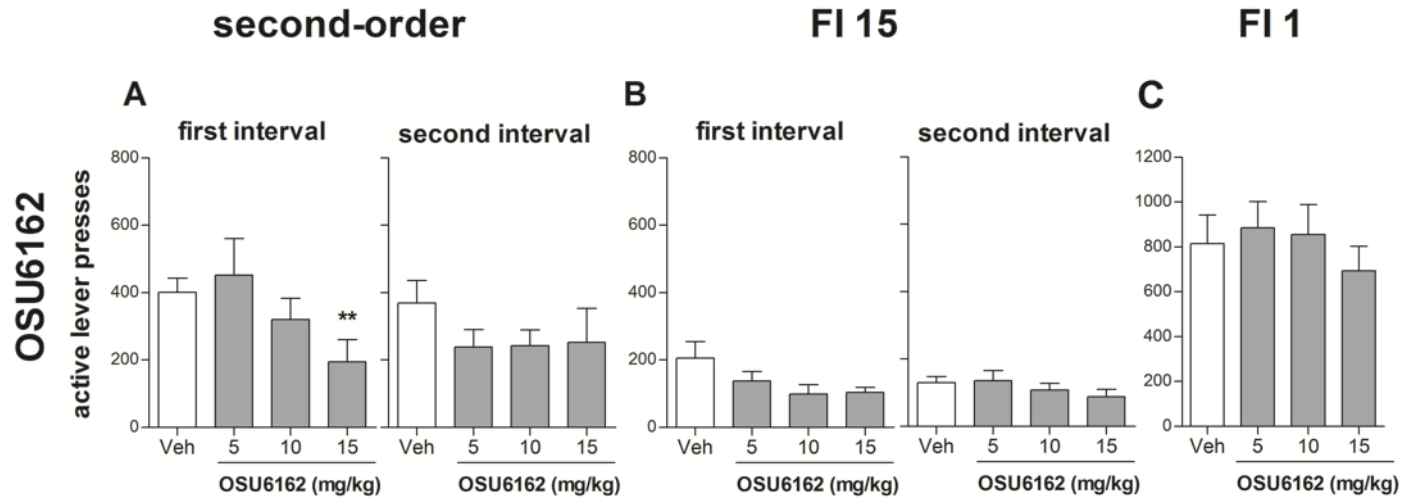
FI 1: 1min, 1 pellet → until 40 pellets
FI 15: 15 min, 20 pellets → two intervals

Effects of (-)-OSU6162 on food seeking

second-order schedule reinforcement



Effects of (-)-OSU6162 on food seeking



Paper 4:

**(-)-OSU6162 reduces both binge-like eating
and cue-controlled seeking of palatable food**

Conclusions

1. Long-term drinking induces a hypodopaminergic state
2. OSU6162 counteracts these drinking-induced dopamine deficits
3. Both D2R and 5-HT2AR are involved in (-)-OSU6162's reduction on drinking
4. OSU6162 might be a potential novel treatment for both AUD & BED

Papers

- I. **Feltmann K**, Borroto-Escuela DO, Rüegg J, Pinton L, de Oliveira Sergio T, Narváez M, Jimenez-Beristain A, Ekström T, Fuxe K and Steensland P. (2018) Effects of Long-Term Alcohol Drinking on the Dopamine D2 receptor: Gene expression and Heteroreceptor complexes in the Striatum in Rats. *Alcoholism Clinical Experimental Research* 42 (2): 338-351
- II. **Feltmann K**, Fredriksson I, Wirf M, Schilström B, Steensland P. (2016) The monoamine stabilizer (-)-OSU6162 counteracts downregulated dopamine output in the nucleus accumbens of long-term drinking Wistar rats. *Addiction Biology* 21(2):438-49
- III. **Feltmann K**, Fredriksson I and Steensland P: The role of the dopamine D2 receptor and serotonin 5-HT2A receptor in the ability of the monoamine stabilizer (-)-OSU6162 to reduce voluntary alcohol intake in long-term drinking rats (Manuscript)
- IV. **Feltmann K**, Giuliano C, Everitt BJ, Steensland P, Alsiö J. (2018) The Effects of the Monoamine Stabilizer (-)-OSU6162 on Binge-Like Eating and Cue-Controlled Food-Seeking Behavior in Rats. *Neuropsychopharmacology* 43(3): 617-626

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Thank you for listening!

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