



Animal Models and Novel Insights into the Neurobiology of ADHD

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

Financial Interest in

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Animal Models and Novel Insights into the Neurobiology of ADHD

Two Mouse Models

1. Prenatal Nicotine Exposure
2. Fragile X Syndrome

Prenatal Nicotine Exposure Mouse Model of ADHD



- 1. Why this animal model?*
- 2. What can we learn from it?*

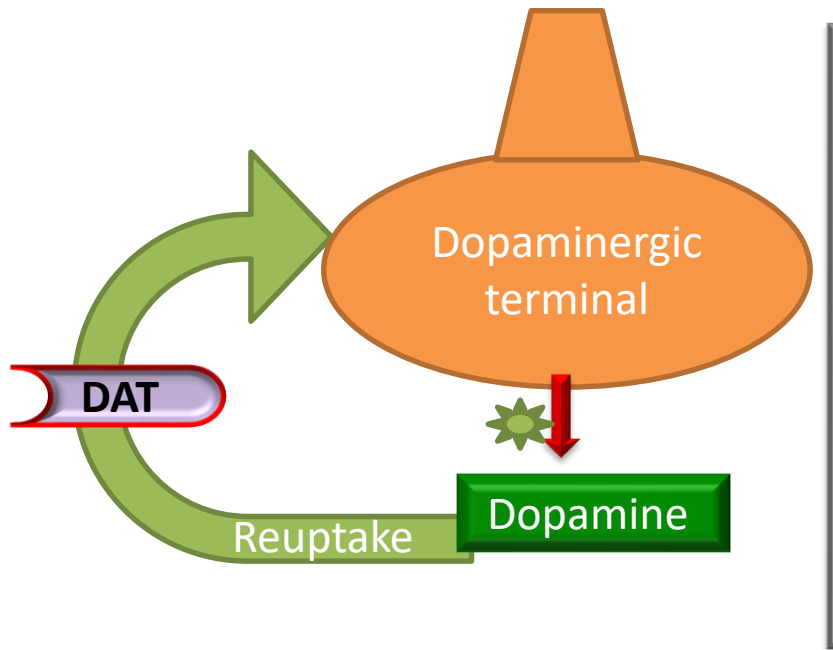
Prenatal Nicotine Exposure Mouse Model of ADHD

- Prenatal nicotine exposure is a significant risk factor for ADHD (Construct Validity)
- The mouse model shows behavioral, neuroanatomical and neurochemical changes that are consistent with those seen in ADHD (Face Validity)
- Stimulants ameliorate the ADHD-like phenotypes in the mouse model (Predictive Validity)

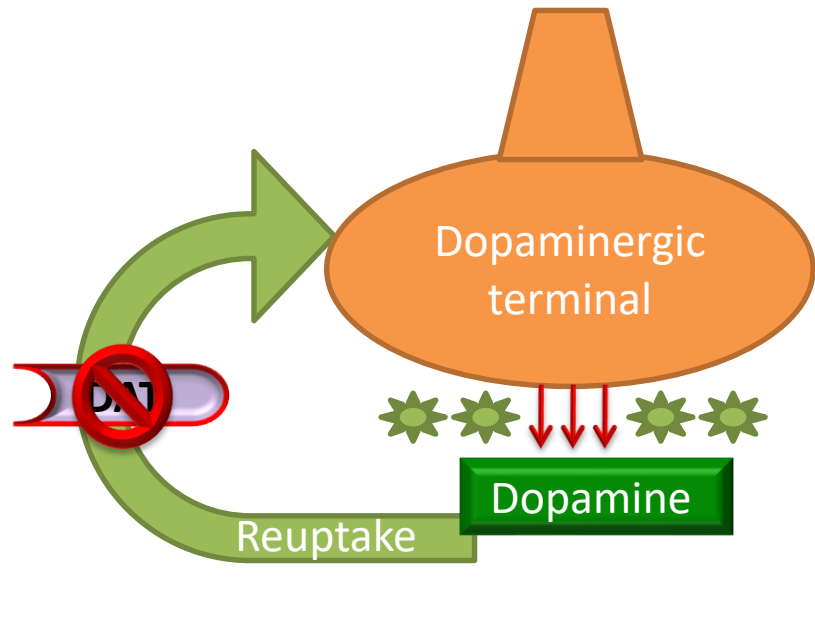
Prenatal Nicotine Exposure Mouse Model of ADHD

Novel Treatment Options: A Mechanistic Approach

Dopamine - ADHD



ADHD – Low dopamine



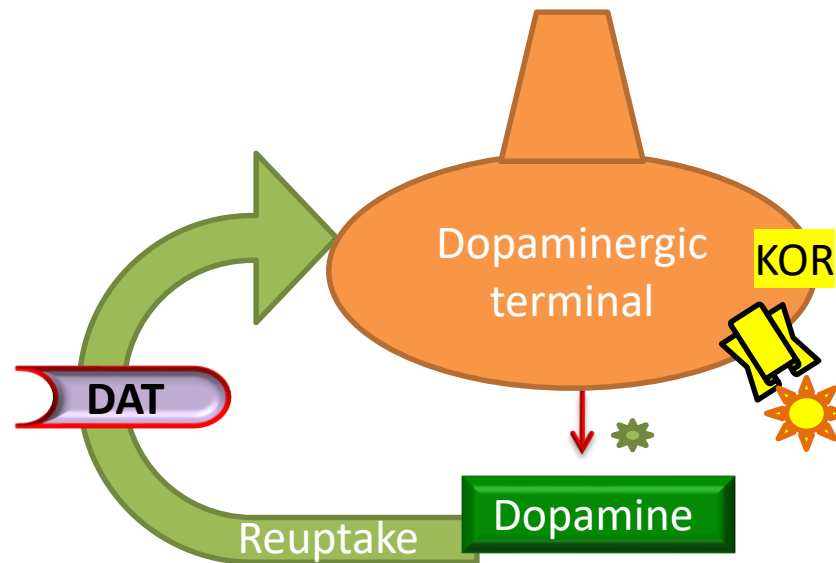
Stimulant Drugs: Highly Effective

*Supra-therapeutic doses:
Significant Abuse Potential*

Dopamine - ADHD

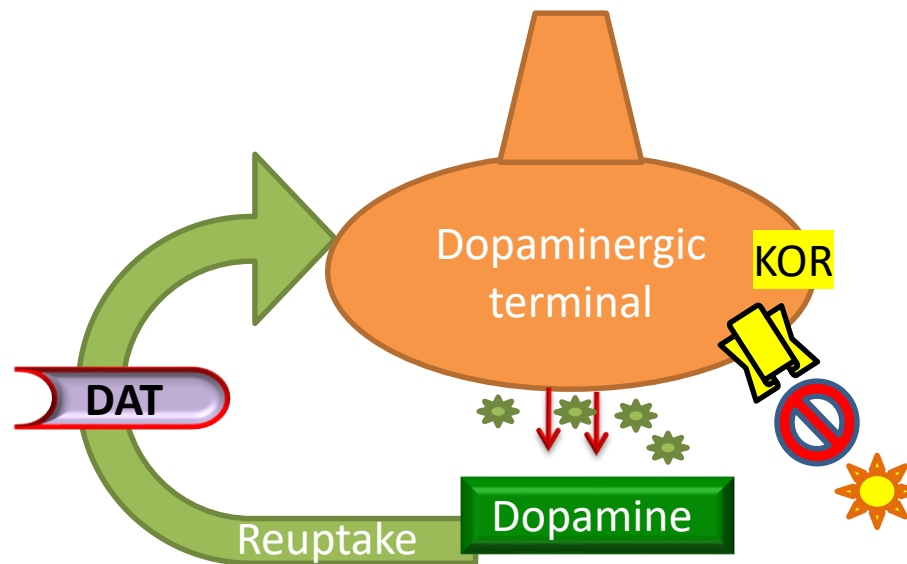
A Mechanistic Approach to Achieve
Gradual Increase in Dopamine
Release at the Synapse

Dopamine and Kappa Opioid Receptor (KOR)



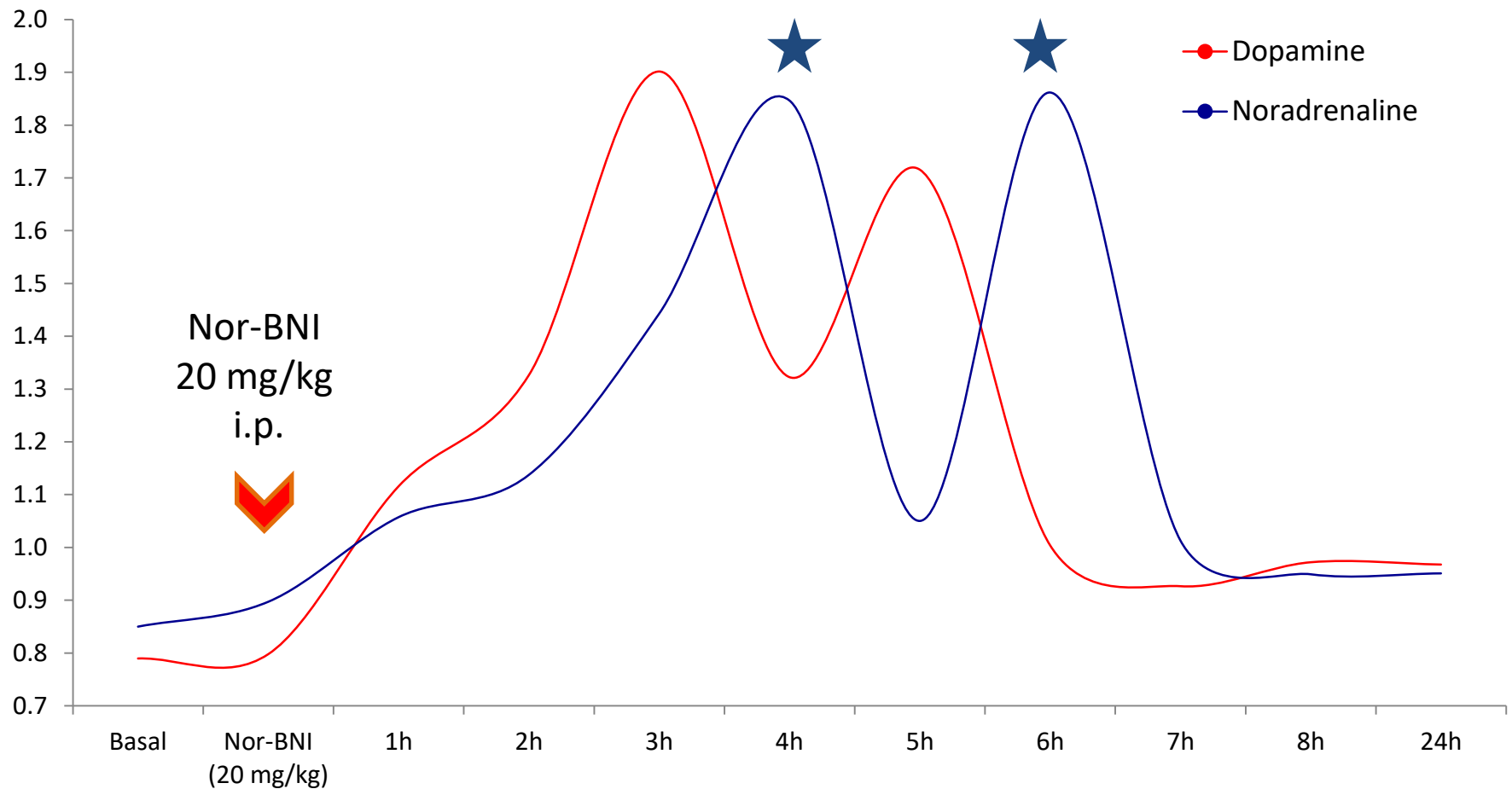
KOR Activation Reduces Dopamine Release

Dopamine and Kappa Opioid Receptor



Could KOR Antagonism Increase Dopamine Release in the Frontal Cortex?

The selective KOR antagonist norbinaltorphimine (norBNI) increases frontal cortical dopamine and noradrenaline release



NorBNI *versus* Methylphenidate

Frontal Cortical Neurotransmitters

DOPAMINE

	MPH (0.75 mg/kg)	Nor-BNI (20 mg/kg)
Peak(s) at	1 hr	2 Peaks: 3 hr, 5 hr
Return to basal	2.5 hr	6 hr

NOR-ADRENALINE

	MPH (0.75 mg)	Nor-BNI (20 mg)
Peak at	1 hr	2 Peaks: 2.5, 5.5 hr
Return to basal	2 hr	6 hr

The effects of nor-BNI are **slower in onset and longer lasting** than the effects of MPH

NorBNI *versus* Methylphenidate

Behavioral Effects: Attention and Working memory

	0.5hr	2.5hr	5.5 hr	24hr
Methylphenidate	✓	Deficit	Deficit	Deficit
Nor-BNI	Deficit	✓	✓	Deficit

The effects of nor-BNI are **slower in onset and longer lasting** than the effects of MPH

NorBNI: ADHD Mouse Model

- Increase in frontal cortical dopamine and noradrenaline
- Improves attention and working memory
- Effects comparable to those of methylphenidate
- Effects gradual in onset and longer lasting

Mouse Model: #2

Fragile X Syndrome

Fragile X Syndrome

Fragile X Syndrome (FXS)

- Mutation in the Fragile X mental retardation 1 (*FMR1*) gene
- # 1 *inherited* cause of intellectual disabilities
- The most common genetic etiology of autism

Mouse model of FXS

- Deletion of the *Fmr1* gene (Fmr1-KO)
- Hyperactivity and impaired nesting behavior

NorBNI and FXS

- Reduces hyperactivity
- Improves nesting behavior
- Effects last up to 3 weeks

Kappa Opioid Receptor Antagonism: ADHD and FXS

- Increases dopamine and noradrenaline in the frontal cortex
- Improvements in attention, working memory and nesting
- Reduces hyperactivity
- In ADHD mouse model
 - ❖ Effects are comparable to those of methylphenidate
 - ❖ Effects are gradual in onset and last longer than methylphenidate

Animal Models and Novel Insights into the Neurobiology of ADHD

- Animal models play a critical role in the identification of:
 - Mechanism of action of drugs
 - Molecular targets for drug discovery and development

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Thank you!

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