Psychostimulants & ADHD: Roadmap for Drug Discovery

Craig W. Berridge
Psychology Dept.
University of Wisconsin Madison

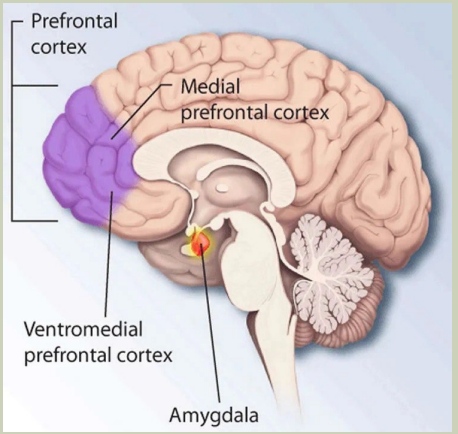
PFC AND ADHD

PFC supports higher 'executive' cognitive processes that regulate goal-directed behavior

ADHD associated with dysregulated PFC-dependent cognition & PFC hypoactivity

PFC = acts in concert with multiple regions to support higher cognitive function

Striatum
Midline Thalamic (Mediodorsal)



PSYCHOSTIMULANTS & ADHD

Most effective treatments = Psychostimulants (*low-doses*)

- *Methylphenidate (MPH; Ritalin), Amphetamine (Adderall)*
- *Rapidly (< 1 hour) reverse PFC-dependent cognitive deficits of ADHD*
- *Safe when used as prescribed*

PSYCHOSTIMULANTS & ADHD

But…can be abused and misused

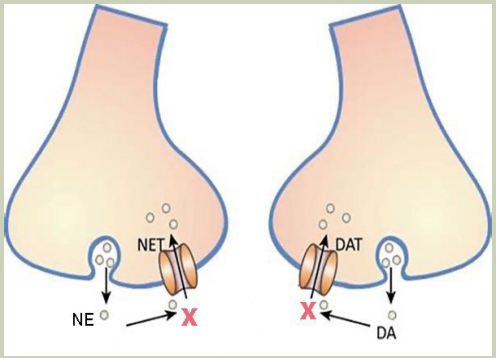
Side effects…

New treatments limited by:

➔ Lack of understanding of how psychostimulants improve cognition

NEUROCHEMISTRY OF PSYCHOSTIMULANT?

Catecholamine (NE/DA) reuptake blockers (disrupters)



High doses ➔ Large increases in NE/DA (*500%-1000%*) widely throughout the brain

Early studies: Prominent role of striatal DA in behavioral actions of high-doses

➔ *Posited central role of striatal DA in the therapeutic effects of psychostimulants in ADHD (and etiology)*

But…we don't treat ADHD with high doses of psychostimulants

How do *Clinically-Relevant* Doses of Psychostimulants Work?

Clinically relevant doses ➔ improve PFC-dependent cognition *in healthy human subjects*.

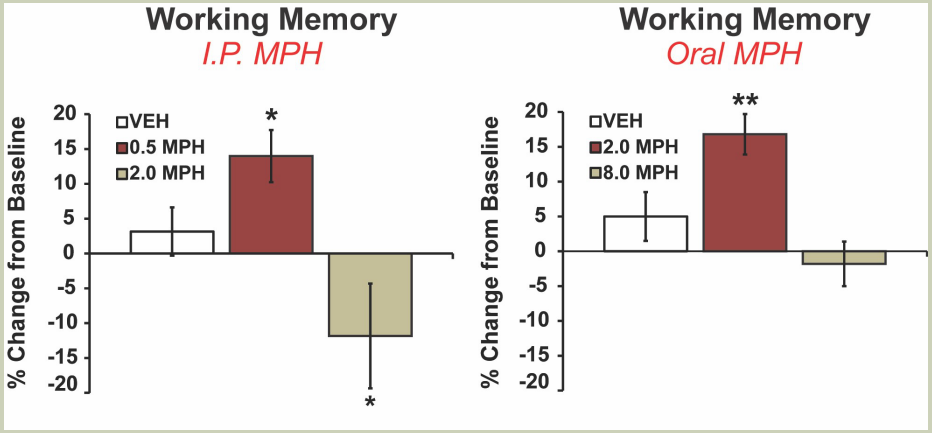
Do not need an animal model of ADHD to study the neurobiology of *procognitive* actions of psychostimulants

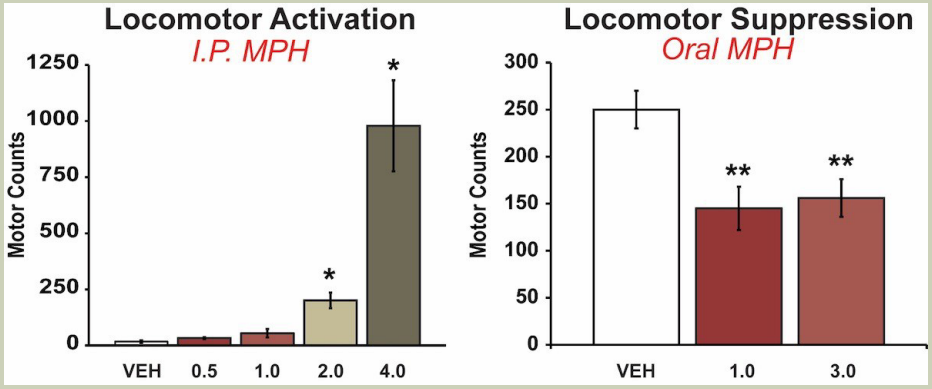
How do *Clinically-Relevant* Doses of Psychostimulants Work?

What is a *Clinically-Relevant Dose*?

We know plasma concentrations elicited by clinically-efficacious doses of MPH…

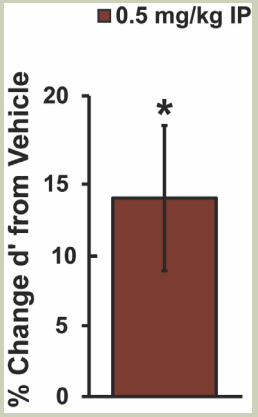
Behavioral Actions of Clinically-Relevant Doses





Sustained Attention

(Operant Signal Detection)



Identical to that seen in humans

Kuczenski, Segal, 2002, J. Neuroscience; Berridge et al., Biological Psychiatry 2006, 2011; Spencer et al., Biological Psychiatry 2015

NE/DA Actions of Clinically-Relevant Doses of MPH?

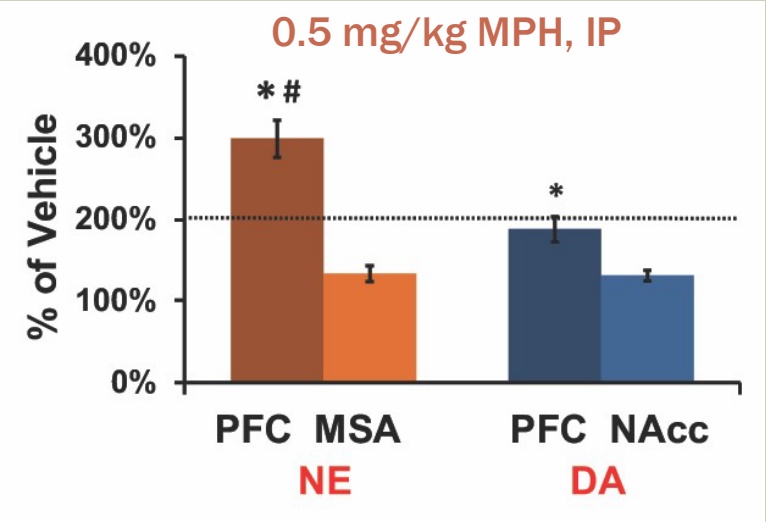
Microdialysis (NE, DA)

Varying Routes (IP, Oral)

Varying Doses (*IP*, 0, 0.25, 0.5, 1.0; *Oral*, 0, 2.0)

Varying Regions

- PFC (NE, DA; *cognition*)
- MSA (NE, *arousal*)
- NAcc (DA, motor activation, reinforcement)



***Clinically-relevant doses elevate NE & DA levels** preferentially in the PFC*

Berridge et al., Biological Psychiatry 2006

NE/DA Actions of Clinically-Relevant Doses of MPH?

Hypotheses:

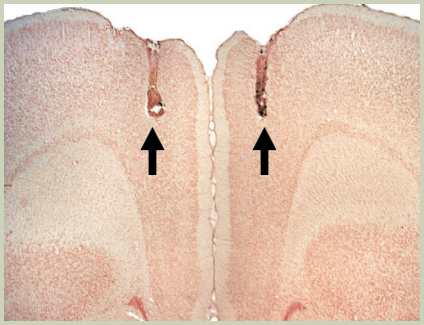
Psychostimulants acts in the PFC to promote cognition

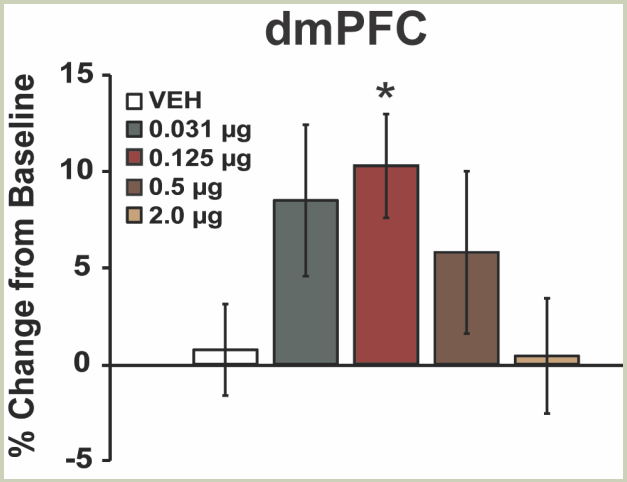
Via actions of NE and DA

Berridge et al., Biological Psychiatry 2006

Does MPH Act in the PFC to Improve Cognition?

Robert Spencer

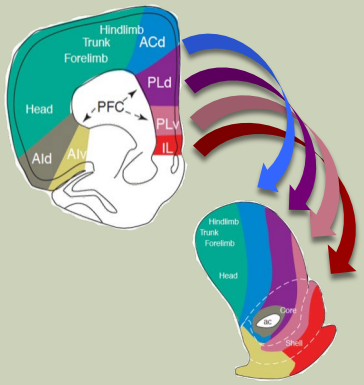




- *Bilateral MPH into the dorsomedial PFC*
- *Improves working memory in an inverted-U manner*
- *(not seen with ventromedial PFC MPH)*

Spencer et al., Biological Psychiatry 2012

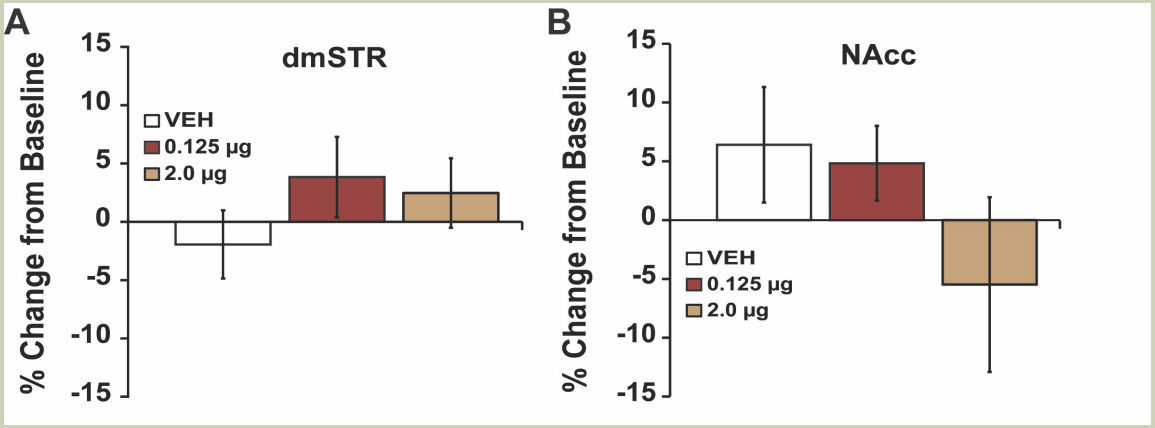
Frontostriatal Projections



Topographically-organized projections

dmSTR = Necessary for PFC-dependent cognition

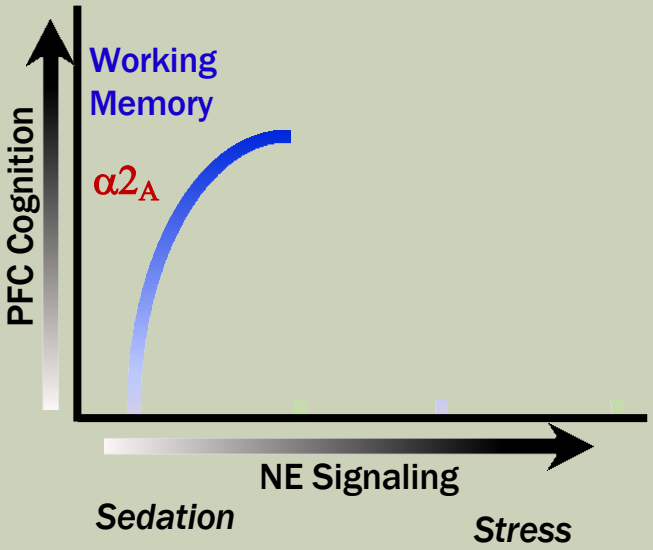
MPH in the dmSTR – or vmSTR – does *NOT* improve working memory

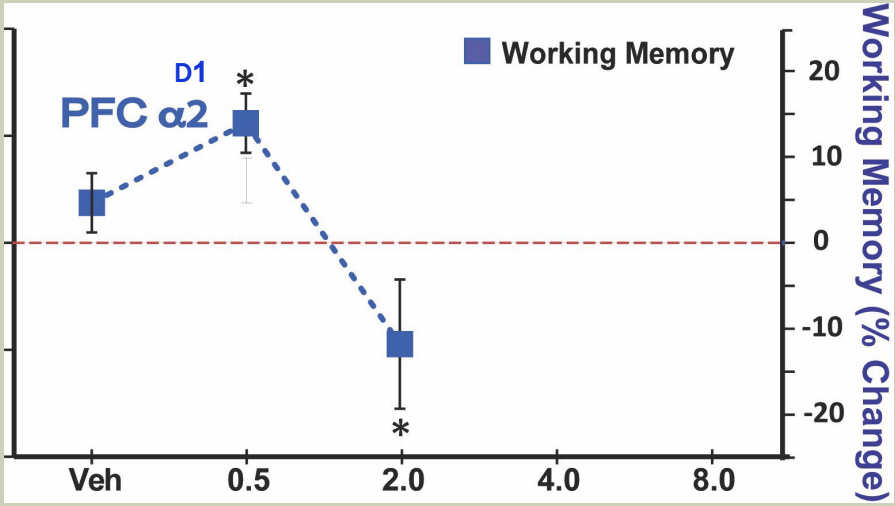


Spencer et al., Biological Psychiatry 2012

PFC Receptor Mechanisms?

NE *differentially* modulates PFC Dependent Cognitive Processes





Clinically Relevant
(Plasma Concentrations)

PFC Receptor Mechanisms?

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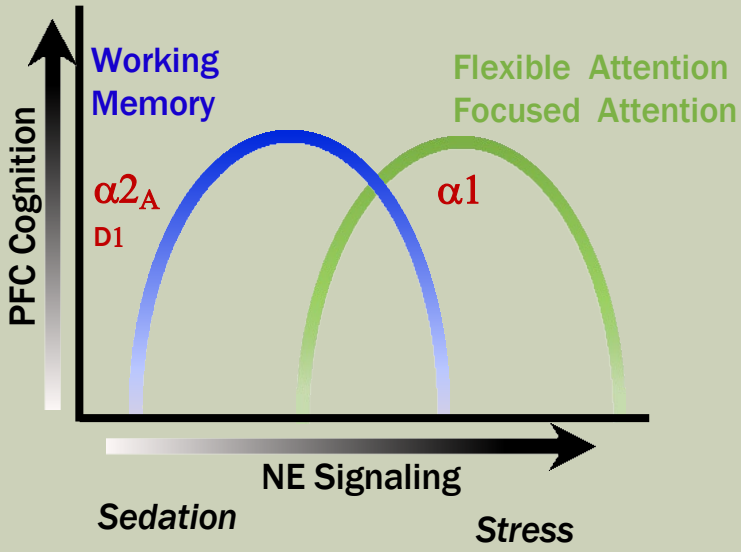
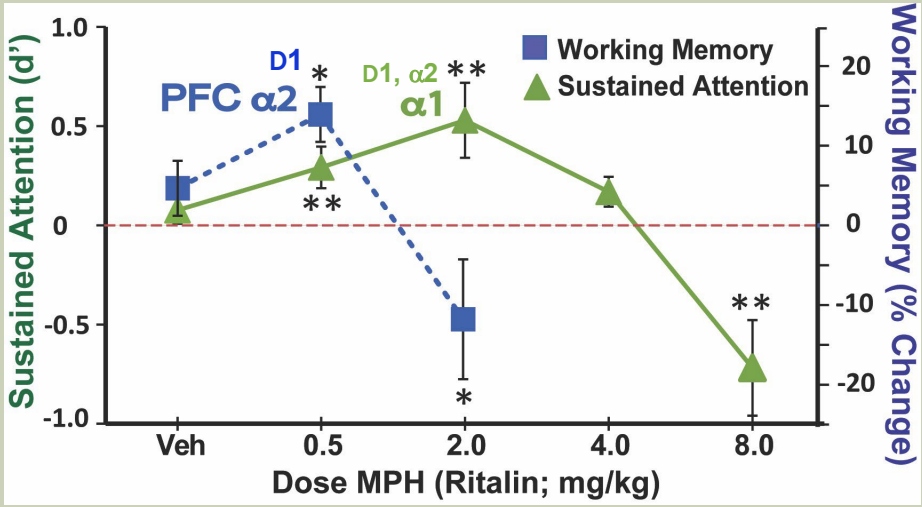
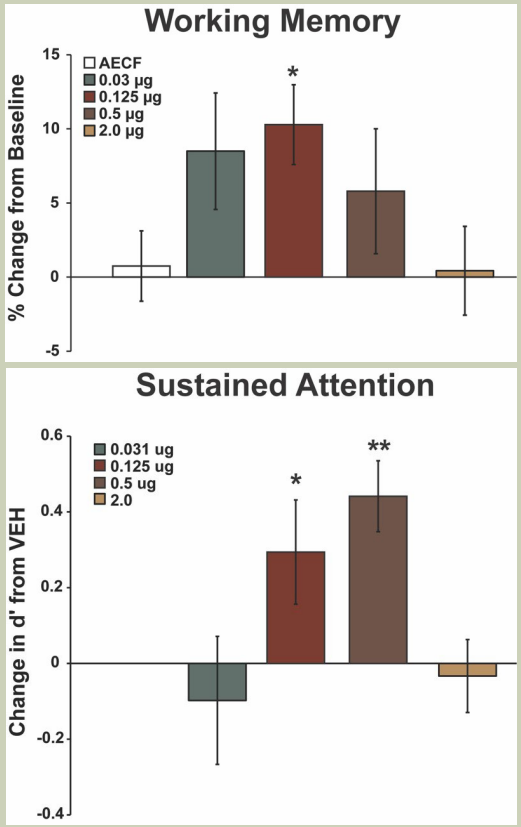




Clinically Relevant
(Plasma Concentrations)

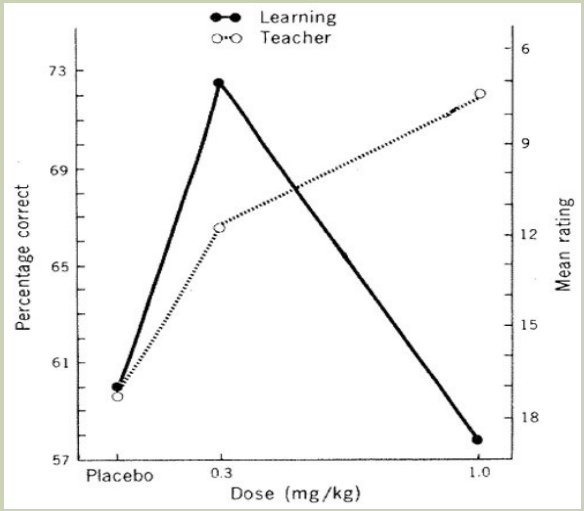
PFC & Divergent Dose-Response Curves

Intra-PFC MPH



Spencer & Berridge, 2019, Neuropsychopharmacology

ADHD Children: ‘Learning’ vs. Teacher Ratings



Sprague and Sleator, 1977, Science

‘Learning’ = Working memory task.

Tannock: Response Inhibition vs. Overt Behavior

Are there clinically/functionally-relevant consequences of divergent DR-curves in ADHD patients?

PSYCHOSTIMULANTS

Act directly in the PFC:

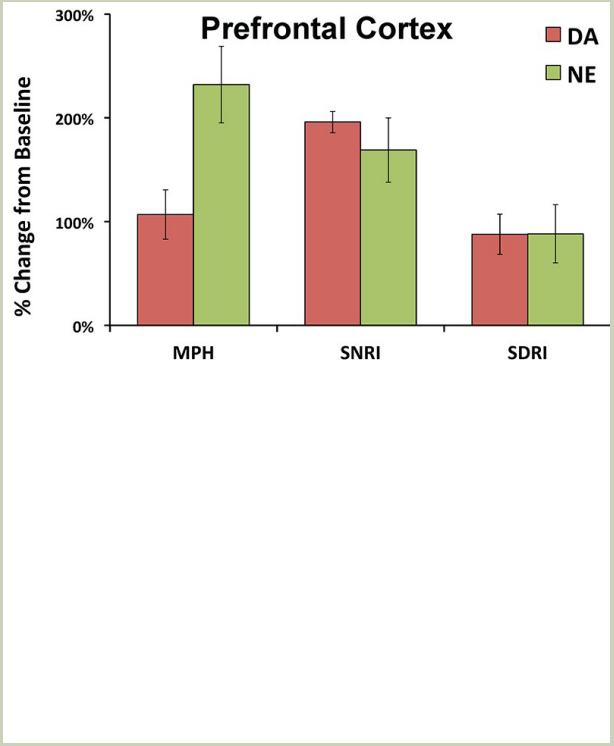
- To improve PFC-dependent cognitive processes
  - *In a complex dose-dependent manner*
- via elevated NE & DA receptor signaling

PSYCHOSTIMULANTS

Involvement of NE is consistent with:

- *All 3 classes of ADHD-approved drugs target NE*
  - *Psychostimulants*
  - *SNRIs (atomoxetine)*
  - *$\alpha 2_A$ agonist (guanfacine; also acts directly in the PFC)*

Neurochemistry of Cognitive Enhancement



Psychostimulants (MPH)
SNRIs (Atomoxetine)
SDRIs (Preclinically, AHN-2005)

All increase PFC NE and DA

All roads point to the PFC and away from striatal DA

Highly divergent actions on striatal DA

Berridge et al., Biological Psychiatry 2006; Bymaster et al., 2002, Neuropsychopharmacology; Schmeichel et al., 2013, Neuropharmacology

Implications

Policy:

- Low-dose psychostimulants do NOT act like '*psychostimulants*':
  Cognitive-Enhancers

Clinical:

- Suggests a prominent role of *PFC catecholamines* in the therapeutic actions of psychostimulants

Drug Development:

- Potential *Roadmap* for Novel Treatments

Roadmap for Drug Discovery?

Evidence does not warrant an emphasis on Striatal DA
in Drug Discovery Programs

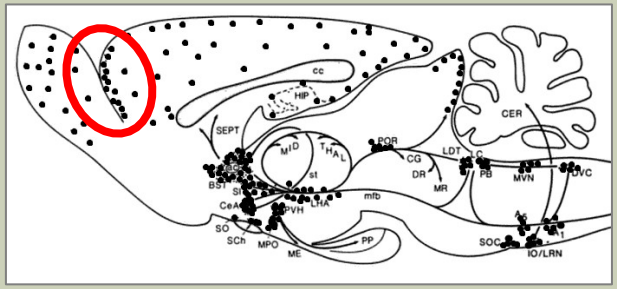
Roadmap for Drug Discovery?

What other molecules in the PFC can be targeted to improve PFC-dependent cognition?

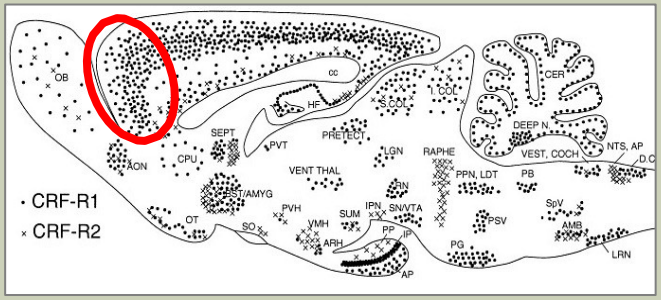
(*while lacking the abuse potential of psychostimulants*)

Corticotropin-Releasing Factor (CRF) & the PFC

CRF neurons



CRF receptors



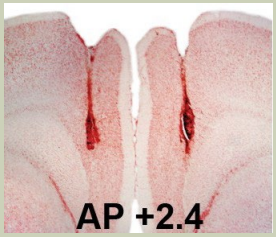
- 41-Amino acid neuropeptide
- Present in the PFC
- Studied intensively for decades
- The *cognitive* actions of CRF in the PFC = unknown

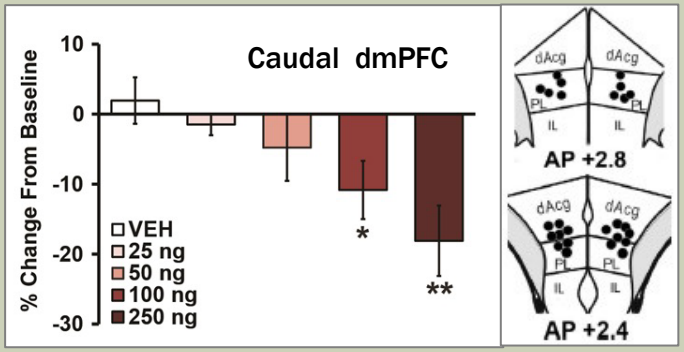
Seidel et al., 2017; Sawchenko & Swanson 1989; Van Pett et al., 2000

Do *PFC* CRF Receptors Modulate Working Memory?

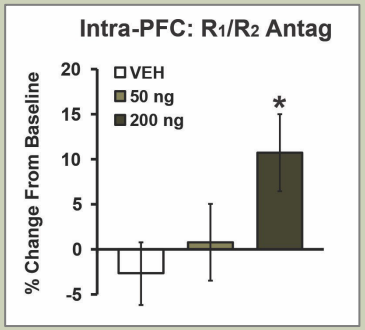
Sofiya Hupalo

Intra-*caudal* dmPFC CRF



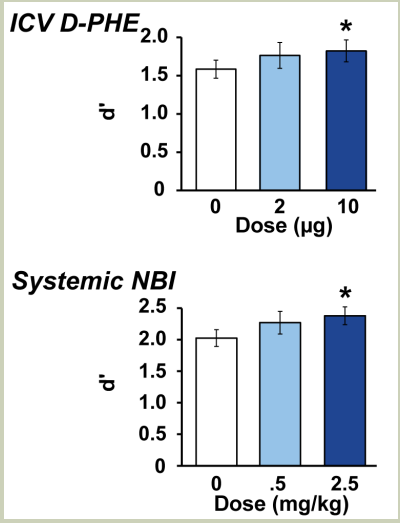


Receptor Blockade



D-Phe CRF (R1/R2)

Sustained Attention



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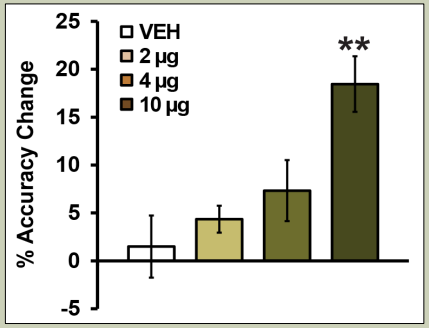
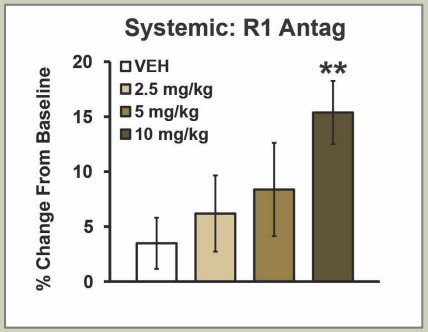


D-Phe CRF

Systemic

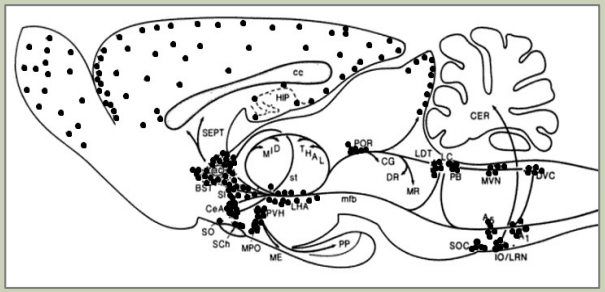


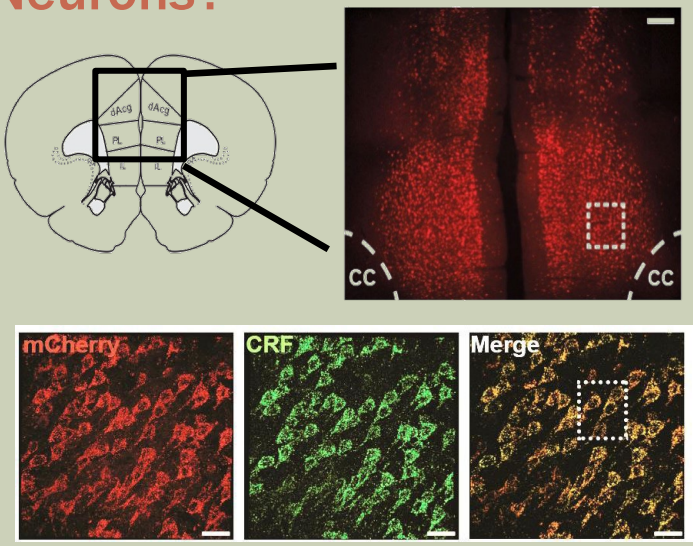
NBI 35965 (R1)

Hupalo & Berridge, Neuropsychopharmacology 2016; Hupalo et al., Eur. J. Neuroscience, 2021

Source of CRF for cognition-modulating PFC CRF receptors?

PFC CRF Neurons?





- PFC CRF neurons release *locally* to regulate *working memory*
- *Distally* to regulate *sustained attention (MD Thalamus)*

~90% of PFC neurons express CRF

Hupalo et al., J. Neuroscience, 2019

SUMMARY

Caudal dmPFC contains rich population of CRF Neurons that regulate PFC-dependent cognition

In males and females (w/exception of proestrus)

Inhibition of CRF neurotransmission globally improves PFC-dependent cognition

Similar to that seen with ADHD-approved compounds

What other molecules can be targeted to reverse PFC-dependent cognitive deficits?

mGlu Receptors (Arnsten & Colleagues)

Or non-pharmacological

TMS

??

Acknowledgements

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& many more…

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