Methylphenidate - antidepressants coadministration:
A bad combo during adolescence?

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The Chicago Medical School, USA

III International Congress Dual Disorders, October 2013, Barcelona
1/ Methylphenidate (Ritalin®) = psychostimulant used to treat ADHD

- ADHD ~ 8% of children / adolescents
  ~ 4% of adults
  (Kollins, 2008)

- In 2008: 3 million children / adolescents in the USA alone
  (Swanson et al., 2011)

2/ Also used off-label as cognitive enhancer

“We should welcome new methods of improving our brain function.”

“Double espresso… Why not methylphenidate?”
Greely and colleagues, Nature 2008
3/ Recreational use: MP snorted or injected

- Chronic use of psychostimulants during adolescence and addiction?

- Methylphenidate: No?
- Cocaine: +++
- Amphetamine: +++
**METHYLPHENIDATE: Mode of action**

- Blocks the reuptake of dopamine and norepinephrine

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**Overflow**

<table>
<thead>
<tr>
<th></th>
<th>DA</th>
<th>NE</th>
<th>5-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>IC₅₀ 84</td>
<td>IC₅₀ 514</td>
<td>&gt;50000</td>
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<tr>
<th></th>
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<th>NE</th>
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<tbody>
<tr>
<td>Cocaine</td>
<td>IC₅₀ 120</td>
<td>IC₅₀ 2100</td>
<td>190</td>
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</table>

**METHYLPHENIDDATE: Molecular consequences**

- Induces gene expression in corticostriatal circuits

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**DA:** critical for gene regulation (D1 receptors, in interaction with D2 receptors)

**NE, 5-HT and glutamate:** play modulatory role

*Hyman et al., Annu. Rev. Neurosci. 2006*
Gene regulation in the striatum:

- Transcription factors (immediate-early genes):
  - c-fos
  - zif 268
  - arc
  - ΔFosB

- Neuropeptide transmitters:
  - substance P (dynorphin)
  - enkephalin

- Scaffolding proteins (receptor trafficking):
  - homer 1a
Acute administration

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Basal/challenge</th>
<th>Effect</th>
<th>Refs</th>
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<td>c-fos</td>
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<td>[17,27,28,89]</td>
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<tr>
<td>zif268</td>
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<td>[16,27,38]</td>
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<td>homer 1a</td>
<td>Challenge</td>
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<td>[16,38]</td>
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<tr>
<td>Substance P</td>
<td>Challenge</td>
<td>++++</td>
<td>[17]</td>
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<tr>
<td>Dynorphin</td>
<td>Challenge</td>
<td>(+)</td>
<td>[17]</td>
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<tr>
<td>Enkephalin</td>
<td>Challenge</td>
<td>0</td>
<td>[17]</td>
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<td>[18,35,36,45]</td>
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<td>Challenge</td>
<td>+</td>
<td>[36,41]</td>
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Yano and Steiner, Trends Pharmacol. Sci., 2007

Methylphenidate ≠ Cocaine → 5HT?
Concern for addiction liability?

Gene induction

Behavioral effects
- Antidepressant, among the first-line treatments for depressive disorders (Prozac®)
**METHODS**

- **Treatment:**

  - Adolescent rats (5 weeks old)

  - Single i.p. injection of
    - Vehicle
    - MP (2 or 5 mg/kg)
    - FLX (5 mg/kg)
    - MP + FLX combination (n=5-7)

- **In Situ Hybridization Histochemistry:**

  Gene expression in corticostriatal circuits

  - IEGs

  (marker of cellular activity + role in neuroplasticity)
Parallel anatomical loops that arise in the cortex, project in a topographical manner to the striatum and come back to the cortex.
Measurement of gene regulation in 23 striatal sectors mainly defined by their cortical input.

- Distributed in 3 rostrocodal levels of the striatum
- These sectors reflect specific corticostriatal loops.
FLX potentiates MP-induced IEG regulation in the striatum

Van Waes et al., EJN 2010
Steiner et al., Biol. Psychiatry, 2010
FLX potentiates MP-induced IEG regulation in the striatum

Van Waes et al., EJN 2010
Steiner et al., Biol. Psychiatry, 2010
- **Dorsolateral striatum**: Sectors that receive sensorimotor cortical inputs (habit formation/compulsive behaviors)

- **Nucleus accumbens**: medial core + lateral shell (reward processing)
Generalization to other SSRIs (e.g.: citalopram)

**zif 268 expression**

Middle level

Van Waes et al., EJN 2010
What is the striatal cell type affected?

- The striatum has 2 output pathways
• **Treatment:**

- Adolescent rats (5 weeks old)

- Single i.p. injection of
  - Vehicle
  - MP (2 or 5 mg/kg)
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  - MP + FLX combination (n=5-7)

• **In Situ Hybridization Histochemistry:**

Gene expression in corticostriatal circuits

- Neuropeptides: SP, DYN, ENK (cell type markers)
Neuropeptide induction

What striatal cell type is affected?

- Direct striatal output pathway
- Indirect striatal output pathway

Van Waes et al., JNC 2012
Neuropeptide induction

What striatal cell type is affected?

- Direct striatal output pathway

Role in addiction

SP & DYN

basal  |  rostral  |  middle  |  caudal

MP  |  POT5  |  POT5  |  MP+FLX
**DYN : Dysphoria during drug withdrawal**

- Reward system $\rightarrow$ release of DA
- DYN acts through a negative feedback mechanism to limit DA release $\rightarrow$ implication in addiction

Adapted from McClung et al., PNAS 2004
Behavioral correlate?
Behavioral correlates of the SSRI-potentiated striatal gene regulation in the sensorimotor part of the striatum

Steiner et al., Biol. Psychiatry 2010
Addiction liability?
MP + FLX triggers reinstatement of cocaine seeking behavior

- Periadolescent rats were allowed to self administer cocaine (600 µg/100µl/kg/infusion, i.v.) by nose poking
- 2h daily sessions
1) FLX potentiates IEGs and neuropeptides induction by MP in brain areas associated with addiction.

2) FLX potentiates motor stereotypies induced by MP, which are thought to reflect dysfunction in sensorimotor striatal circuits.

3) MP + FLX combination triggers robust reinstatement of cocaine seeking in the cocaine self-administration model

**SUMMARY and CONCLUSION**

Suggest that SSRI antidepressants may potentiate the addiction liability of methylphenidate
1/ Comorbidity ADHD and anxiety/depression

Patients with ADHD, under MP, are also often treated with SSRIs.

2/ MP used as an adjunct to improve the effects of SSRIs

Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series

Stoll AL, Pillay SS, Diamond L, Workum SB, Cole JO
Psycho-pharmacology Unit, Division of Psychiatry,
Brigham and Women's Hospital, Boston, MA 02115, USA.
J Clin Psychiatry 1996 Feb; 57(2):72-6

3/ Uncontrolled co-administration

Patients on SSRI using methylphenidate as cognitive enhancer
Acknowledgments

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- Pr Heinz Steiner
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