18-MC Data Slides

Non-confidential

Version: October 21, 2013
Coronaridine Congeners

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>$\mathbf{R_1}$</th>
<th>$\mathbf{R_2}$</th>
<th>$\mathbf{R_3}$</th>
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</thead>
<tbody>
<tr>
<td>18-Methoxycoronaridine</td>
<td>H</td>
<td>CO$_2$CH$_3$</td>
<td>OCH$_3$</td>
</tr>
<tr>
<td>18-Ethoxycoronaridine</td>
<td>H</td>
<td>CO$_2$CH$_3$</td>
<td>OC$_2$H$_5$</td>
</tr>
<tr>
<td>Coronaridine</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>
18-MC Animal Studies

- 18-MC is effective in reducing drug self-administration in established animal studies
  - Opioid, nicotine, methamphetamine, cocaine, alcohol, sucrose rich diet, fat rich diet
- 18-MC is effective in reducing symptoms of drug withdrawal
  - Teeth chattering, wet dog shakes, diarrhea, grooming, burying
- 18-MC is effective in reducing craving
Drug Self-administration
The ideal treatment will not affect responding for a non-drug reinforcer (e.g., water, food, sucrose).

The ideal treatment will depress responding for a drug of abuse.
Effects of 18-MC on Responding for Morphine, Cocaine and Water

18-MC selectively decreases morphine and cocaine self-administration.
18-MC selectively decreases methamphetamine and nicotine self-administration.
Effects of 18-MC on Alcohol Intake

18-MC decreases alcohol intake at doses that do not affect food intake.

18-MC reduces the efficacy of morphine by producing a significant downward shift in the dose-response curve for morphine self-administration.
A Single Dose Of 18-MC

- 18-MC decreases morphine self-administration for 48 hours.
- 18-MC decreases cocaine self-administration for 24 hours.

**Morphine Infusions/hour**

- **Test Session**: BASE, Day 1, Day 2, Day 3, Day 6, Day 7
- **Graph**: Comparison of Morphine infusions between control and 18-MC (40mg/kg, i.p.) conditions.

**Cocaine Infusions/hour**

- **Test Session**: BASE, Day 1, Day 2, Day 3, Day 6, Day 7
- **Graph**: Comparison of Cocaine infusions between control and 18-MC (40mg/kg, i.p.) conditions.

Legend:
- **Control**
- **18-MC (40mg/kg, i.p.)**
Opioid Withdrawal

- Morphine
  - Weight loss
  - Wet dog shakes
  - Flinching
  - Teeth chattering
  - Grooming
  - Burying
  - Diarrhea

- Naltrexone
  - 7 days

- Morphine
  - Weight loss
  - Wet dog shakes
  - Flinching
  - Teeth chattering
  - Grooming
  - Burying
  - Diarrhea

- Naltrexone
  - 7 days
Effects of 18-MC on Opioid Withdrawal Signs

18-MC reduces the intensity of several signs of morphine withdrawal.
18-MC may be a potential treatment for obesity
Effect Of 18-MC On Consumption Of Sucrose

18-MC decreases sucrose intake but not water intake (*p<0.02-0.01)
Effect of 18-MC on Sucrose-induced Weight Gain

18-MC (20 mg/kg for 14 days) blocks the development of sucrose-induced obesity (*p<0.05-0.001)
Effect Of 18-MC on Fat-induced Weight Gain

HF Diet
- VEH (n=6)
- 18-MC (n=6)

LF Diet

Time, days

Weight, g

(20 Mg/Kg, I.P.)
Effect of Repeated Administration of 18-MC on Body Fat Depots

On the eighth day after the last injection of 18-MC, animals were euthanized, and necropsies were performed to remove periovarian, perirenal and inguinal fat pads.

(20 Mg/Kg I.P. For 14 Days)
What is the Mechanism of Action of 18-MC?

18-MC interacts with the “reward pathways”

PFC = prefrontal cortex
NAC = nucleus accumbens
VTA = ventral tegmental area

Dopaminergic neurons
In Vivo Microdialysis
Acute cocaine increases dopamine release in the nucleus accumbens.
After chronic cocaine administration, much more dopamine is released in the nucleus accumbens. This is called sensitization.
18-MC abolishes the sensitization of cocaine-induced dopamine release.
18-MC, administered 19 hours beforehand, abolishes nicotine-induced dopamine release in the nucleus accumbens.
Movement of positive ions from the outside to the inside of the cell is an INWARD current and is shown as a DOWNWARD deflection.

This is due to receptor desensitization.
Recent studies have demonstrated a link between polymorphisms in the \( \alpha_3 \) and \( \beta_4 \) region of chromosome 15 and smoking addiction.

18-MC blocks the nAch receptor currents in cells co-transfected with rat \( \alpha_3 \) and \( \beta_4 \) receptor subunits.
18-MC does not Interact with α4β2 Nicotinic Receptors

• 18-MC does not block the nAch receptor currents in cells co-transfected with rat α4 and β2 receptor subunits.
### 18-MC Off Target Effects

#### 18-MC binding affinities (Ki in μM)

<table>
<thead>
<tr>
<th>Target</th>
<th>18-MC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa opioid</td>
<td>5.1 ± 0.50</td>
</tr>
<tr>
<td>Mu opioid</td>
<td>1.1 ± 0.30</td>
</tr>
<tr>
<td>Delta opioid</td>
<td>3.5 ± 0.05</td>
</tr>
<tr>
<td>Nociceptin</td>
<td>&gt;100</td>
</tr>
<tr>
<td>NMDA</td>
<td>&gt;100</td>
</tr>
<tr>
<td>D1</td>
<td>&gt;100</td>
</tr>
<tr>
<td>D2</td>
<td>16 ± 0.60</td>
</tr>
<tr>
<td>D3</td>
<td>25 ± 2.5</td>
</tr>
<tr>
<td>M1</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>M2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>5-HT1A</td>
<td>46 ± 4.9</td>
</tr>
<tr>
<td>5-HT1B</td>
<td>&gt;100</td>
</tr>
<tr>
<td>5-HT1C</td>
<td>&gt;100</td>
</tr>
<tr>
<td>5-HT1D</td>
<td>&gt;10</td>
</tr>
<tr>
<td>5-HT2A</td>
<td>40 ± 3.4</td>
</tr>
<tr>
<td>5-HT2C</td>
<td>&gt;100</td>
</tr>
<tr>
<td>5-HT3</td>
<td>3.8 ± 0.067</td>
</tr>
<tr>
<td>Sodium channel</td>
<td>6.4 ± 0.68</td>
</tr>
<tr>
<td>Sigma 1</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Sigma 2</td>
<td>13 ± 1.2</td>
</tr>
<tr>
<td>GABA B</td>
<td>&gt;100</td>
</tr>
<tr>
<td>NE uptake</td>
<td>&gt;10</td>
</tr>
<tr>
<td>5-HT uptake</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

- **18-MC has no affinity for NMDA receptors.**
- **18-MC has very low affinity for sigma receptors.**
- **18-MC has no affinity for 5-HT uptake sites.**
Where Are α3β4 Nicotinic Receptors Located?

What is the mechanism of action of 18-MC?

18-MC may interact with the “reward pathways”.

PFC = prefrontal cortex
NAC = nucleus accumbens
VTA = ventral tegmental area

dopaminergic neurons
Target Validation Papers

18-MC has no cerebellar toxicity

Ibogaine at very high doses damages Purkinje cells.

18-MC at very high doses does not produce any Purkinje cell damage.

IBOGAINE

18-MC

One month after 3x100mg/kg, i.p.
18-MC (200 mg/kg, ip) has no apparent effects on heart rate and blood pressure.

Ibogaine (200 mg/kg, ip) decreases heart rate without altering blood pressure.
Ibogaine, but not 18-MC, increases extracellular serotonin levels in the nucleus accumbens.
18-MC itself is not reinforcing

- Saline
- Cocaine (0.4 mg/kg infusion)
- 18-MC (0.8 mg/kg infusion)
18-MC blocks musical cue-induced reinstatement in rats