Receptors, Pharmacology, and Medical Management of Addiction

Frank J. Vocci, Ph.D.
Friends Research Institute
Disclosures

- I have performed consultant work for the following companies: Catalyst Pharmaceutical Partners, Purdue Pharma, Reckitt Benckiser, Roxane Laboratories, Teva Pharmaceuticals, and US World Meds.

All consulting fees go to Friends Research Institute, Inc.
Opiate Receptors

- Mu, Kappa, delta, and ORL-1 receptors
- Belong to a superfamiliy of 7 transmembrane spanning G-Protein coupled receptors
- Interact with second messenger systems; e.g. adenylate cyclase
- Have recently added the ORL-1 or nociceptin receptor to the family
Collateral Efficacy
Collateral Efficacy
New Interpretation of the Pharmacology of Buprenorphine

• Buprenorphine is a partial agonist at mu opiate receptor and a kappa receptor antagonist
• Buprenorphine also is a full agonist at ORL-1 or nociceptin receptors (Wnendt et al, 1999)
• Buprenorphine produces a bell-shaped dose effect curve for analgesia
• Is this due to its partial agonist effect or a mu-ORL-1 interaction?
Effects of Buprenorphine Maintenance Dose on μ-Opioid Receptor Availability

Specific Binding of [18F] cyclofoxy

Source: Kling et al., JPET,
Stimulation of MAP Kinase through Mu and ORL-1 Receptors in CHO Cells (Lufty et al, 2003)
Buprenorphine antinociception in Mu and ORL-1 KO mice
Buprenorphine antinociception - effect of an ORL-1 antagonist

% MPE

WT-V  WT-J  KO-V  KO-J

Buprenorphine (0.3 mg/kg, s.c.)
Antagonism of the Bell-Shaped Curve of Buprenorphine by J-113397 (ORL-1 antagonist)
Buprenorphine and ORL-1 Agonism

- The auto-antagonistic activity of the analgesic effect of buprenorphine is due to its ORL-1 agonist effect.
- Given that opiate dependence is treated with supra-analgesic doses it’s safe to assume that ORL-1 agonism occurs when doses of 2 to 24 mg are given.
- It's currently not known whether ORL-1 antagonizes buprenorphine-induced respiratory depression.
- Combining buprenorphine with an ORL-1 antagonist or synthesizing buprenorphine analogs that lack ORL-1 agonism should increase buprenorphine’s analgesic activity but the effect on respiratory depression and physical dependence capacity are not known.
Induction of opioid dependence is not a concern because *mu*-opioid receptors are blocked by naltrexone.

How does bup/naltrexone differ from naltrexone alone?

1) Increased *kappa*-opioid receptor antagonism
2) ORL-1 receptor (NOP receptor) activation
<table>
<thead>
<tr>
<th>Ki or IC$_{50}$ (nM)</th>
<th>mu-opioid</th>
<th>kappa-opioid</th>
<th>ORL-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>1.5</td>
<td>0.8</td>
<td>8.4</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>0.2</td>
<td>0.4</td>
<td>5,200</td>
</tr>
</tbody>
</table>

Smooth muscle pA$_2$:
- 9.2
- 8.1
Naltrexone and buprenorphine combination in the treatment of opioid dependence

“Buprenorphine Rapid Opioid Detoxification”

Day 1: Bup (s.l.) 2 mg, 4x/day
Day 2: Bup (s.l.) 2 mg 3x/day + naloxone 0.04 mg (i.v.) 10x/day
Day 3: Bup (s.l.) 2 mg 2x/day + naloxone 0.4 mg (i.v.)
Day 4: Bup (s.l.) 4 mg + naltrexone (p.o.) 10 mg

Group A
50 mg naltrexone (p.o.)
(daily, Mon – Sat)

Group B
50 mg naltrexone (p.o.)
+ 4 mg buprenorphine (s.l.)
(daily, Mon – Sat)
Naltrexone and buprenorphine combination in the treatment of opioid dependence
Naltrexone and buprenorphine combination in the treatment of opioid dependence

Rates (%) of Positive Urines for Morphine

- **Naltrexone only**: 100% (Week 1), 33.33% (Week 4), 25% (Week 12)
- **Naltrexone & buprenorphine**: 100% (Week 1), 18.18% (Week 4), 4.45% (Week 12)
Naltrexone and buprenorphine combination in the treatment of opioid dependence

Rates (%) of Positive Urines for Cocaine Metabolites
Gerra et al.

Naltrexone only

Naltrexone & buprenorphine

- Irritability
- Depression
- Tiredness
- Psychosomatic symptoms

Baseline
12 week

Group A

Group B
Buprenorphine Reduces Alcohol Drinking Through Activation of the Nociceptin/Orphanin FQ-NOP Receptor System

Roberto Ciccocioppo, Daina Economidou, Roberto Rimondini, Wolfgang Sommer, Maurizio Massi, and Markus Heilig

**Background:** Activation of the NOP receptor by its endogenous ligand nociceptin/orphanin FQ reduces ethanol intake in genetically selected alcohol preferring Marchigian Sardinian alcohol preferring (msP) rats. Here we evaluated whether buprenorphine, a partial agonist at µ-opioid and NOP receptors, would reduce ethanol consumption in msP rats via activation of NOP receptors.

**Methods:** Marchigian Sardinian alcohol preferring rats trained to drink 10% alcohol 2 hours/day were injected with buprenorphine (0.3, 3.0, or 6.0 mg/kg intraperitoneally [IP]) 90 min before access to ethanol.

**Results:** Similar to prototypical µ-agonists, the two lowest doses of buprenorphine significantly increased ethanol consumption (p < .01); in contrast, the two highest doses reduced it (p < .05). Pretreatment with naltrexone (.25 mg/kg IP) prevented the increase of ethanol intake induced by .03 mg/kg of buprenorphine (p < .001) but did not affect the inhibition of ethanol drinking induced by 3.0 mg/kg of buprenorphine. Conversely, pretreatment with the selective NOP receptor antagonist UFP-101 (10.0 or 20.0 µg/rat) abolished the suppression of ethanol drinking by 3.0 mg/kg of buprenorphine.

**Conclusions:** Buprenorphine has dualistic effects on ethanol drinking; low doses increase alcohol intake via stimulation of classic opioid receptors, whereas higher doses reduce it via activation of NOP receptors. We suggest that NOP agonistic properties of buprenorphine might be useful in the treatment of alcoholism.

**Key Words:** Buprenorphine, nociceptin/orphanin FQ, alcohol abuse, addiction

Buprenorphine has long been in clinical use for treatment of moderate-to-severe pain (Finco et al. 1995; Gundersen et al. 1986; Hayes et al. 1979; Maunuksela et al. 1998; Murphy and MacEvilly 1984; Picard et al. 1997; Vanacker et al. 1986). More recently, evidence has accumulated in support of its efficacy for maintenance treatment of heroin dependence (Johnson and McCagh 2000; Kakko et al. 2003; Ling et al. 1996, 1998; Litten and Allen 1990; Mello et al. 1993), and the drug has been receptors (Cowan et al. 1977; Leader 1987; Negus et al. 2002; Pick et al. 1997; Rovati et al. 1987; Sadee et al. 1982; Tyers 1980). In an unexpected development, it has recently been realized that buprenorphine is also agonist/partial agonist at the NOP nociceptin/orphanin FQ (N/OFQ) receptors (Bloms-Funke et al. 2000; Lutfy et al. 2003; Wnendt et al. 1999; Huang et al. 2001).

As a result of the aforementioned agonist/antagonist opiodergic properties, and principally owing to the partial stimulation of the µ-opioid receptor, buprenorphine induces most of the known opioid effects like pain relief, feelings of wellbeing and pleasure, respiratory depression, and so forth, but with less
Nociceptin prevents stress-induced ethanol- but not cocaine-seeking behavior in rats

Rémi Martin-Fardon, CA Roberto Ciccocioppo, MA Maurizio Massi and Friedbert Weiss

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Received 14 March 2000; accepted 5 April 2000

This study examined whether nociceptin/orphanin FQ (NC), the endogenous ligand of the opioid receptor-like1 (ORL1) receptor, can block drug-seeking behavior induced by footshock stress. Male Wistar rats were trained to operantly self-administer ethanol or cocaine, and then subjected to daily extinction training until responding ceased. Subsequent exposure to 15 min of intermittent footshock elicited robust reinstatement of responding at the previously drug-paired lever. NC (0.1–2.0 μg, i.c.v.) significantly inhibited the effects of footshock stress on ethanol- but not cocaine-seeking behavior. The results support the hypothesis that the NC system participates in the regulation of behavioral responses to stress, and that drugs interacting with NC receptors may have therapeutic potential for the treatment of stress-induced alcohol-seeking behavior and relapse. NeuroReport 11:1939–1943 © 2000 Lippincott Williams & Wilkins.

Key words: Alcohol; Cocaine; Drug-seeking behavior; Footshock stress; Nociceptin; Orphanin FQ; Self-administration

INTRODUCTION

Nociceptin/orphanin FQ (NC), the endogenous ligand of the opioid receptor-like1 (ORL1) receptor, is a 17 amino acid neuropeptide structurally related to the opioid peptide
ORIGINAL INVESTIGATION

G. B. Varty · L. A. Hyde · R. A. Hodgson · S. X. Lu ·
M. F. McCool · T. M. Kazdoba · R. A. Del Vecchio ·
D. H. Guthrie · A. J. Pond · M. E. Grzelak · X. Xu ·
W. A. Korfmancher · D. Tulshian · E. M. Parker ·
G. A. Higgins

Characterization of the nociceptin receptor (ORL-1) agonist,
Ro64-6198, in tests of anxiety across multiple species

Received: 4 February 2005 / Accepted: 11 April 2005 / Published online: 15 July 2005
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Abstract Rationale: Previous studies have demonstrated behaviors indicative of anxiolysis in rats pretreated with the nociceptin receptor (opioid receptor like-1, ORL-1) agonist, Ro64-6198. Objectives: The aim of this study was to examine the effects of Ro64-6198 in anxiety models across three species: rat, guinea pig, and mouse. In addition, the receptor specificity of Ro64-6198 was studied, using the ORL-1 receptor antagonist, J-113397, and ORL-1 receptor knockout (KO) mice. Finally, neurological studies examined potential side effects of Ro64-6198 in the rat and mouse. Results: Ro64-6198 (3–10 mg/kg) increased punished responding in a rat conditioned lick suppression test similarly to chlordiazepoxide (6 mg/kg). This effect of Ro64-6198 was attenuated by J-113397 (10 mg/kg), but not the μ opioid antagonist, naltrixone (3 mg/kg). In addition, Ro64-6198 (1–5.6 mg/kg) was effective in both genotypes. In rats, Ro64-6198 reduced locomotor activity (LMA) and body temperature and impaired rotarod, beam walking, and fixed-ratio (FR) performance at doses of 10–30 mg/kg, i.e., three to ten times higher than an anxiolytic dose. In WT mice, Ro64-6198 (3–10 mg/kg) reduced LMA and rotarod performance, body temperature, and FR responding, but these same measures were unaffected in ORL-1 KO mice. Haloperidol (0.3–3 mg/kg) reduced these measures to a similar extent in both genotypes. These studies confirm the potent, ORL-1 receptor-mediated, anxiolytic-like effects of Ro64-6198, extending the findings across three species. Ro64-6198 has target-based side effects, although the magnitude of these effects varies across species.

Keywords Nociceptin · ORL-1 receptor · NOP receptor · Anxiety · Behavior · Rat · Guinea pig · Mouse
Nociceptin System as a Target for Treatment of Substance Abuse and Affective Disorders

• ORL-1 or nociceptin agonists may have a role in the treatment of cocaine dependence and alcohol dependence
• Nociceptin blocks stress responses and may reduce stress induced alcohol use
• Nociceptin agonists may also have anxiolytic effects
Kappa Receptors
Kappa Receptors and Stress

- Swim stress increases dynorphin (kappa agonist) (Land et al, 2008) and increases immobility in this test (McLaughlin et al, 2003)
- Behaviors associated with this stress are dysphoria and anxiety and depression-like behaviors (Carlezon et al, 1998; Beardsley et al, 2005)
- Dynorphin release during ETOH withdrawal may mediate the dysphoria-induces stimulation of ETOH self-administration (Walker and Koob, 2008)
Differential effects of the novel kappa opioid receptor antagonist, JDTic, on reinstatement of cocaine-seeking induced by footshock stressors vs cocaine primes and its antidepressant-like effects in rats

Received: 12 August 2005 / Accepted: 12 August 2005 / Published online: 24 September 2005
© Springer-Verlag 2005

Abstract Rationale: Stress and depression have been linked to relapse of cocaine abuse. Antagonism of the kappa opioid receptor (KOR) has been reported to attenuate some effects of stressors, and antagonism of the KOR has been reported to have antidepressant-like properties. Objectives: Our objective was to determine whether the potent and selective KOR antagonist, (3R)-7-hydroxy-N-{[(1S)-1-[[[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl]-1,2,3,4-tetrahydro-3-isoquinolincarboxamide (JDTic), can reduce the ability of a stressor (intermittent footshock) to reinstate cocaine-seeking behavior and to have antidepressant-like effects in the forced swim test (FST). Methods: Male Long–Evans hooded rats were trained to lever-press, reinforced with 0.5 mg/kg i.v. infusion of cocaine, according to fixed ratio 1 reinforcement schedules during daily 2-h experimental sessions (vehicle), 3, 10, and 30 mg/kg JDTic were then administered i.g. to separate groups of 12 rats. Twenty four hours later, the rats were given 15 min of intermittent footshock (0.87 mA, 0.5 s activation time, average interactivation interval of 40 s) or a 17-mg/kg i.p. administration of cocaine prime followed by a 2-h reinstatement test session. JDTic was also evaluated for its ability to block diuresis induced by the KOR agonist, U50,488H (10 mg/kg, s.c.), during 5-h test sessions beginning 1 h after footshock reinstatement tests to verify its KOR antagonist activity. In the FST, male Sprague–Dawley rats were treated with either nor-binaltorphimine (nor-BNI) or JDTic (both at 0.3, 1, 3, or 10 mg/kg, injected s.c. 23 h before), or desipramine (5.6, 10, or 17 mg/kg, injected i.p. 23, 5, and 1 h before) and placed in a cylinder of water, during which the predominance of immobility swimming and climbing...
Effects of JDTic (kappa-opioid antagonist) in a Rat Model of Stress-Induced Relapse to Cocaine

Beardsley et al 2005
JDTic, Nor BNI and Desipramine in the Swim Test
Pharmacological Evidence for a Motivational Role of $\kappa$-Opioid Systems in Ethanol Dependence

Brendan M Walker$^{*,1}$ and George F Koob$^1$

$^1$Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, La Jolla, CA, USA

The purpose of this study was to test the hypothesis that activation of the dynorphin-$\kappa$ (k)-opioid system has a role in the increased consumption of ethanol in dependent animals. The effects of three opioid receptor antagonists with different effects on opioid receptors, naltrexone, nalmefene, and nor-binaltorphimine (nor-BNI), were compared in their ability to decrease ethanol self-administration in nondependent and ethanol-dependent male Wistar rats. Nalmefene and naltrexone are both opioid receptor ligands with comparable molecular weights and pharmacokinetic profiles, but differing specificity for the three opioid receptor subtypes at low doses, while nor-BNI is a selective $\kappa$-opioid receptor antagonist. Dependence was induced in half the animals by subjecting them to a 4-week intermittent vapor exposure period in which animals were exposed to ethanol vapor for 14 h per day. Subsequent to dependence induction, nalmefene, naltrexone, and nor-BNI were tested for their ability to modulate self-administration of ethanol in vapor-exposed and control rats. The results indicated that both nalmefene and naltrexone induced a significant dose-dependent decrease in the number of lever presses for ethanol in both groups of animals. However, in ethanol-dependent animals, nalmefene was significantly more effective in suppressing ethanol intake than naltrexone. Nor-BNI selectively attenuated ethanol-dependent self-administration while leaving nondependent ethanol self-administration intact. Because naltrexone is primarily selective for the $\mu$-opioid receptor, and nalmefene is primarily selective for the $\mu$- and $\kappa$-opioid receptor subtypes, the fact that nalmefene demonstrates more suppression in dependent animals suggests that opioid systems distinct from the $\mu$-regulated portion may be involved in the increased drinking seen during withdrawal in dependent animals. The results with nor-BNI confirm that $\kappa$-opioid receptor antagonism selectively decreases dependence-induced ethanol self-administration, which supports the hypothesis that dynorphin/$\kappa$-opioid systems are dysregulated in dependence and contribute to the increased drinking seen during acute withdrawal in dependent rats.

Neuropsychopharmacology (2008) 33, 643–652; doi:10.1038/sj.npp.1301438; published online 2 May 2007
NorBNI (Kappa Antagonist) and Ethanol Self-Administration
Kappa Receptor Antagonists

• NorBNI and JDTic have long durations of action … several weeks in rats
• The duration is not attributed to irreversible or pseudo-irreversible binding
• Intracellular mechanisms proposed:
  – High affinity association between a JNK substrate and the KOR that blocks G protein association
  – Linker scaffolding protein required for KOR and its effectors… if the linker protein is inactivated by JNK then coupling between KOR and its effectors would be disrupted (Bruchas et al, 2007)
Anxiolytic-Like Effects of κ-Opioid Receptor Antagonists in Models of Unlearned and Learned Fear in Rats


Behavioral Genetics Laboratory, Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont, MA 02478 (ATK, EGM, WAC)

and

Research Triangle Institute, Organic and Medicinal Chemistry, Research Triangle Park, NC 27709 (JBT, FIC)
Effects of JDTic on Behavior in Elevated Plus Maze

C. JDTic

- Percent Time in Open Arms [open/(open + closed)]
- Drug Dose (mg/kg; IP): VEH 1.0, 3.0, 10

D. JDTic

- Open Arm Entries
- Drug Dose (mg/kg; IP): VEH 1.0, 3.0, 10

** indicates statistically significant difference.
Kappa Receptor Antagonists

- May have a role in inhibiting stress-induced relapse to cocaine and alcohol seeking
- May have antidepressant properties
- Have long durations of action
- JDTic is being developed as a potential treatment for cocaine dependence under a NIDA grant
Mu-Delta Heterodimers

- Mu and delta receptors exist on the same neuron
- Mu and delta receptors form heterodimers that have pharmacological properties
- Mu agonist and delta agonist combination produced increased antinociception
- Mu agonist and delta antagonist combinations reduced tolerance and physical dependence
Mu-Delta Heterodimers Gomes et al. 2000

Graphs showing binding curves for \( \mu - \delta \) and \( \mu \) receptors in SKNSH cells with and without TIPPP\(\Psi\) and DPDPE.
Mu-Delta Heterodimers

**Graph A:**
- **μ-δ**
  - Control vs. +CTOP
  - Binding curves for binding of 3H-Deltorphin II and pMAPK/Tubulin

**Graph B:**
- **Control** vs. ligands (10 nM DAMGO, 10 nM TIPPP, 10 nM DAMGO + TIPPP, +Delt II, +Delt II + CTOP)
- Western blot images for Tubulin and pMAPK

**EC50 Values:**
- **Ligand**
  - DAMGO 4.5 ± 1.5
  - TIPPP 0.8 ± 0.4
  - Delt II 0.05 ± 0.03
- **Ligand**
  - Delt II 3.8 ± 1.5
  - CTOP 1.4 ± 0.5
Mu-Delta Bivalent Ligands
Daniels et al 2005

• A bivalent series of mu agonist- delta antagonists was synthesized that contained different spacer lengths
• Series was evaluated for analgesia, tolerance and physical dependence
• Mu agonist = Oxymorphone
• Delta antagonist = NTI
Mu-Delta Bivalent Ligands

3 - 8, MDAN Series

9 - 13, MA Series

9 (MA-16), n = 2
10(MA-17), n = 3
11(MA-19), n = 5
12(MA-20), n = 6
13(MA-21), n = 7

14, DN-20
## Mu-Delta Ligands

### Table 1. Acute antinociceptive activity of the $\mu$-$\delta$ bivalent ligands and $\mu$ monovalent ligands in the mouse tail-flick assay after i.c.v. administration

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Spacer length,* Å</th>
<th>ED$_{50}$, † nmol (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (MDAN-16)</td>
<td>19.1</td>
<td>1.79 (1.54–2.04)</td>
</tr>
<tr>
<td>4 (MDAN-17)</td>
<td>20.4</td>
<td>1.49 (1.04–1.95)</td>
</tr>
<tr>
<td>5 (MDAN-18)</td>
<td>21.6</td>
<td>0.95 (0.68–1.23)</td>
</tr>
<tr>
<td>6 (MDAN-19)</td>
<td>22.9</td>
<td>0.43 (0.36–0.50)</td>
</tr>
<tr>
<td>7 (MDAN-20)</td>
<td>24.1</td>
<td>0.17 (0.15–0.19)</td>
</tr>
<tr>
<td>8 (MDAN-21)</td>
<td>25.4</td>
<td>0.08 (0.06–0.10)</td>
</tr>
<tr>
<td>9 (MA-16)</td>
<td>19.1</td>
<td>0.039 (0.032–0.046)</td>
</tr>
<tr>
<td>10 (MA-17)</td>
<td>20.4</td>
<td>0.040 (0.033–0.046)</td>
</tr>
<tr>
<td>11 (MA-19)</td>
<td>22.9</td>
<td>0.040 (0.023–0.050)</td>
</tr>
<tr>
<td>12 (MA-20)</td>
<td>24.1</td>
<td>0.037 (0.029–0.045)</td>
</tr>
<tr>
<td>13 (MA-21)</td>
<td>25.4</td>
<td>0.044 (0.039–0.048)</td>
</tr>
<tr>
<td>11 and 14 (MA-19 and DN-20)</td>
<td></td>
<td>0.037 (0.031–0.043)</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td></td>
<td>0.043 (0.034–0.052)</td>
</tr>
</tbody>
</table>

*Spacer length represents the maximum linear distance between the pharmacophores.
# Development of Tolerance and Physical Dependence

<table>
<thead>
<tr>
<th>Ligand</th>
<th>ED$_{50}$, nmol (95% C.I.)</th>
<th>Ligand ED$<em>{50}$/saline ED$</em>{50}$*</th>
<th>No. of jumps (S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>i.c.v. saline</td>
<td>i.c.v. ligand</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>4.54 (3.51–5.56)</td>
<td>26.80 (20.82–32.78)</td>
<td>6.0</td>
</tr>
<tr>
<td>3 (MDAN-16)</td>
<td>1.62 (1.35–1.89)</td>
<td>4.72 (3.47–5.91)</td>
<td>2.8</td>
</tr>
<tr>
<td>4 (MDAN-17)</td>
<td>1.54 (0.89–2.20)</td>
<td>5.61 (4.39–6.83)</td>
<td>3.6</td>
</tr>
<tr>
<td>5 (MDAN-18)</td>
<td>1.29 (0.97–1.61)</td>
<td>4.75 (3.50–6.00)</td>
<td>3.7</td>
</tr>
<tr>
<td>6 (MDAN-19)</td>
<td>0.42 (0.37–0.47)</td>
<td>0.40 (0.33–0.47)</td>
<td>1.0</td>
</tr>
<tr>
<td>7 (MDAN-20)</td>
<td>0.17 (0.15–0.20)</td>
<td>0.17 (0.13–0.21)</td>
<td>1.0</td>
</tr>
<tr>
<td>8 (MDAN-21)</td>
<td>0.10 (0.09–0.11)</td>
<td>0.10 (0.09–0.11)</td>
<td>1.0</td>
</tr>
<tr>
<td>11 (MA-19)</td>
<td>0.04 (0.03–0.05)</td>
<td>0.22 (0.19–0.26)</td>
<td>5.5</td>
</tr>
<tr>
<td>11 and 15 (MA-19 and DN-20)</td>
<td>0.04 (0.02–0.05)</td>
<td>0.33 (0.28–0.37)</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Saline or the indicated ligand were infused i.c.v. for 3 days via osmotic minipump. On day 4, naloxone (1 mg/kg, s.c.) was administered and the number of jumps was counted. The minipump was removed, and 4 h later, ligands were administered i.c.v. and antinociceptive ED$_{50}$ values were determined.

*Ligand ED$_{50}$/saline ED$_{50}$ ratio is an indicator of fold tolerance development.*
### Table 4. Comparison of i.v. to i.c.v. administration potencies for MDAN-21, MA-19, and morphine

<table>
<thead>
<tr>
<th>Ligand</th>
<th>i.c.v. ED$_{50}$, nmol</th>
<th>i.v. ED$_{50}$, nmol</th>
<th>i.v./i.c.v. ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% C.I.)</td>
<td>(95% C.I.)</td>
<td></td>
</tr>
<tr>
<td>8 (MDAN-21)</td>
<td>0.08 (0.06–0.10)</td>
<td>3.3 (3.0–3.6)</td>
<td>41.3</td>
</tr>
<tr>
<td>11 (MA-19)</td>
<td>0.04 (0.03–0.05)</td>
<td>1.61 (1.29–1.92)</td>
<td>40.3</td>
</tr>
<tr>
<td>Morphine</td>
<td>4.1 (3.7–4.8)</td>
<td>168 (146–178)</td>
<td>41.0</td>
</tr>
</tbody>
</table>
Mu-Delta Heterodimer Ligands

- Can be equipotent to morphine by the parenteral route
- Can lack tolerance and physical dependence
- May be an advance over other opioid analgesics
- Could have a role in treatment of opioid dependence
Summary

• A review of mu, delta, kappa, and nociceptin systems has revealed new directions in the development of analgesics, and new treatment approaches for substance abuse and affective disorders, including possible treatment of comorbid conditions.

• The ORL-1 or nociceptin system has a role in the pharmacology of buprenorphine and nociceptin agonists may have a future role in the treatment of alcohol and cocaine use disorders as well as anxiety disorders.

• Bup/Naltrexone is a current approach for the treatment of combined opiate-cocaine dependence and may be an approach for the treatment of cocaine dependence in the future.

• The kappa system is involved in stress responses and may have a role in the treatment of stress-induced relapse to cocaine and alcohol and also affective disorders.

• Mu-Delta heterodimers potentiate the effects of mu agonists, combined mu-delta heterodimer ligands are new targets for analgesia that may be devoid of tolerance and physical dependence and should be evaluated as treatments for opioid dependence.
Effects of Non-selective Narcotic Antagonists on Amphetamine Effects

- Blockade of mu, kappa, and delta receptors by naloxone and naltrexone
- Preclinical and clinical data implicate the endogenous opioid system in the effects of amphetamine
Naloxone Modulation of Amphetamine Behaviors - Hitzemann et al, 1982

Fig. 1. Effect of naloxone on d-amphetamine-induced increases in rearing activity. Animals were pretreated with various doses of naloxone (0.3–10.0 mg/kg, s.c.) 5 min prior to the injection of 1 mg/kg (s.c.) of d-amphetamine. Rearing, ambulation and stereotyped behavior were measured for 5 min trials at 30, 60, 120 and 180 min after administration of d-amphetamine in the open field apparatus de-
Naloxone’s Effects on Amphetamine-induced DA Release

<table>
<thead>
<tr>
<th>Group</th>
<th>Brain region</th>
<th>DA (µg/g)</th>
<th>DOPAC (µg/g)</th>
<th>DA/DOPAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline–saline</td>
<td>CN</td>
<td>14.9 ± 1.6</td>
<td>0.8 ± 0.1</td>
<td>19.1 ± 2.1</td>
</tr>
<tr>
<td>Saline–amphetamine</td>
<td>CN</td>
<td>21.6 ± 1.4†</td>
<td>0.3 ± 0.1†</td>
<td>63.7 ± 3.5†</td>
</tr>
<tr>
<td>Naloxone–saline</td>
<td>CN</td>
<td>16.6 ± 0.2</td>
<td>0.6 ± 0.1</td>
<td>26.0 ± 1.7</td>
</tr>
<tr>
<td>Naloxone–amphetamine</td>
<td>CN</td>
<td>10.9 ± 1.0‡§</td>
<td>0.9 ± 0.1‡</td>
<td>12.8 ± 1.8‡§</td>
</tr>
<tr>
<td>Saline–saline</td>
<td>NA</td>
<td>8.6 ± 0.2</td>
<td>0.7 ± 0.1</td>
<td>12.4 ± 1.5</td>
</tr>
<tr>
<td>Saline–amphetamine</td>
<td>NA</td>
<td>14.1 ± 1.7†</td>
<td>0.6 ± 0.1</td>
<td>23.0 ± 3.5†</td>
</tr>
<tr>
<td>Naloxone–saline</td>
<td>NA</td>
<td>9.4 ± 0.9</td>
<td>0.4 ± 0.1</td>
<td>20.9 ± 5.1</td>
</tr>
<tr>
<td>Naloxone–amphetamine</td>
<td>NA</td>
<td>9.7 ± 0.9‡</td>
<td>0.6 ± 0.1</td>
<td>16.4 ± 1.1‡</td>
</tr>
</tbody>
</table>

* Animals were given naloxone (s.c.) 5 min prior to the administration of d-amphetamine, (s.c.). The animals were sacrificed 30 min later, the caudate nucleus (CN) and nucleus accumbens (NA) were isolated and the levels of DA and DOPAC were determined using an HPLC–EC technique (Westernik and Mulder, 1981). Data are the mean ± S.E. N = 4–6 animals/group.

† Significantly different from saline–saline, P > 0.05.
‡ Significantly different from saline–amphetamine, P > 0.05.
§ Significantly different from naloxone–saline, P > 0.05.
Amphetamine-Naltrexone interactions

![Graph showing Locomotion and Rearing behaviors](image-url)
Naltrexone and Amphetamine-Primed Reinstatement

![Graph showing the number of leverpresses during self-administration, extinction, and various treatments. The treatments include NaCl, 0.3 NTX, 1.0 NTX, 3.0 NTX, and an inactive lever. The graph indicates a significant increase in leverpresses with 3.0 NTX compared to other treatments.](image-url)
Amphetamine-Naltrexone Interactions in Healthy Volunteers
Jayaram-Lindstrom et al, 2004

• Effects of an oral dose of 30 mg of dexamphetamine given to 12 healthy volunteers in the presence and absence of 50 mg of naltrexone
• Study was double-blind and placebo controlled
Amphetamine-Naltrexone Interactions in Healthy Volunteers
Jayaram-Lindstrom et al, 2004

• VAS Scores of Subjective “High”
Amphetamine-Naltrexone Interactions in Healthy Volunteers

Jayaram-Lindstrom et al, 2004
Amphetamine-Naltrexone Interactions in Amphetamine Dependent Patients
Jayaram-Lindstrom et al, 2007
Amphetamine-Naltrexone Interactions in Amphetamine Dependent Patients
Jayaram-Lindstrom et al, 2007
Amphetamine-Naltrexone Interactions in Amphetamine Dependent Patients
Jayaram-Lindstrom et al, 2007

- Mean Craving Scores
An Open Clinical Trial of Naltrexone for Amphetamine Dependence – Jayaram-Lindstrom et al, 2005

- 20 amphetamine dependent patients were recruited and placed on 50 mg per day of naltrexone
- 11 of 20 patients were considered compliant
- Compliant patients were more likely to complete Tx (77 versus 22%) and more likely to use less amphetamine than non-compliant subjects
Randomized, Placebo-Controlled Trial of Naltrexone for the Treatment of Amphetamine Dependence

Randomized, Placebo-Controlled Trial of Naltrexone for the Treatment of Amphetamine Dependence

- Subjects had to become abstinent in the baseline period
- Failure to become abstinent was grounds for exclusion
- 70% of the enrollees were IV users with an average of 10 years of amphetamine use
- Relapse-prevention design- All subjects received a manualized relapse-prevention therapy
- Urine samples were collected twice a week
- Positive urine samples were confirmed by an LCMS method
Randomized, Placebo-Controlled Trial of Naltrexone for the Treatment of Amphetamine Dependence

FIGURE 4. Survival Curves Representing Continuous Rates of Abstinence for the Naltrexone and Placebo Groups During the 12-Week Trial (Intention-to-Treat Analysis)
Amphetamine- Narcotic Antagonists Interactions

• Naloxone affects rearing and CPP
• Naltrexone affects rearing and amphetamine-induced priming of reinstatement
• Naltrexone block subjective effects of amphetamine in healthy volunteers and amphetamine users
• Naltrexone reduced amphetamine use in an open-label and a double blind trial
• More research is warranted by these findings