No Pain, Big Gain:
Truncated G-protein Coupled Receptors and New Targets for Opiate Action

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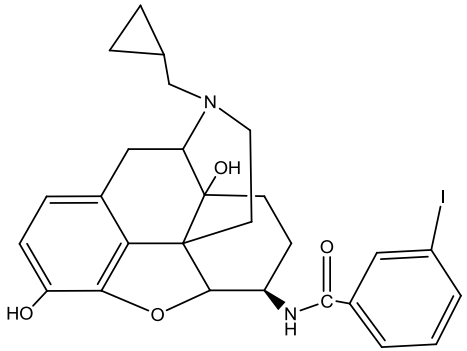
3-Iodobenzoyl-6β-naltrexamide (IBNtxA)



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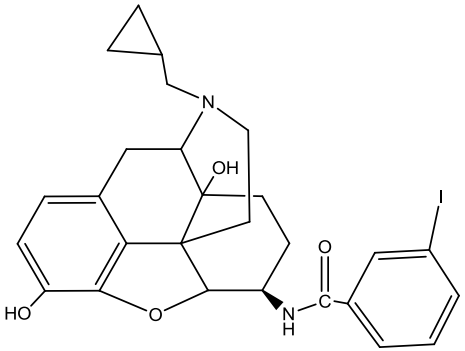

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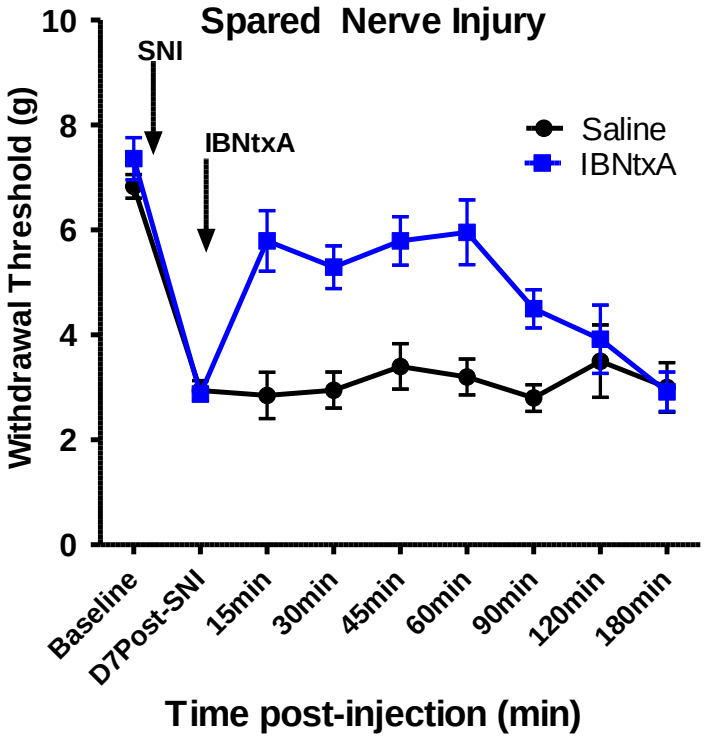

Mogil and Weiskopf

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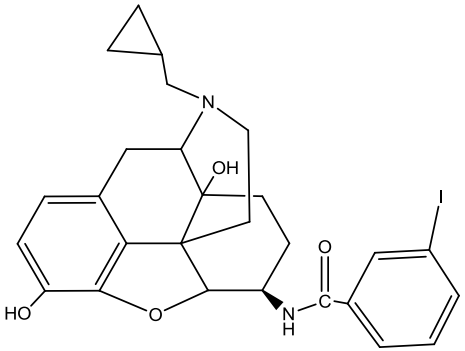

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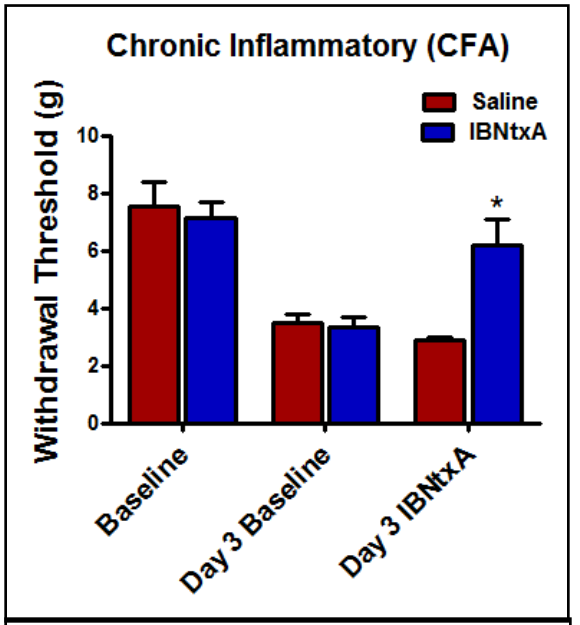

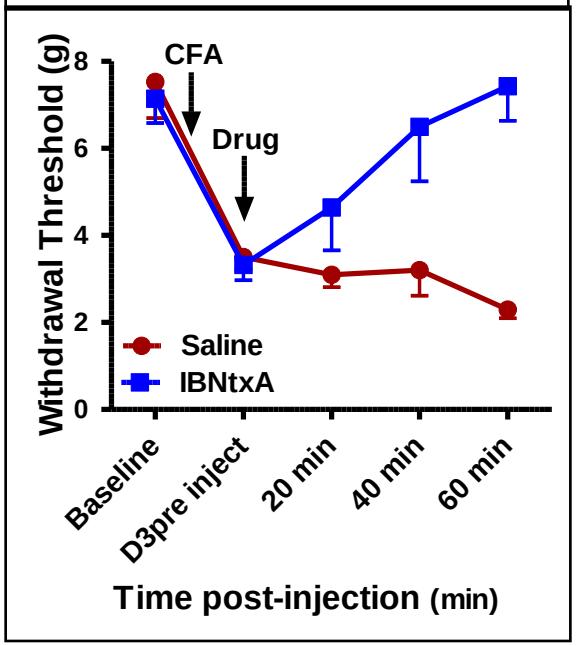

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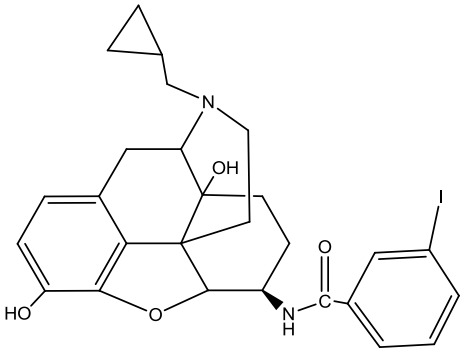

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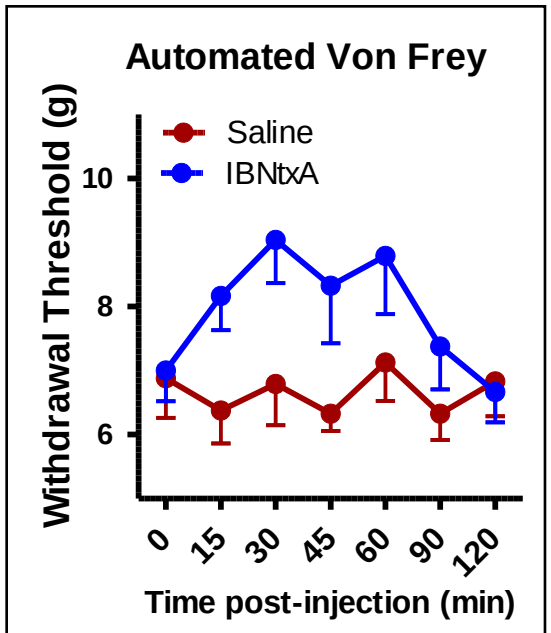

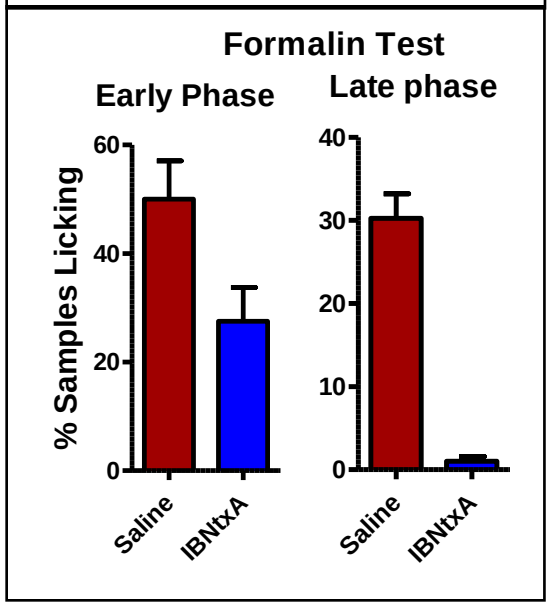

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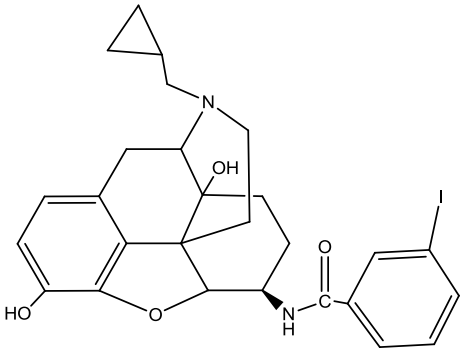

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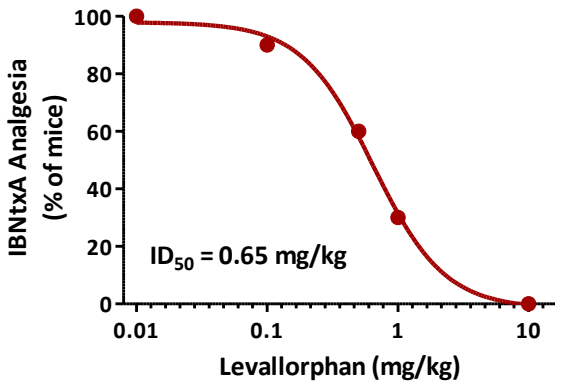

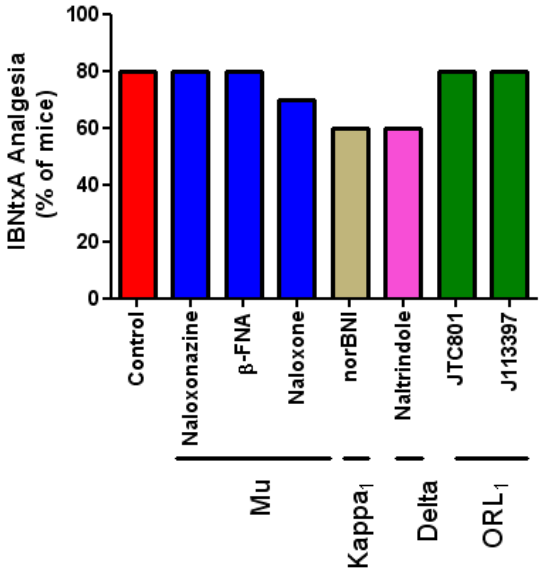

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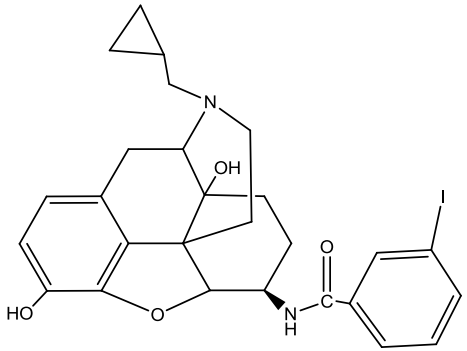

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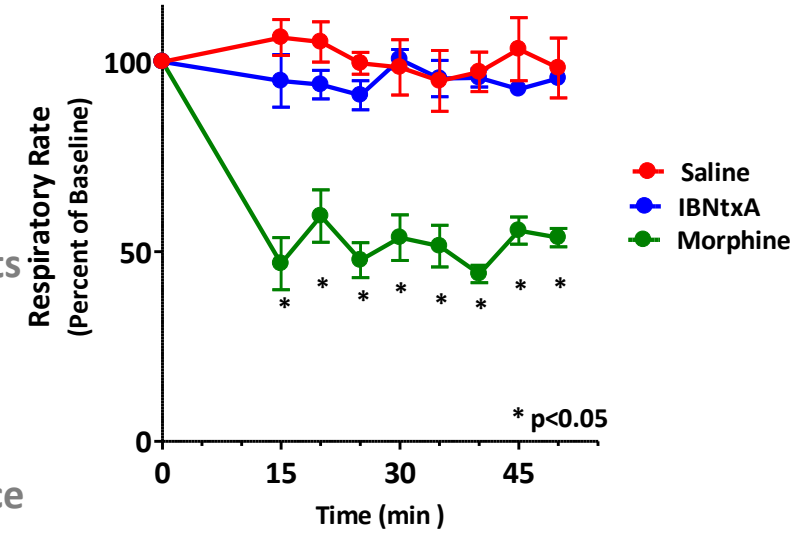

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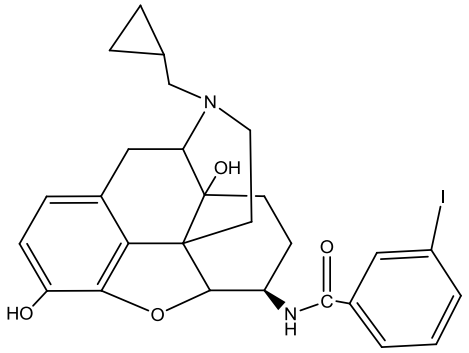

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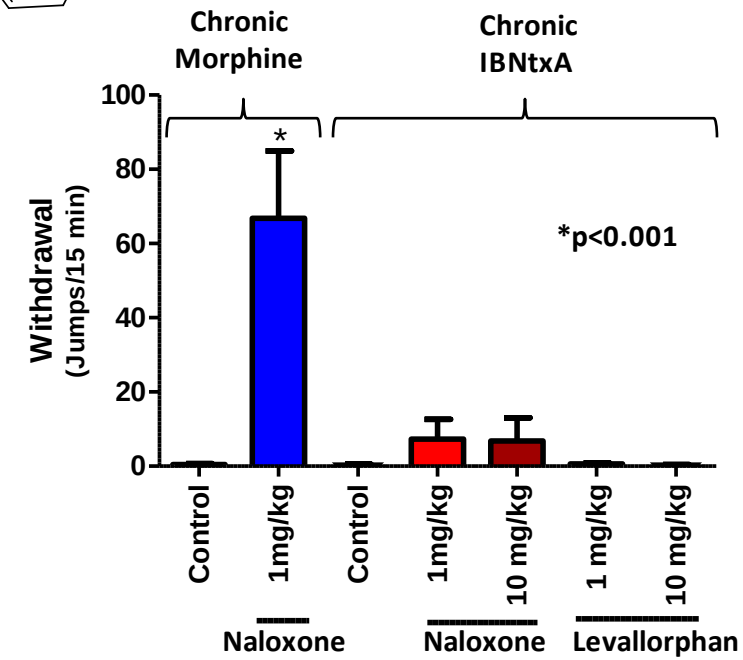

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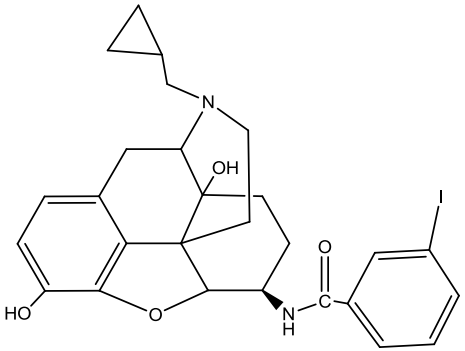

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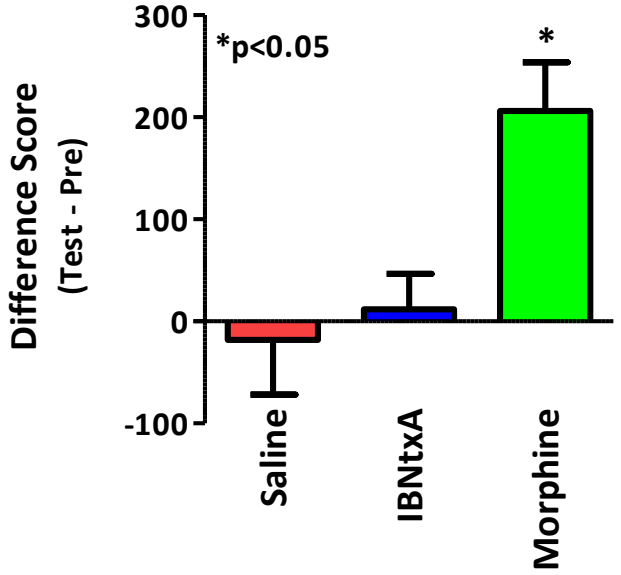

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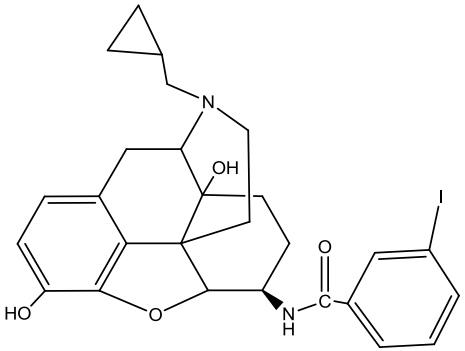

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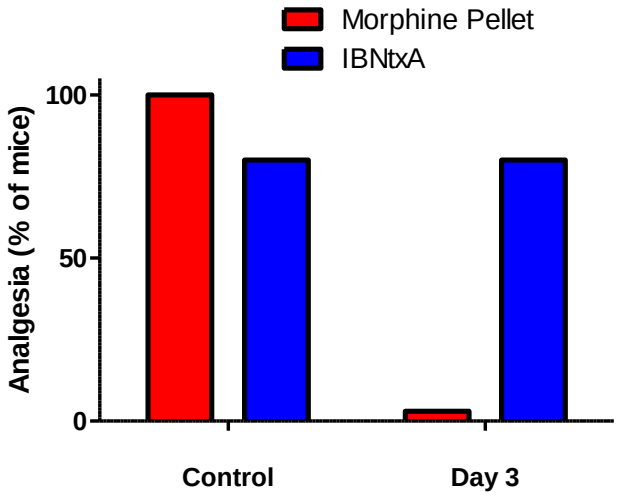

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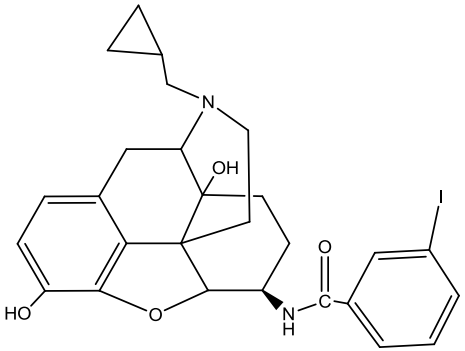

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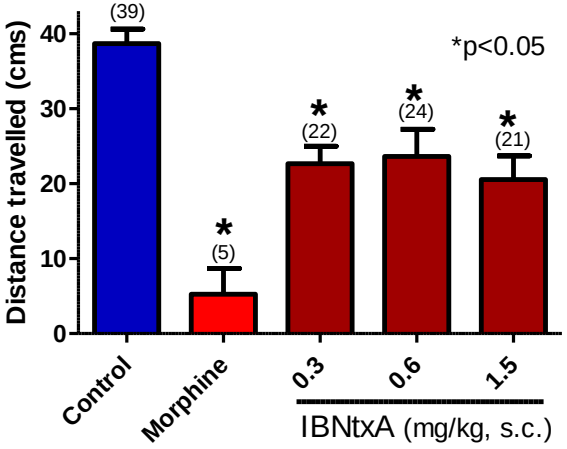
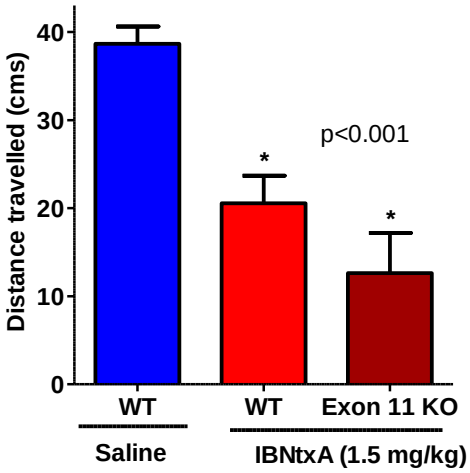
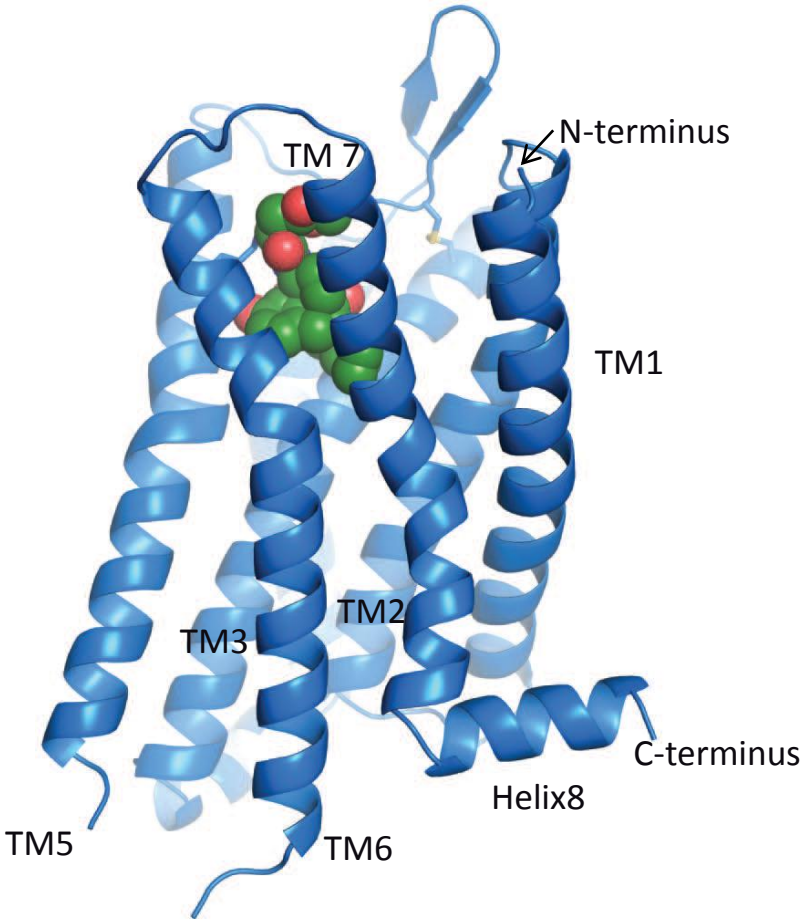
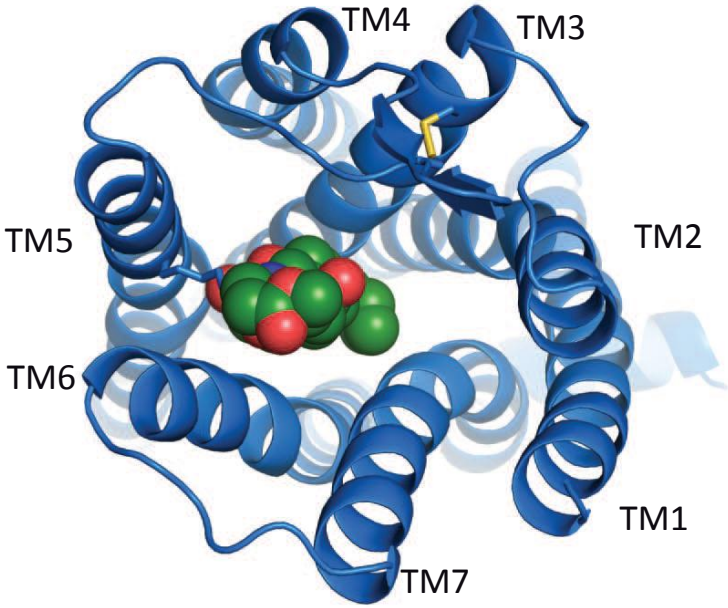


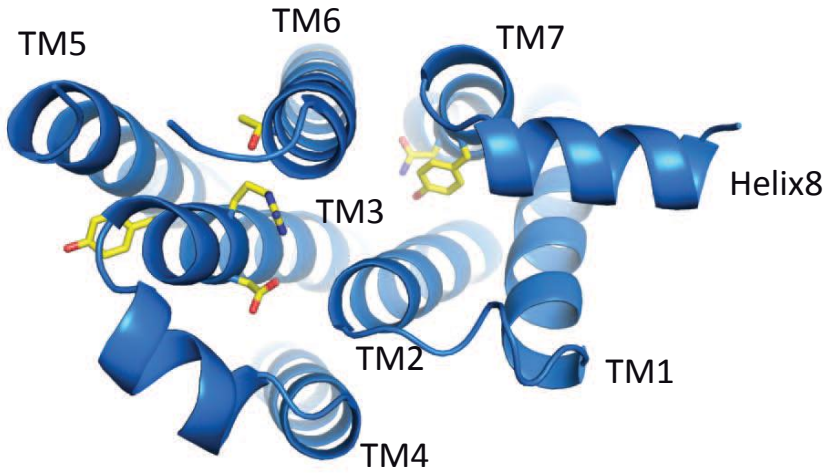


Crystal Structure of the mouse mu opioid receptor

Binding pocket: TM 3, 5, 6, 7



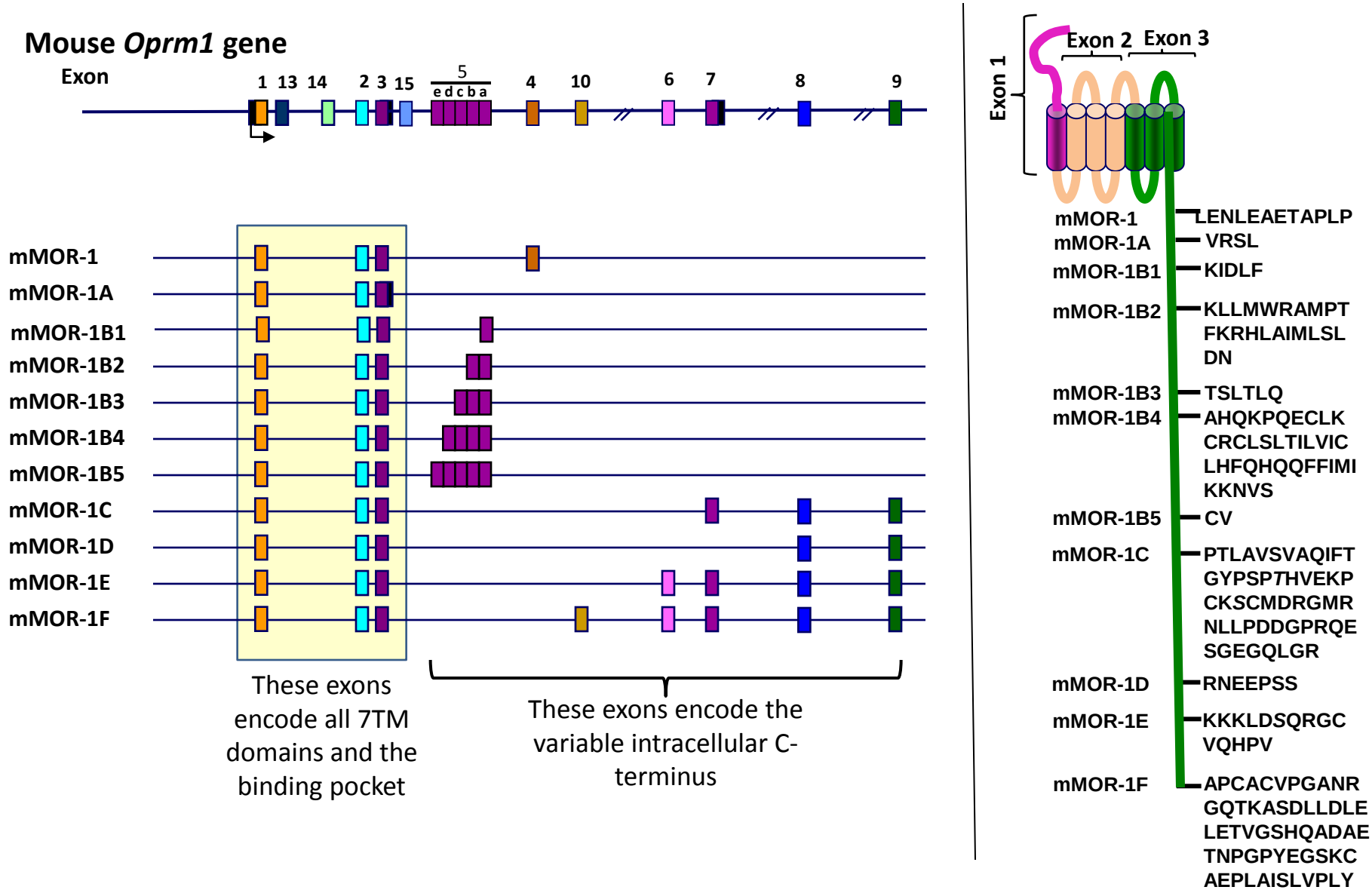




Note: The N- & C-termini have been truncated

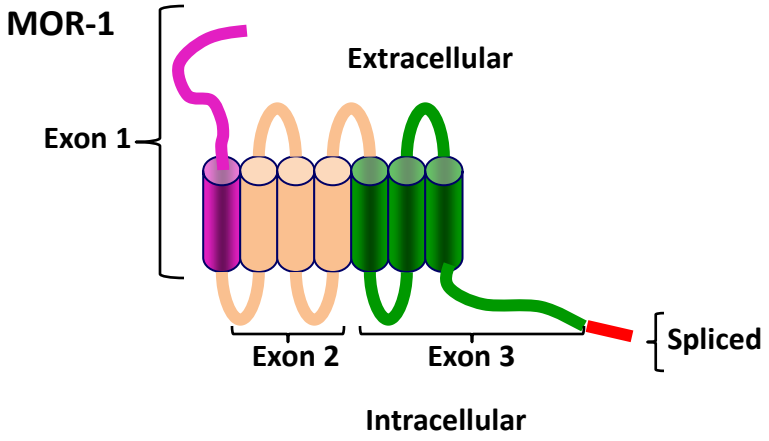
Manglik et al, Nature, 2012
PMID: 22437502

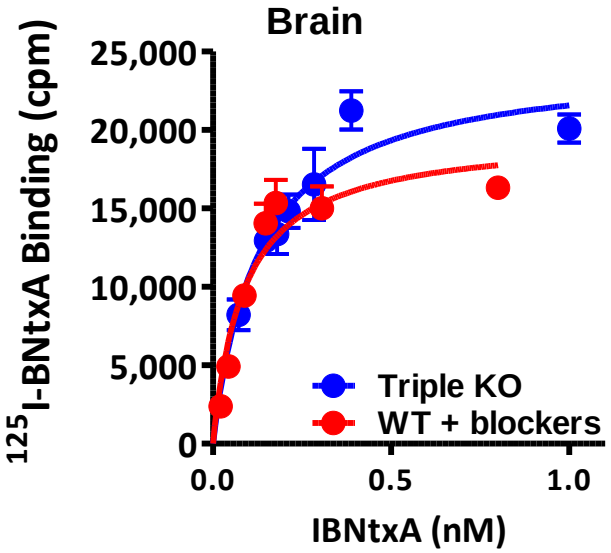
3’- Alternative splicing of selected full length MOR-1 variants

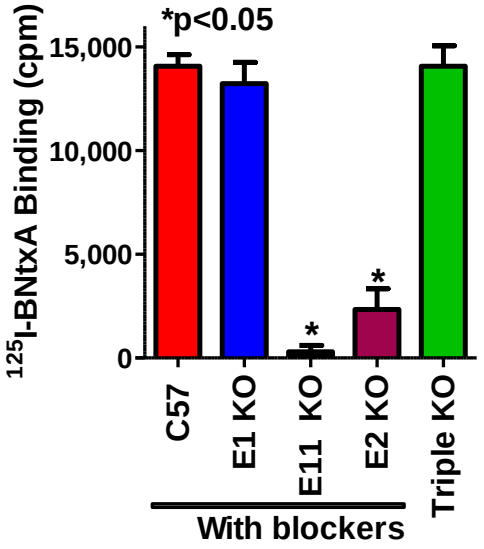


^{125}I-BNtxA Binding in KO Mice

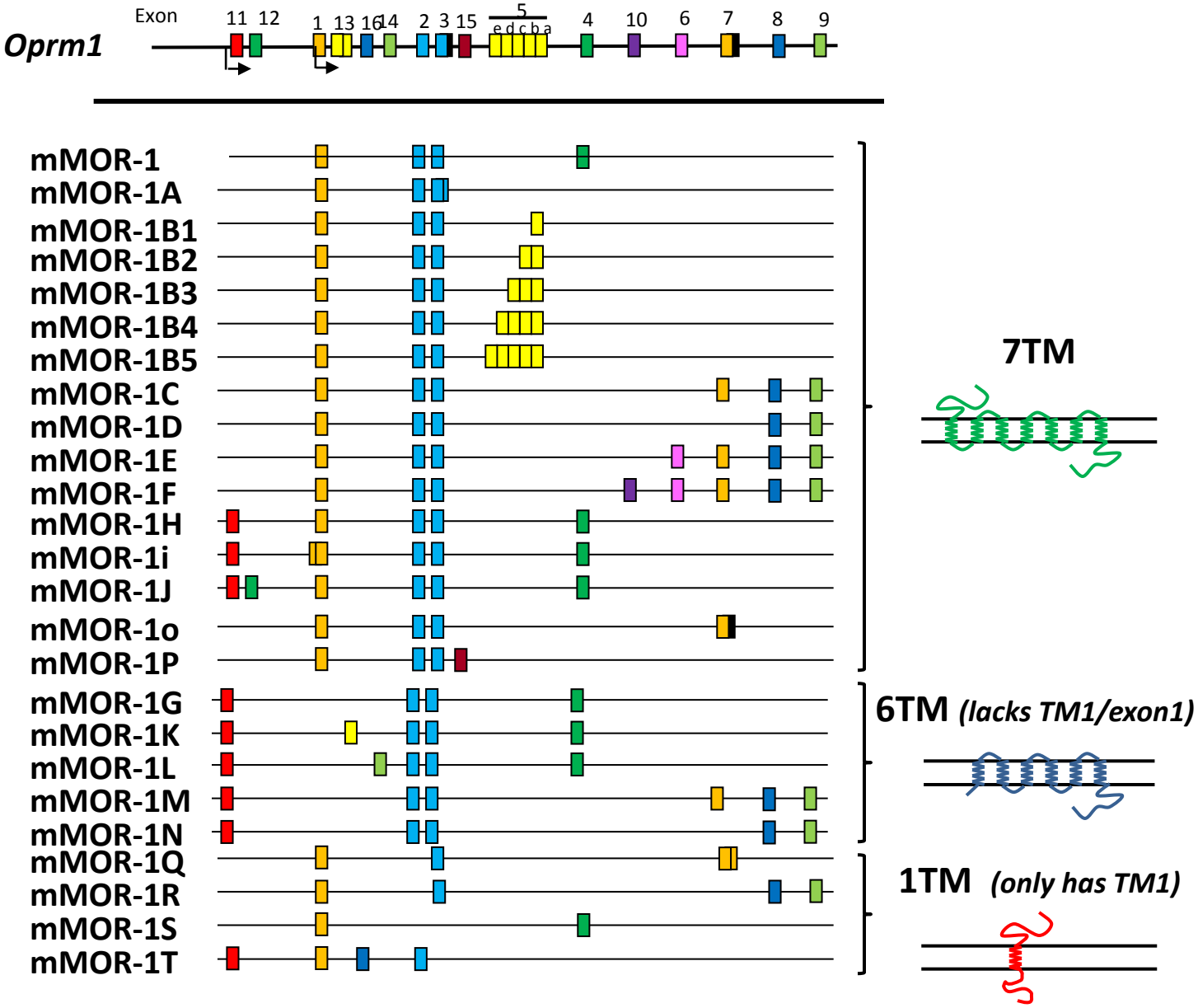
- High affinity binding in triple KO mice
- High affinity binding in WT mice with blockade of traditional opioid receptors
- Loss of binding in E11 and E2 KO mice
- The target lacks MOR-1 exon 1 but contains E11 and E2







Schematic of MOR-1 splicing in the mouse



Selectivity of ^{125}I-IBNtxA Binding in triple KO mouse brains

Inactive Drugs (K_i > 1000 nM)
Mu selective
Morphine
CTAP
DAMGO
Oxymorphone
Oxycodone
Morpine-6-glucuronide
β-Endorphin
Meperidine
Kappa$_1$ selective
U50,488H
DynorphinA
α-Neoendorphin
Delta selective
Enkephalin
DADLE
DPDPE
SNC80

Drug	K_i (nM)
Antagonists	
β-FNA	36
Naloxone	52
Naltrexone	21
Diprenorphine	2.2
Levallorphan	0.34
Benzomorphans	
Ketocyclazocine	0.04
(-)-SKF10,047	14
(-)Ethylketocyclazocine	0.21
Cyclazocine	1.8
Kappa$_3$	
NalBzoH	0.6
Nalorphine	3.7
Levorphanol*	8.8
Buprenorphine*	1.8
Nalbuphine*	3.5
Butorphanol*	2.9

**Used clinically as analgesics*

Analgesia in Exon 11 MOR-1 KO

Drug	ED_{50} (mg/kg)		Shift	^{125}I-BNtxA Binding
	WT C57	Exon 11 MOR-1 KO		Triple KO Ki (nM)
Morphine*	1.6	2.6	1.6	>1000
IBNtxA	0.53	> 20	>35	0.16
NalBzoH	22	>100	>5	0.6
Nalbuphine	41.8	>200	>5	3.5
Ketocyclazocine	4.2	50	12	0.04
Levorphanol *	5	30	6	8.8
Butorphanol *	12.4	200	16	2.9
Buprenorphine*	0.2	>10	>50	1.8

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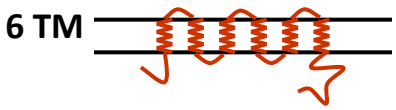
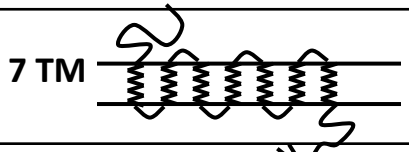
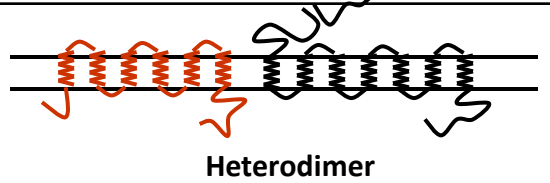
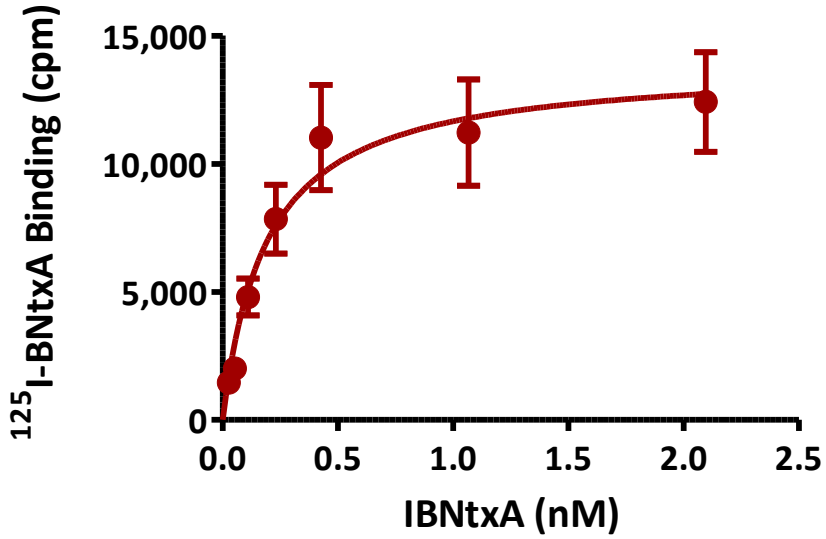
^{125}I-BNtxA Binding to MOR-1G / ORL_1 dimers

Transfection	^{125}I-BNtxA Binding	Structure
MOR-1G alone	None	
ORL_1 alone	None	
MOR-1G + ORL_1	K_D 0.19 nM	



Opioid receptor diversity

Opioid receptor actions are complex, both at the pharmacological and molecular levels

Receptor diversity can be achieved both by alternative splicing and dimerization

Alternative splicing of the C-terminal of the full length variants may impact the composition of the receptor complex, its localization within the cell and within the brain and thereby define their functions

When splice variants contain identical binding pockets, selectivity may be achieved by varying the intrinsic activity/efficacy of a drug at the target rather than by affinity.

Truncated variants can modulate full length MOR-1 variants or generate novel receptor targets through heterodimerization

The molecular mechanisms of opioid receptor diversity may be revealing a generalized approach for generating receptor diversity among G-protein coupled receptors.

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Molecular Biology

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