

April 11. 2003 (Friday) 10:40~11:10

뇌신경행동에 미치는 μ -opioid 수용체의 역할

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Role of μ -Opioid Receptors on Neurobehaviors

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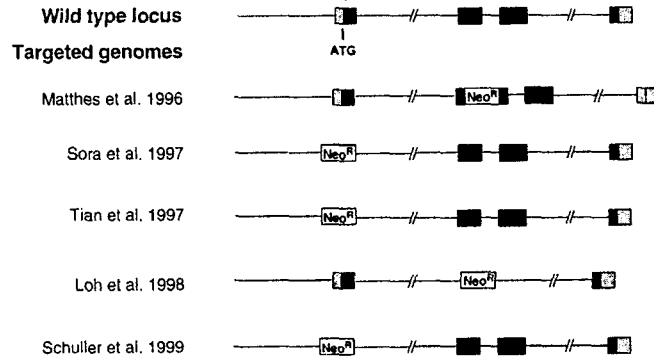
College of Pharmacy, Sungkyunkwan University

The Opioid Systems

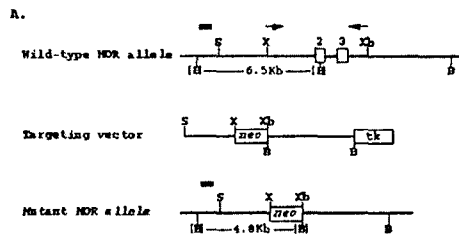
- 1. Nociceptive information, with overlapping contribution of μ -, δ -, and κ -receptors**
- 2. Reinforcing properties of μ - and δ -receptors and aversive activity of κ -receptors**
- 3. Stress responses with a main implication of μ - and δ -receptors**
- 4. Other physiological responses**
 - respiration**
 - gastrointestinal motility**
 - endocrine and immune functions**

μ-Opioid Receptor Knockout Mice

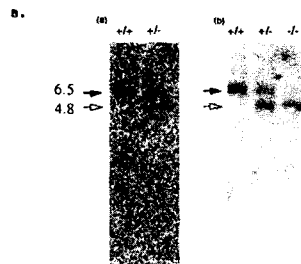
MOR



μ-Opioid Receptor Knockout Mice



- Generated from Dr. H.H. Loh, U. of Minnesota, USA
- Genetic background: C57/BL6 and 129/Ola mouse
- Animals: 3-4 months male & female



in vivo responses to mu-opioid agonists in mice lacking opioid receptors

Opioid	Responses	MOR ^{-/-}
Morphine	Analgesia	Abolished (Matthes et al., 1996; Sora et al., 1997; Loh et al., 1998; Schuller et al., 1999; Sora et al., 1999; Fuchs et al., 1999)
	Tolerance to analgesia	
	Hyperlocomotion	Abolished (Tian et al., 1997; Sora et al., 2001; Becker et al., 2000)
	Reward	Abolished (Matthes et al., 1996; Sora et al., 2001)
	Self-administration	Abolished (Sora et al., 2001; Becker et al., 2000)
	Withdrawal	Abolished (Matthes et al., 1996; Sora et al., 2001)
	Respiratory depression	Abolished (Matthes et al., 1998; Dahan et al., 2001)
	Inhibition of GI transit	Abolished (Roy et al., 1998a)
	Inhibition of VD twitch	Abolished (Maldonado et al., 2001)
	Immunosuppression	Abolished (Gavériaux-Ruff et al., 1998; Roy et al., 1998b) ^a
	Increase in ACTH and corticosterone	Abolished (Roy et al., 2001)
	Potentiation of pentobarbital and apomorphine responses	Abolished (Park et al., 2001; Jang et al., 2000)
	Heroin	Analgesia
M6G		Analgesia Abolished (Loh et al., 1998; Kitanaka et al., 1998) Maintained (Schuller et al., 1999)
Methadone	Analgesia	Abolished (Schuller et al., 1999)
Endomorphins	Analgesia	Abolished (Loh et al., 1998; Mizoguchi et al., 1999)
DAMGO	Analgesia	Abolished (Schuller et al., 1999; Qiu et al., 2000)
	Inhibition of VD twitch	Abolished (Maldonado et al., 2001)
	Respiratory depression	Abolished (Morin-Surun et al., 2001)

ACTH, adrenocorticotropin hormone; GI, gastrointestinal; VD, vas deferens.

^a Some parameters were maintained in a paradigm using morphine pellets.

Experiment 1

Behavioral Characteristics

Experiment 2

The Role of μ -Opioid Receptor by Pharmacological Manipulation

Experiment 3

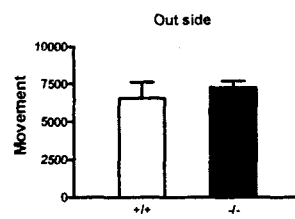
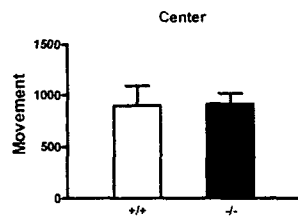
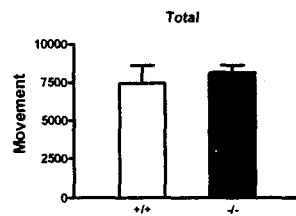
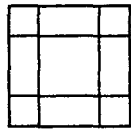
The Role of μ -Opioid Receptor in Behavioral Sensitization

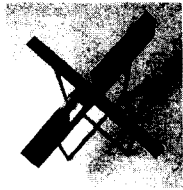
Experiment 1

Behavioral characteristics

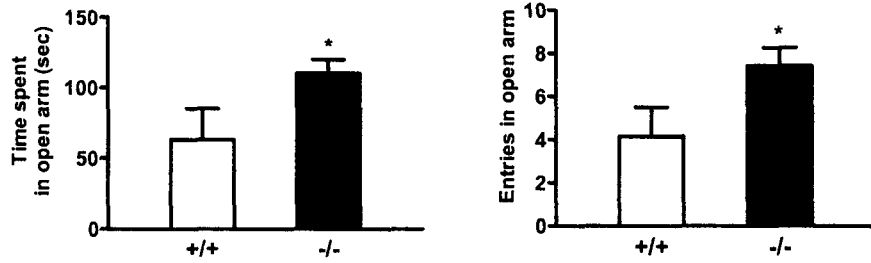
Open field
Elevated plus-maze
Forced Swimming Test
Novelty test
Emergence test
Y-maze
Morris water-maze

Open field test

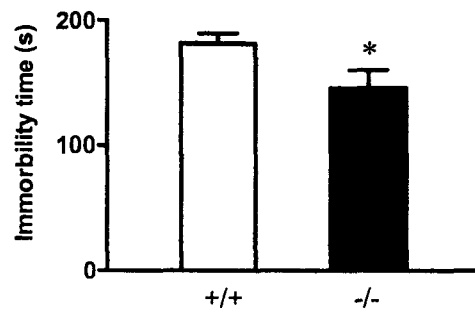
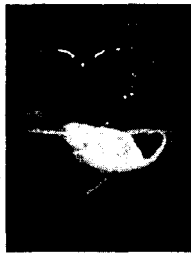


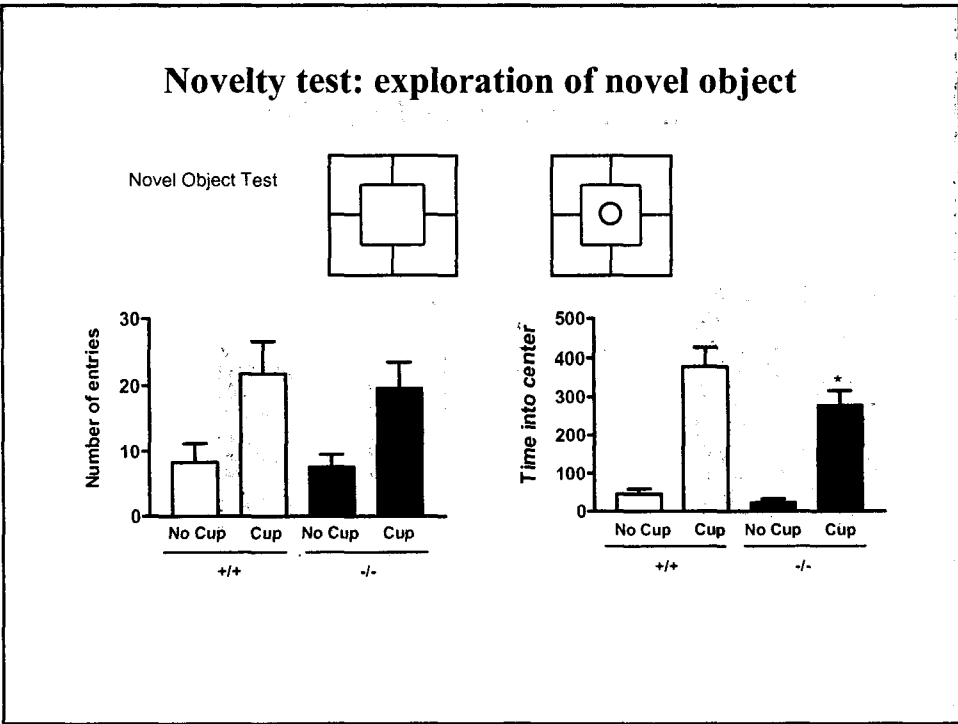
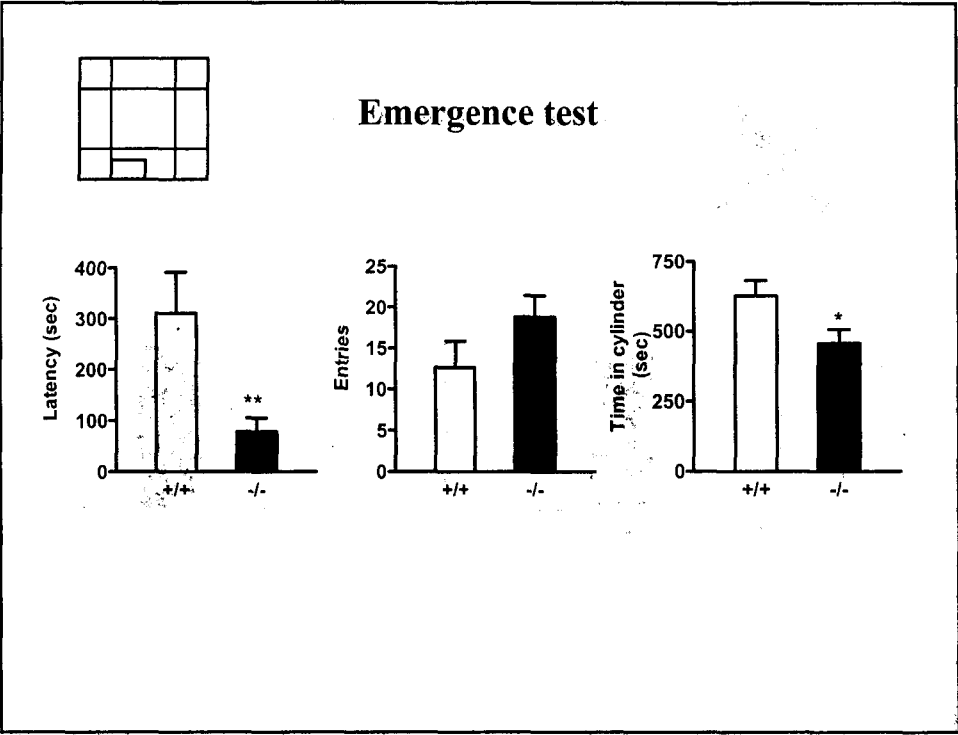


Elevated Plus-Maze

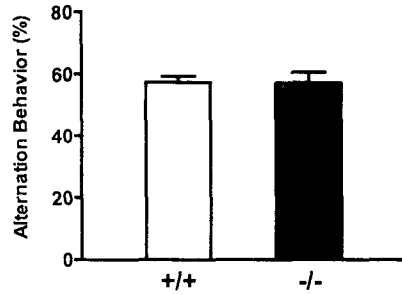
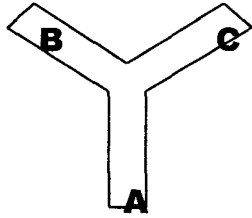


Forced Swimming Test (FST)

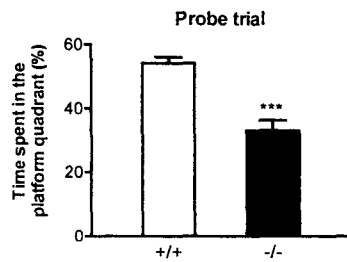
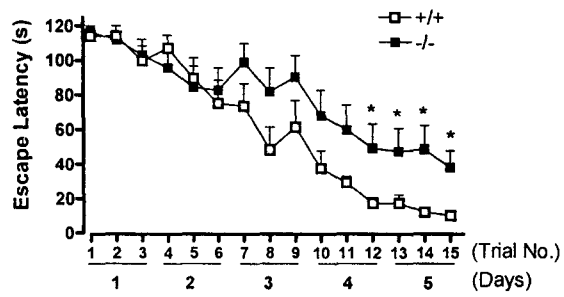
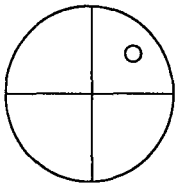




Y-maze test



Morris Water Maze Test



Summary I: Neurobehavioral Phenotypes

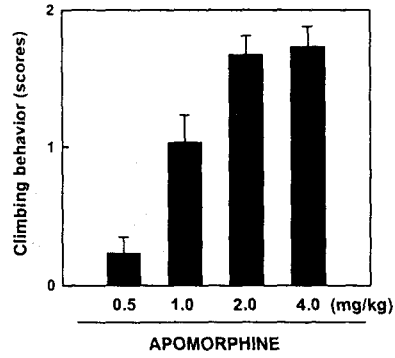
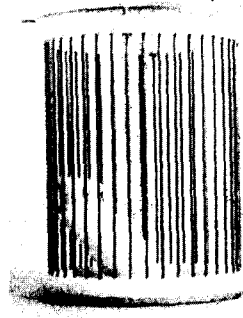
Open field (Movement)	—
Elevated Plus Maze (Anxiety)	↓
FST (Depression)	↓
Novelty (Cognition)	↓
Emergence	↓
Y-maze	—
Water-maze (Spatial memory)	↓

Experiment 2

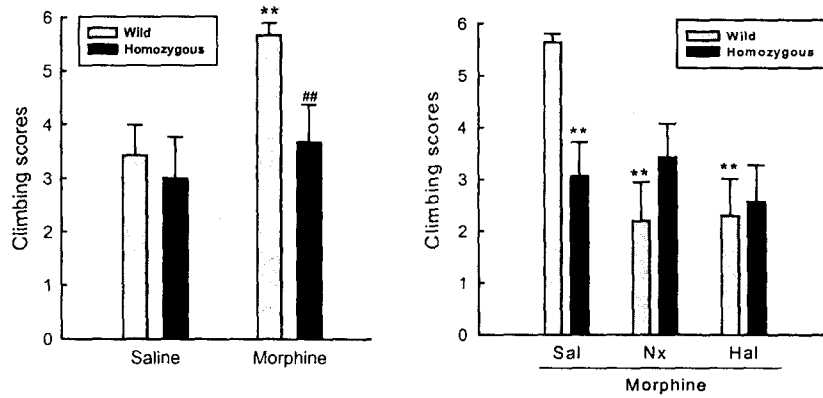
- **Role of Opioid System in DA -Activation**
- **Role of Opioid System in NMDA-Induced Convulsion**

Apomorphine-induced climbing behavior

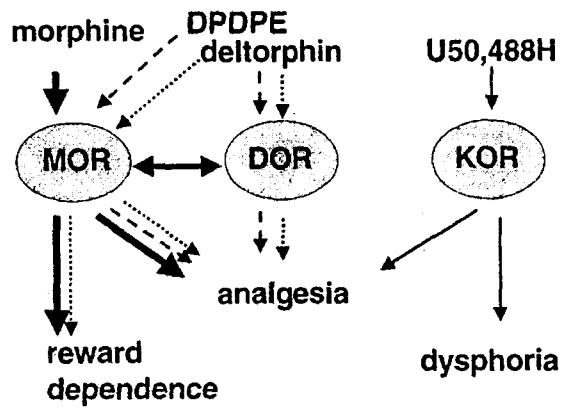
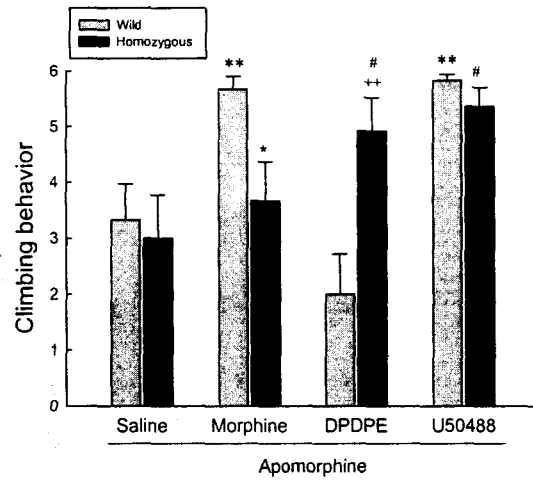
- Postsynaptic DA receptor agonistic behavior
- Scores
 - Point 0: on the floor
 - Point 1: fore feet holding the wall
 - Point 2: climbing the wall



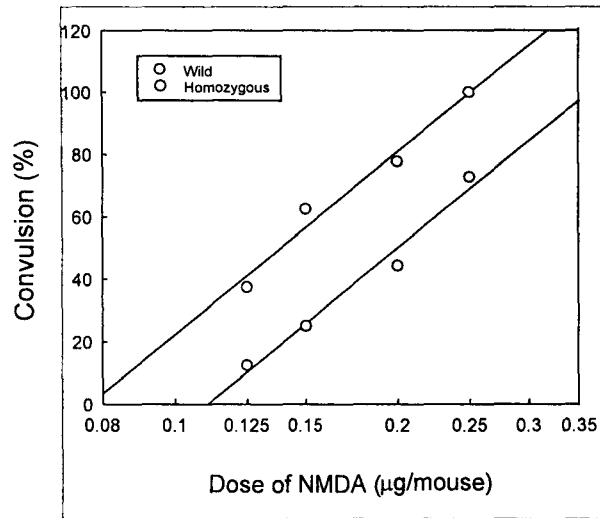
Effects of morphine on apomorphine-induced climbing behavior



Effect of opioid receptors on apomorphine-induced climbing behavior

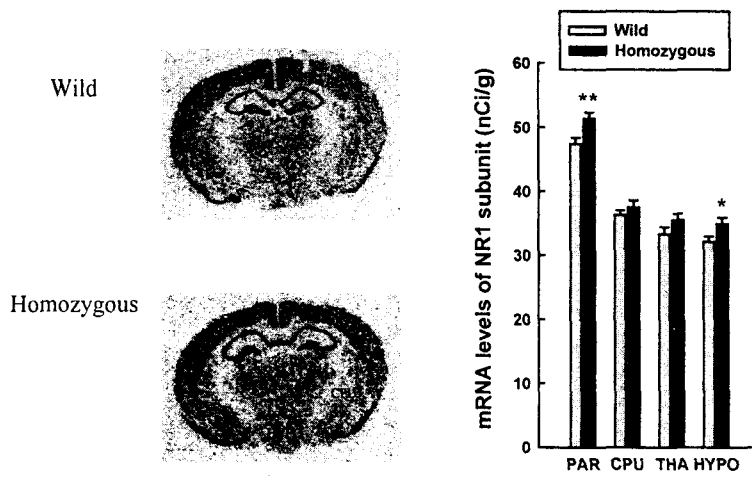


NMDA-induced Convulsion

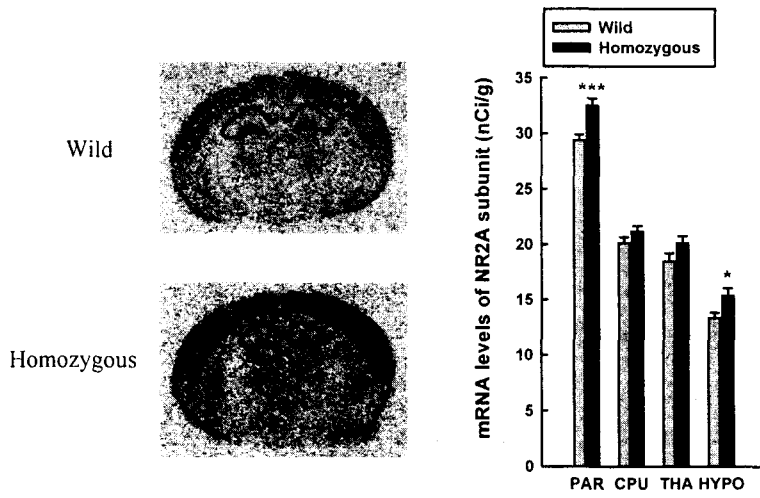


Dose-response curves for NMDA-induced convulsions in the wild type and μ -opioid receptor knockout mice. Each mouse received a single i.c.v. administration of NMDA (0.125 - 0.25 μ g/10 μ l/mouse). Mice were observed immediately by all or none after i.c.v. injection and were scored as showing convulsive responses, such as wild running, jumping, or clonic seizure.

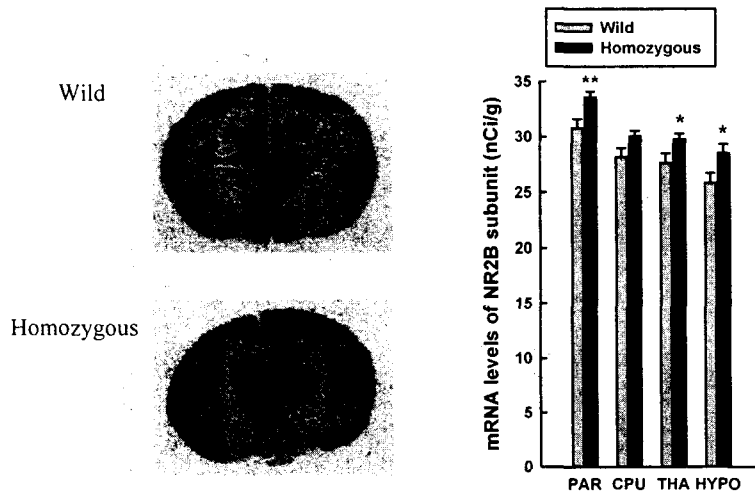
NR1 mRNA



NR2A mRNA



NR2B mRNA



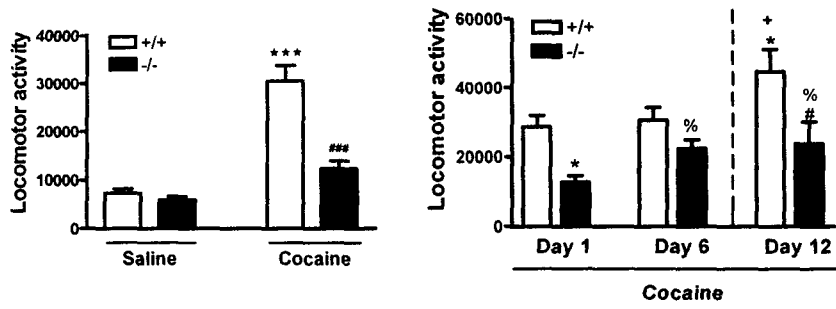
Summary II

1. Stimulation of dopaminergic system by morphine was abolished in μ -opioid receptor knockout mice.
2. Dopaminergic stimulation by opioid agonists, morphine, DPDPE, and U50488, acts independently.
3. Loss of μ -opioid receptors is more sensitive to the response of NMDA-induced convulsion and increase in the expression of mRNA for NMDA receptors.

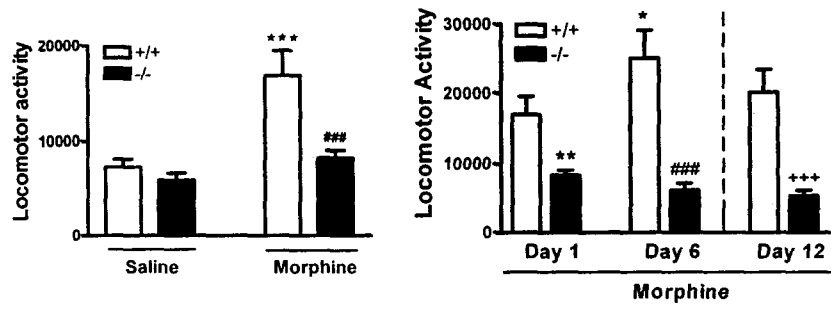
Experiment 3

Role of μ -Opioid Receptor in Locomotion and Behavioral Sensitization by Opioid and Psychostimulants

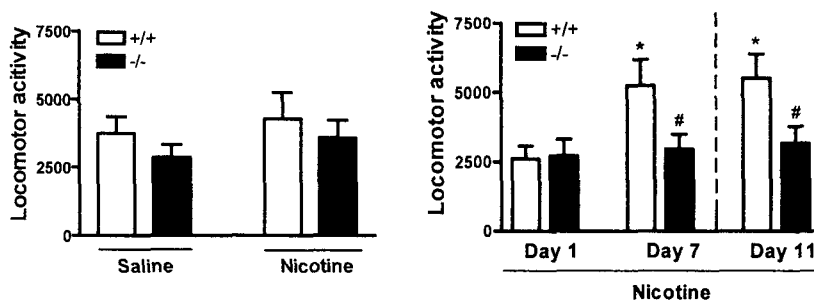
Cocaine Locomotion & Sensitization



Morphine Locomotion & Sensitization



Nicotine Locomotion & Sensitization



Conclusion

- ◆ μ -Opioid receptor knockout mice show anti-anxiety and memory impairment
- ◆ μ -Opioid receptors play an important role in activation of dopaminergic system. Dopaminergic stimulation by κ -opioid agonist acts independently with μ -opioid receptors
- ◆ Loss of μ -opioid receptors is more sensitive to response of NMDA-induced convulsion and increase in expression of mRNA for NMDA receptors
- ◆ μ -Opioid receptors play a key role in the development of behavioral sensitization to morphine, cocaine, and nicotine