

# **Cannabinoids: Nausea, Anxiety, Depression and Addiction**

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# Cannabis Bioactive Compounds

$\Delta^9$ -Tetrahydrocannabinol  
(THC)

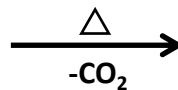
$\Delta^9$ -Tetrahydrocannabinolic acid  
(THCA)

Cannabinol  
(CBN)

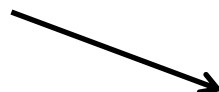
Cannabidiol  
(CBD)

Cannabidiolic acid  
(CBDA)

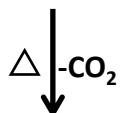
**Cannabigerolic acid  
(CBGA)**



**Cannabigerol  
(CBG)**

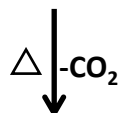


**Cannabidiolic acid  
(CBDA)**



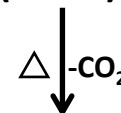
**Cannabidiol  
(CBD)**

**$\Delta^9$ -Tetrahydrocannabinolic acid  
( $\Delta^9$ -THCA)**



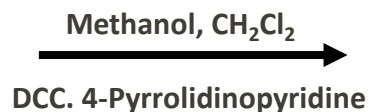
**$\Delta^9$ -Tetrahydrocannabinol  
( $\Delta^9$ -THC)**

**Cannabichromenic acid  
(CBCA)**



**Cannabichromene  
(CBC)**

# Cannabidiolic Acid Methyl Ester: A Stable Synthetic Analogue of Cannabidiolic Acid



**Cannabidiolic Acid  
(CBDA)**

(Krejčí and Šantavý, 1955; Mechoulam and Gaoni, 1965)

**Cannabidiolic Acid Methyl Ester  
(CBDA Me, HU-580)**

(Mechoulam and Ben Zvi, 1969)

# **CBDA Me in Nausea, Anxiety and Depression**

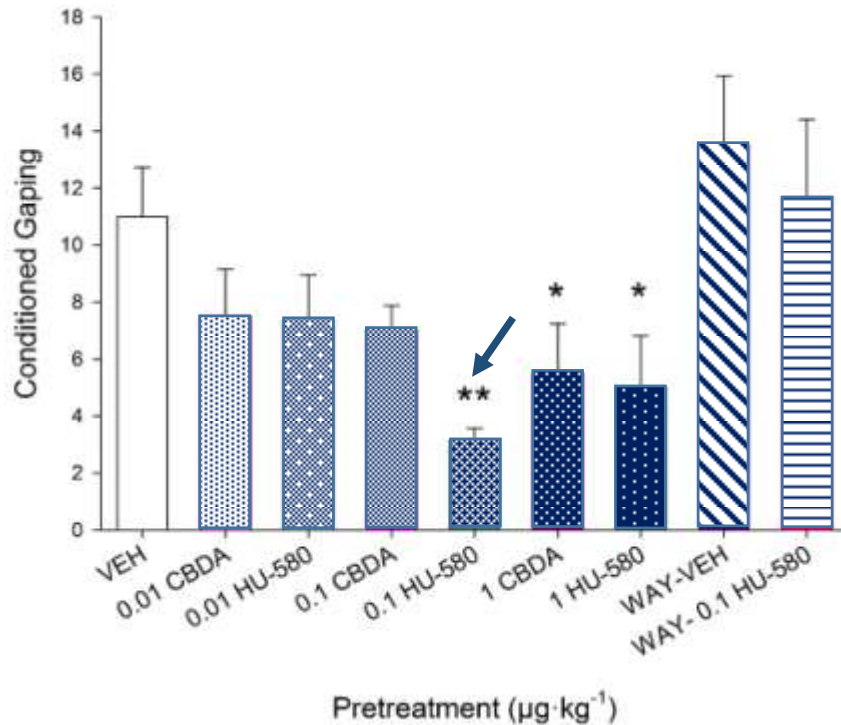
# Nausea

- **The sensation of nausea is one of the most debilitating human experiences**
- **Current antiemetic therapies are less effective in reducing acute nausea and are completely ineffective in reducing anticipatory nausea**
- **Pre-clinical findings suggest that CB1 receptor agonists, FAAH and MAGL inhibitors, CBD and CBDA reduce acute and anticipatory nausea**

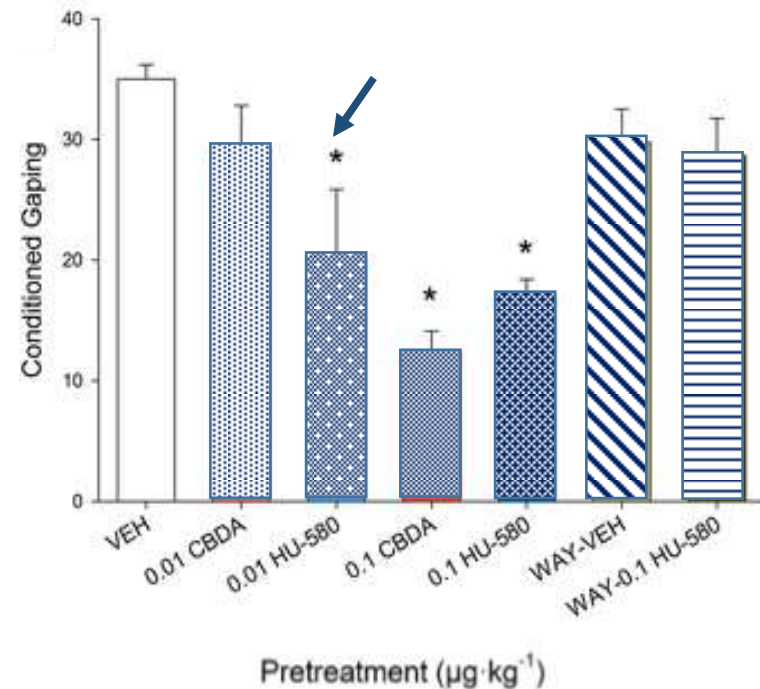
# Nausea

## CBDA Me (HU-580) enhanced 5-HT<sub>1A</sub> receptor activation

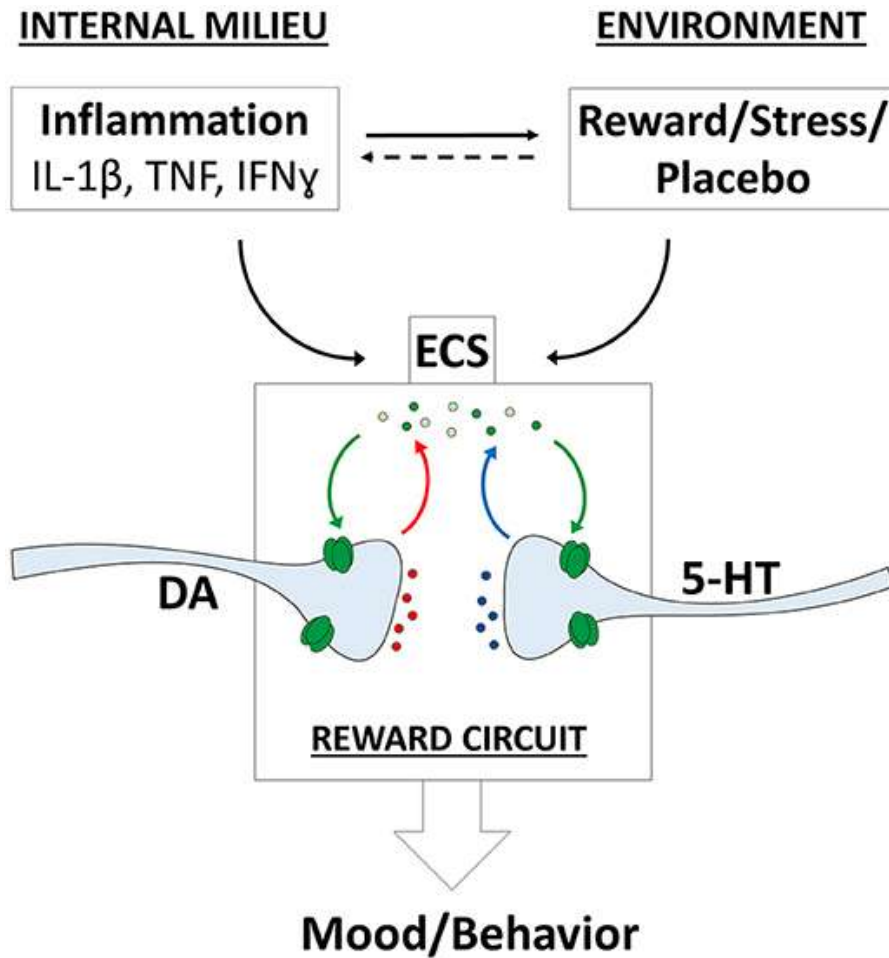
### Acute nausea



### Anticipatory nausea



# Anxiety and Depression



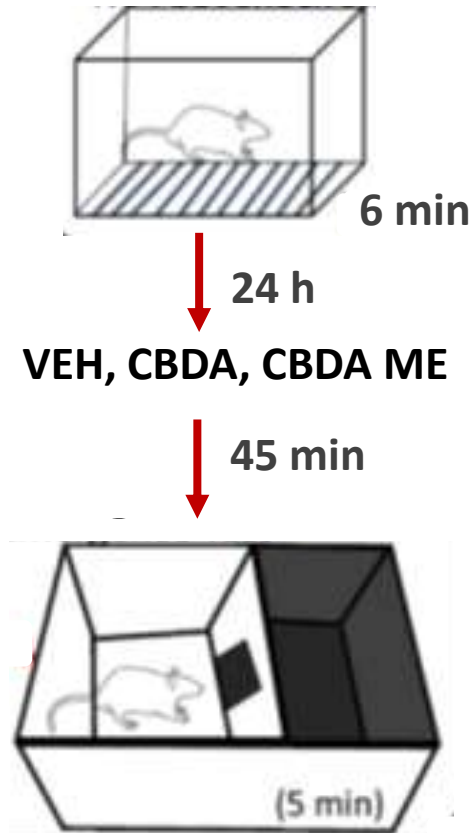
Evidence supporting clinical benefits of cannabis-based therapies in mood disorders is scarce, and limited to low-grade evidence supporting the beneficial effect of CBD in social anxiety & depression & of medical marijuana in PTSD

ECS influences on mood and behavior

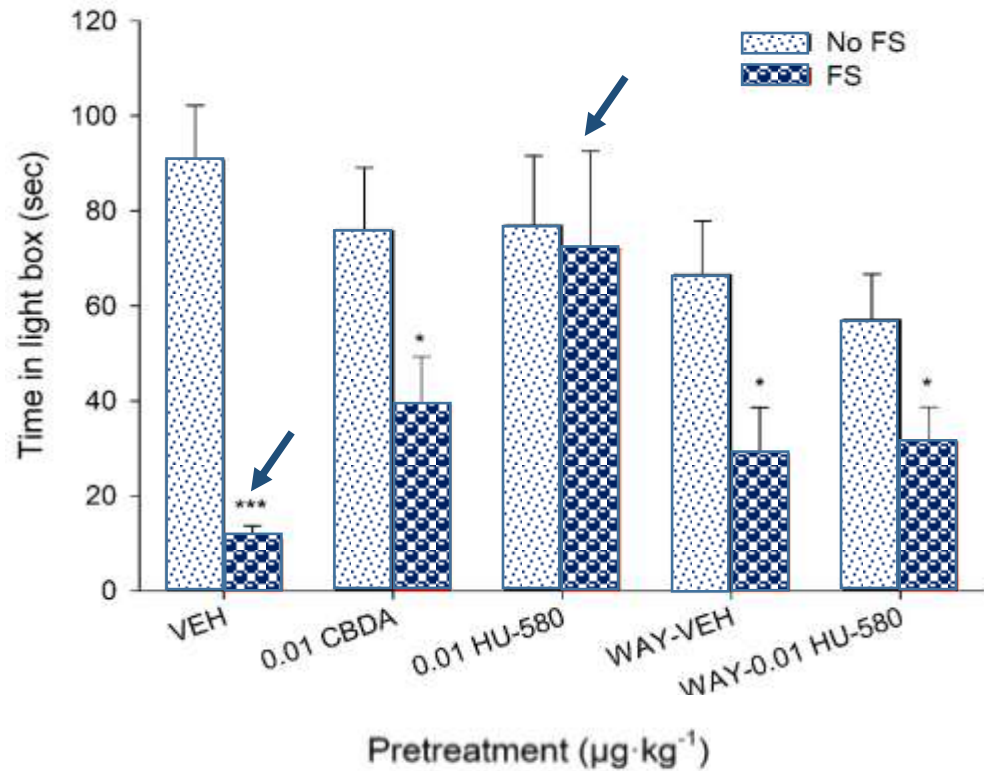


# Anxiety

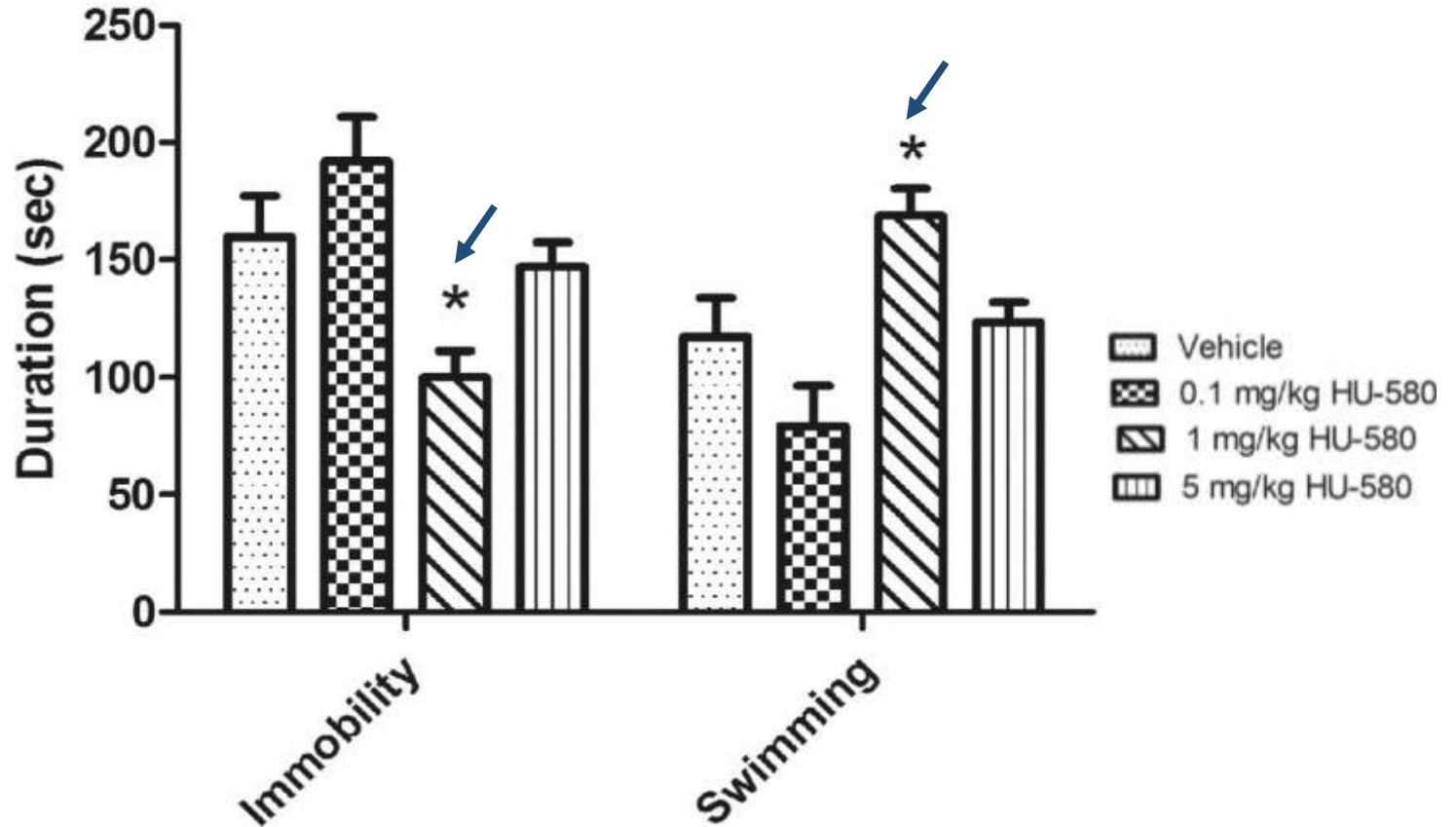
Foot Shock  
or No Foot Shock Stress



## Anxiolytic effects



## Antidepressant effects



**CBDAME reduced depression-like behavior in animal models of depression**

# Summary

**CBDA Me displayed greater potency than CBDA at suppressing signs both of acute nausea and anticipatory nausea, and of stress induced anxiety in rats, and it produced these effects in a 5-HT<sub>1A</sub> receptor-dependent manner**

**CBDA Me showed a very potent anti-depression-like effect in rats**

**CBDA Me could possibly be effective against other disorders ameliorated by enhancement of 5-HT<sub>1A</sub> receptor activation such as cerebral infarction and pain**

# **The Endocannabinoid System and Addiction**

**Substance Use Disorder (SUD) is a global problem, with over 30 million individuals estimated to have an SUD**

**The ECS plays an important role in neurobiological processes underlying SUD, by mediating the rewarding and motivational effects of substances**

**Rimonabant and Nabiximols have the potential for pharmacological treatment for substance dependence**

**Cannabidiol (CBD), has been proposed as a potentially effective treatment for the management of SUD**

# The Endocannabinoids to Date

*N*-Arachidonylethanolamine  
Anandamide (AEA)

2-Arachidonoylglycerol  
(2-AG)

2-Arachidonoylglycerylether  
Noladin-ether

*O*-Arachidonylethanolamine  
Virodhamine

*N*-Arachidonoyldopamine  
(NADA)

# The Endocannabinoid-like Compounds

***N*-Palmitoylethanolamine (PEA)**  
Antiinflammatory, Antinociceptive,  
Neuroprotective and Anticonvulsant

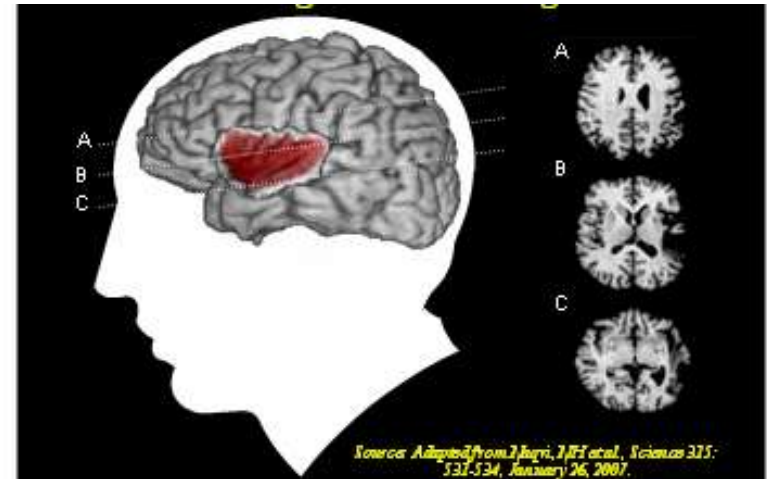
***N*-Oleoylethanolamine (OEA)**  
Regulates food intake

**Arachidonoyl serine (AraS)**  
Vasoactive, Pro-angiogenic, Pro-  
neurogenic

**Oleoyl serine (OS)**  
Antiosteoporotic

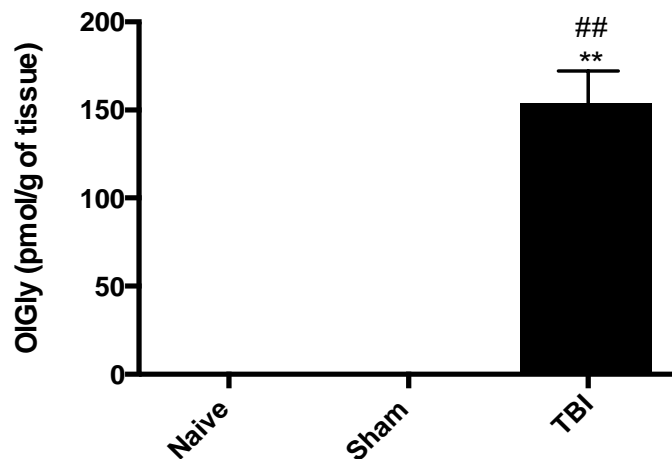
# Nicotine Addiction

Cigarette smokers with brain damage involving the insular cortex display cessation of tobacco smoking, so that this region may contribute to nicotine addiction



*N.H. Naqvi et al. / Science 315 (2007) 531*

## OIGly levels in the Insula



**Oleoyl glycine**

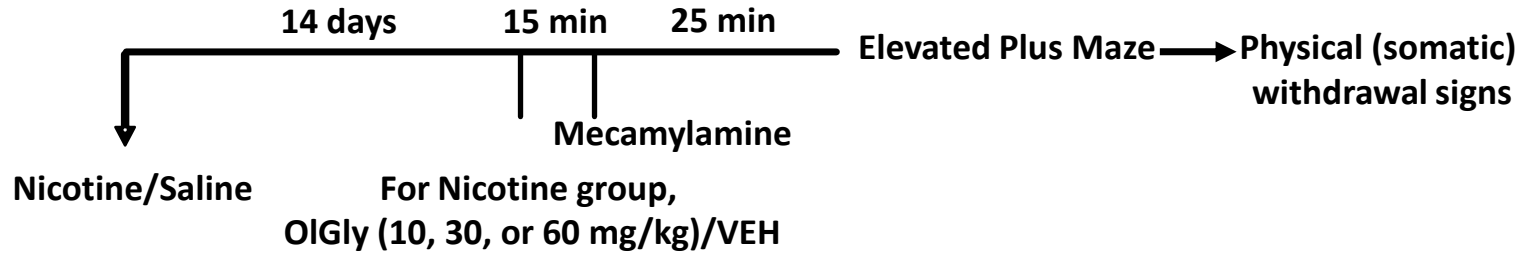
*G. Donvito et al. / Neuropharmacology 148 (2019) 320-331*



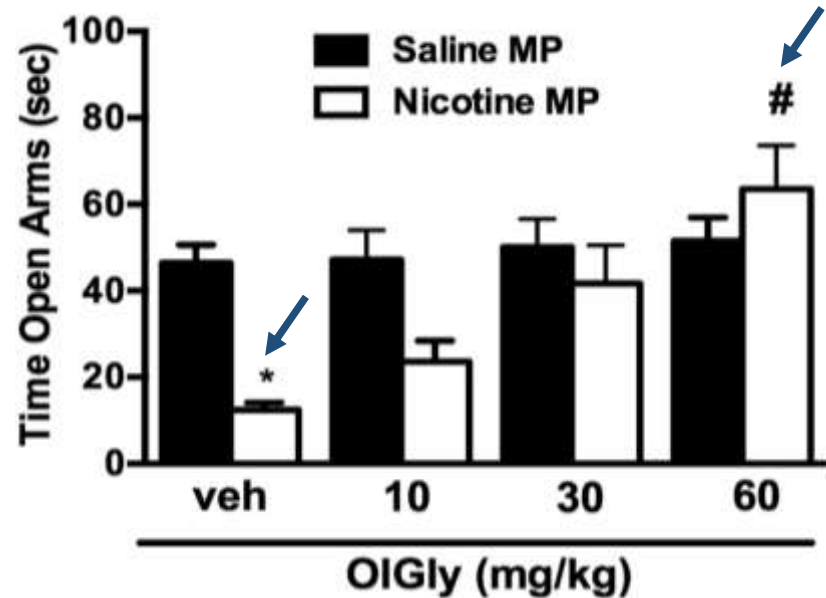
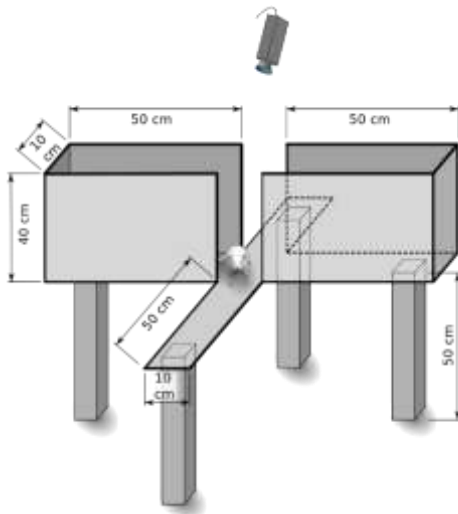
# Nicotine Addiction



Mice

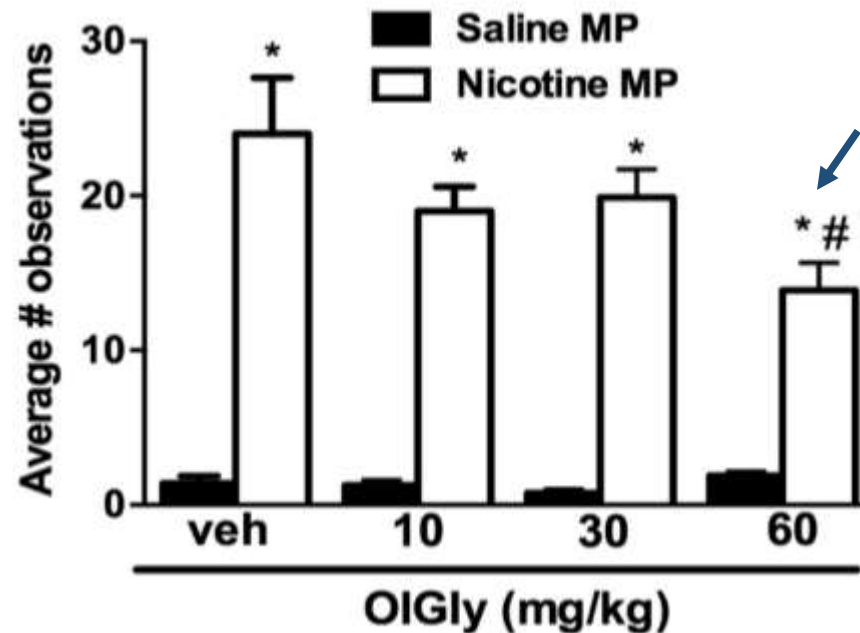


### Elevated Plus-Maze



# Nicotine Addiction

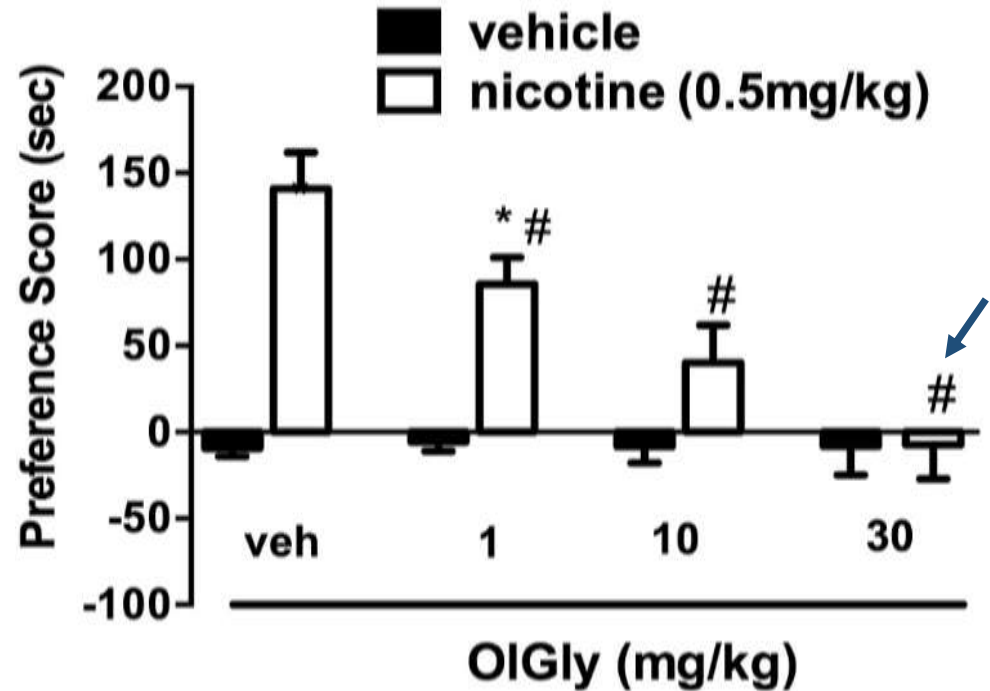
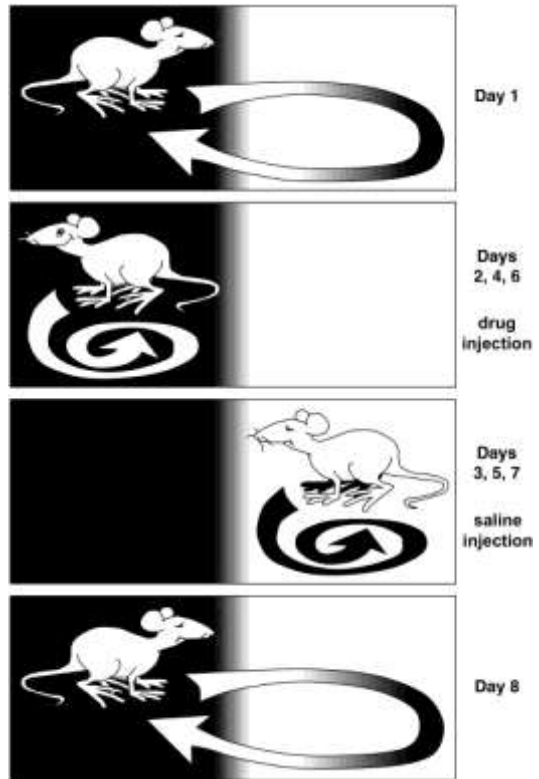
## Somatic signs



**OIGly reduced mecamylamine-precipitated withdrawal responses in nicotine-dependent mice**

# Nicotine Addiction

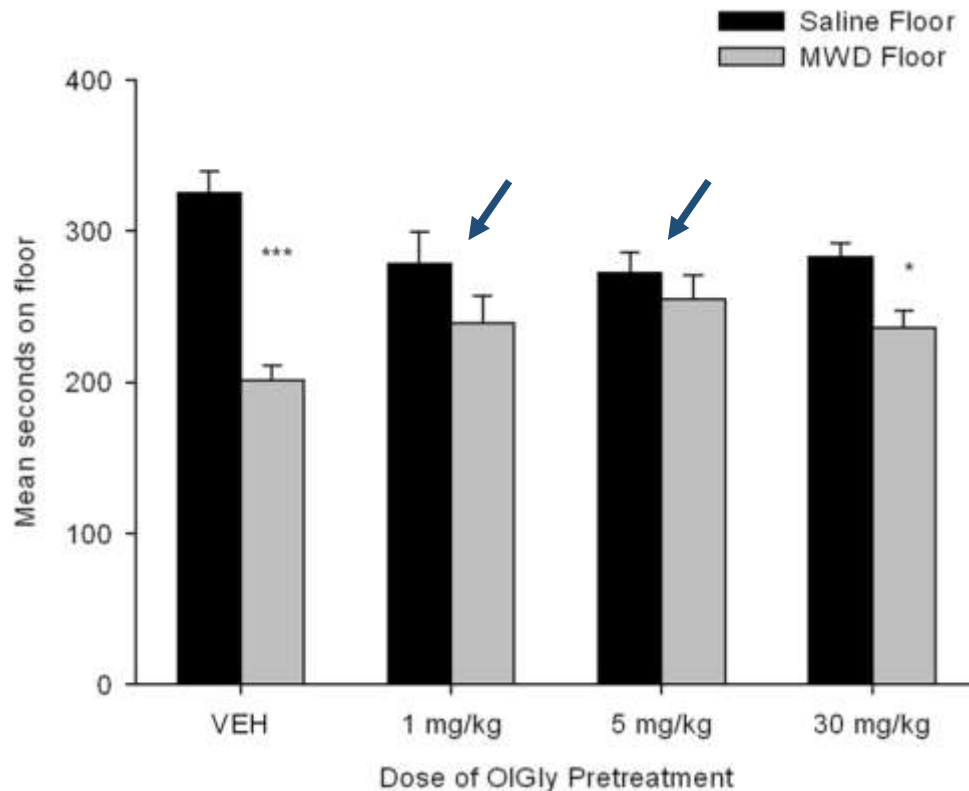
## Conditioned Place Preference (CPP)



**OIGly prevented nicotine reward, weakly inhibited FAAH and behaved as a PPAR- $\alpha$  receptor agonist**

# Morphine Addiction

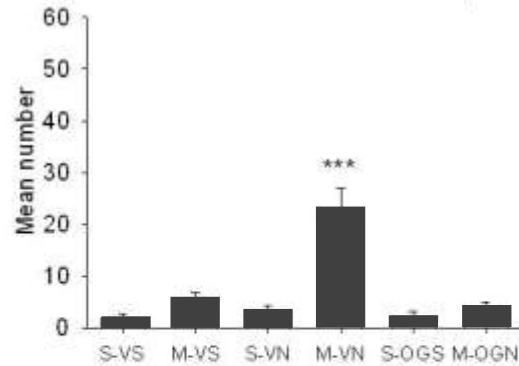
## Conditioned Place Aversion (CPA)



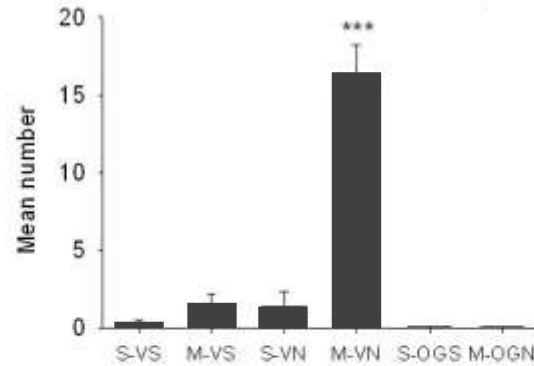
**OIGly blocked the aversive effects of Morphine Withdrawal (MWD), an effect that is reversed by CB1 antagonist**

# Morphine Addiction

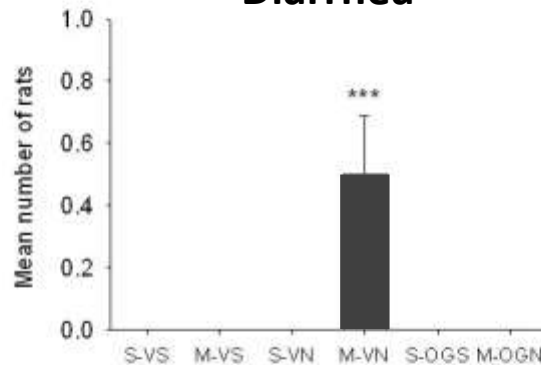
## Mouthing Movement



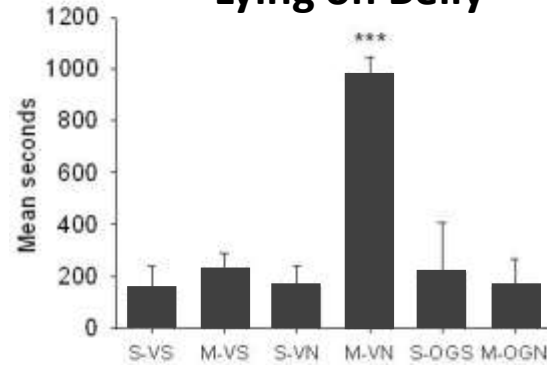
## Abdominal Contractions



## Diarrhea



## Lying on Belly



**OlGly suppressed acute naloxone-precipitated MWD nausea-like somatic behaviors, an effect that was prevented by PPAR- $\alpha$  and CB1 antagonists**

 amide bond

Oleoyl glycine

$\alpha$ -methylation of Anandamide

Anandamide

Methanadamide

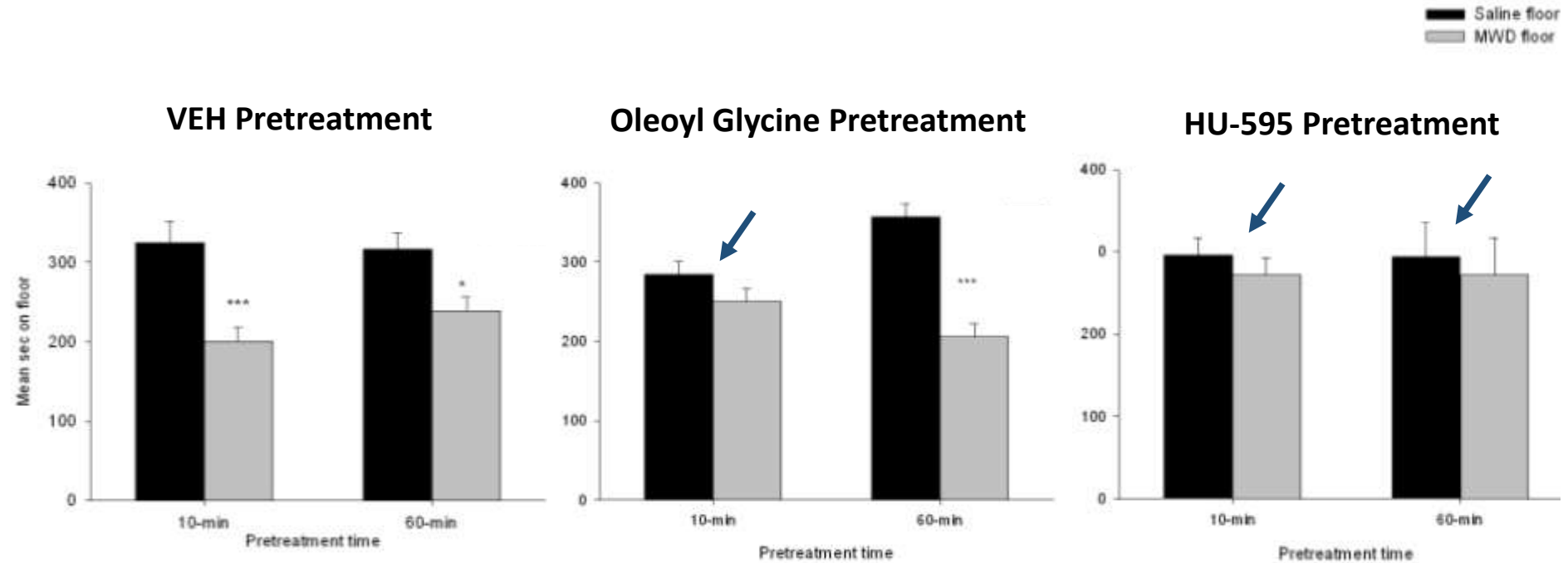
Abadji, V, et al. (1994)



Methyl Oleoyl glycine (HU-595)

Dimethyl Oleoyl glycine (HU-596)

# Morphine Addiction



**Monomethyl oleoyl glycine (HU-595) produced a longer lasting interference than OIGly with acute naloxone-precipitated MWD, an effect that was prevented by both a PPAR- $\alpha$  and a CB<sub>1</sub> antagonists**

# Summary

- The EC-like compound OIGly interferes with nicotine addiction and acute naloxone-precipitated morphine withdrawal
- Monomethylated OIGly, may be a more stable agent to combat the aversive effects of acute naloxone-precipitated MWD than OIGly



# Acknowledgments

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