

# Stimulation of Histamine H3 Receptors Improves Memory in an Animal Model of Memory Disorders.

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# H<sub>3</sub>-type histamine receptors

- Histamine
  - Plays a role in arousal
  - Released from the hypothalamus
  - Binds to four different receptors
- H<sub>3</sub>-type histamine receptor
  - Found in cortex and limbic system
  - Acts as presynaptic receptor
  - Regulates neurotransmitter release



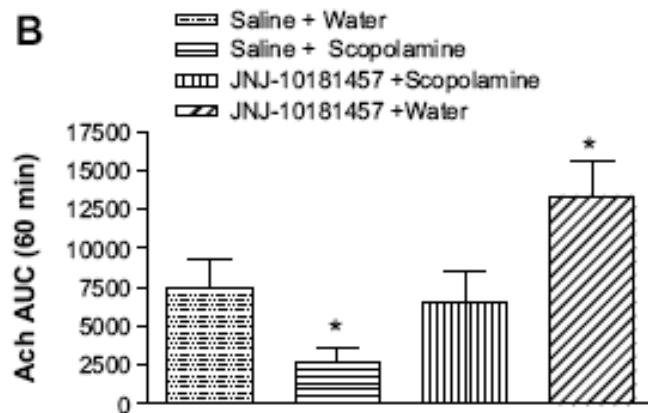
Receptor mRNA

From Pillot, C. et al.

Neuroscience 114:173 (2002)

# H<sub>3</sub> and memory

- Receptor antagonists may enhance cognition.
  - Increase theta-type EEG activity.
  - Elevate cortical dopamine and acetylcholine release.
  - Improve memory in normal rats and alleviate deficits produced by cholinergic blockade.

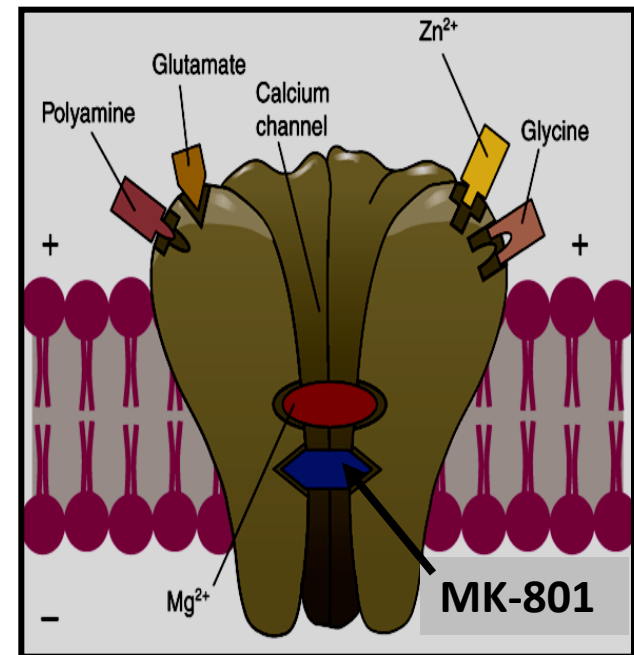


Effects of H<sub>3</sub> antagonist, JNJ-10181457, on acetylcholine release in rat frontal cortex

Galici, R. et al. Neuropharmacol (in press).

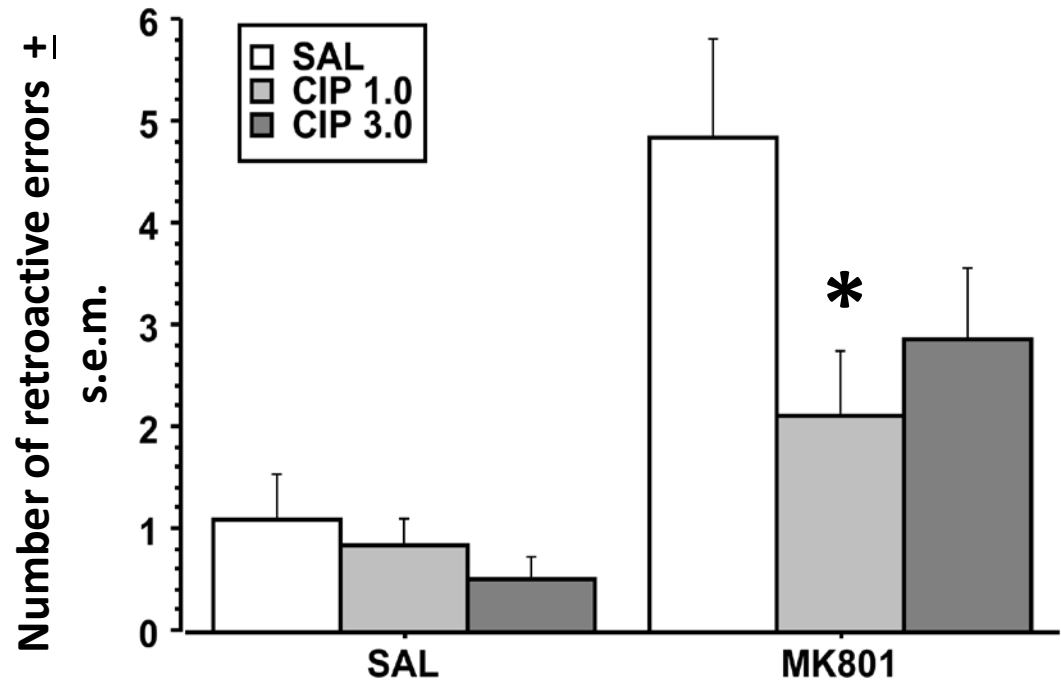
# The NMDA receptor hypofunction (NRH) model of memory deficits

- Blockade of NMDA-type glutamate receptors in humans causes memory impairment and psychosis.
- Similar antagonism in rats causes hyperactivity, sensorimotor gating impairment, and spatial memory deficits.



# An H<sub>3</sub> antagonist alleviates NRH-induced spatial memory deficits

- Tested adult male rats in a radial arm maze.
- Pretreated with H<sub>3</sub> antagonist, ciproxifan (CIP), or saline.
- Treated with NMDA antagonist, MK-801 or saline.



MK-801 effect:  $F(1, 59) = 24.1, p < .0001$ ; Ciproxifan effect:  $F(2, 59) = 3.8, p < .03$  \* indicates different from SAL-MK801 group,  $p < .02$ .

# Does an H<sub>3</sub> agonist exacerbate memory impairment in the NRH model?

- Design:
  - 12 male Long-Evans rats
  - Train in a win-shift version of the radial arm maze task to proficiency.
  - Drug testing
    - Pre-treat with H<sub>3</sub> agonist, imetit, or saline 40 min before testing.
    - Treat with NMDA antagonist, MK-801 or saline 20 minutes prior to testing.

# Radial arm maze task

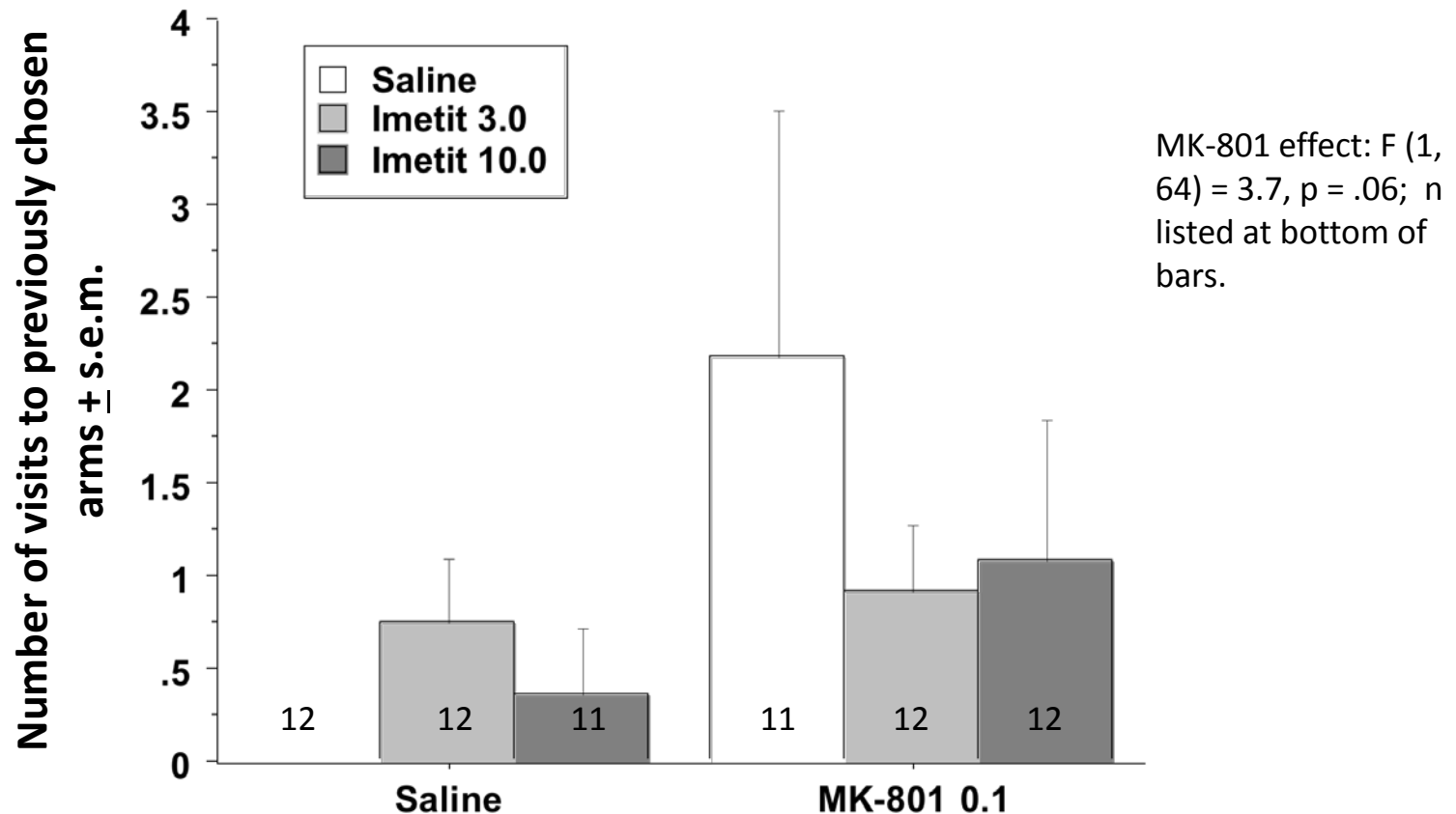
*Forced run:* Block four arms and bait remaining four arms. Measure number of arm revisits.

*30 second delay*

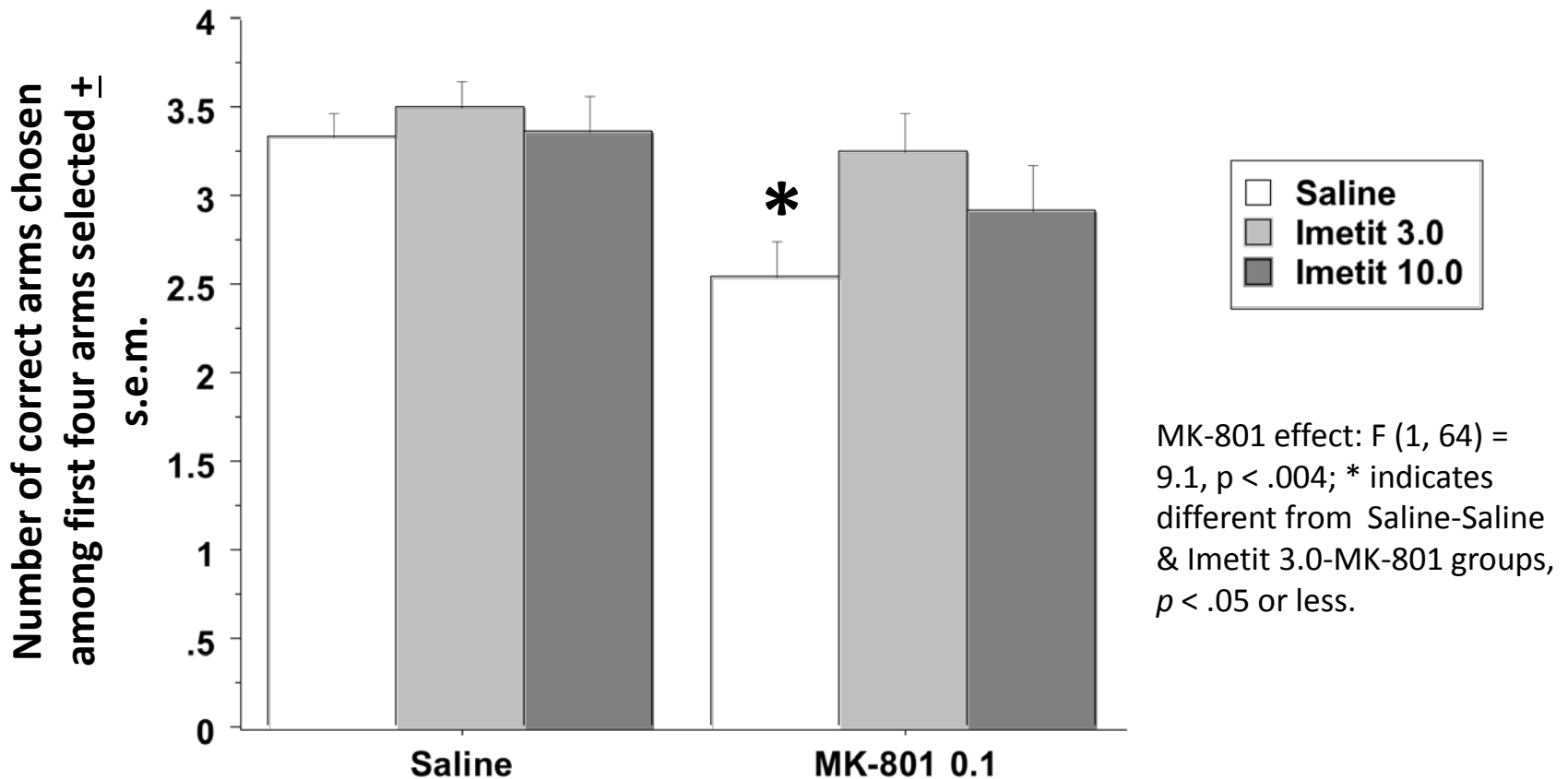
*Free run:* Only bait arms blocked during forced runs. Measure: a) number of correct choices out of first four, b) revisits to baited arms, and c) visits to arms baited during forced run (retroactive errors).



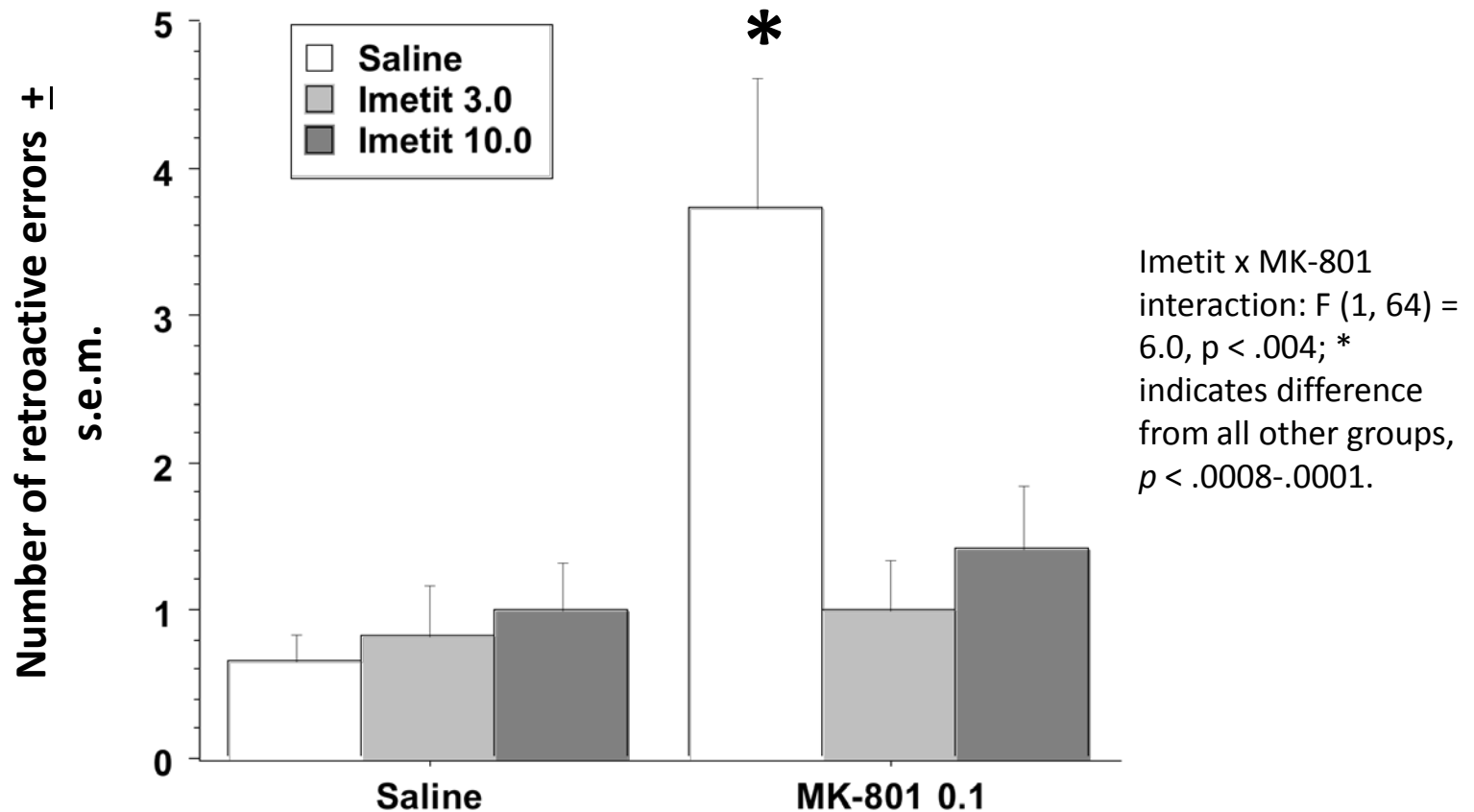
# Revisit errors on forced choice run are increased by MK-801



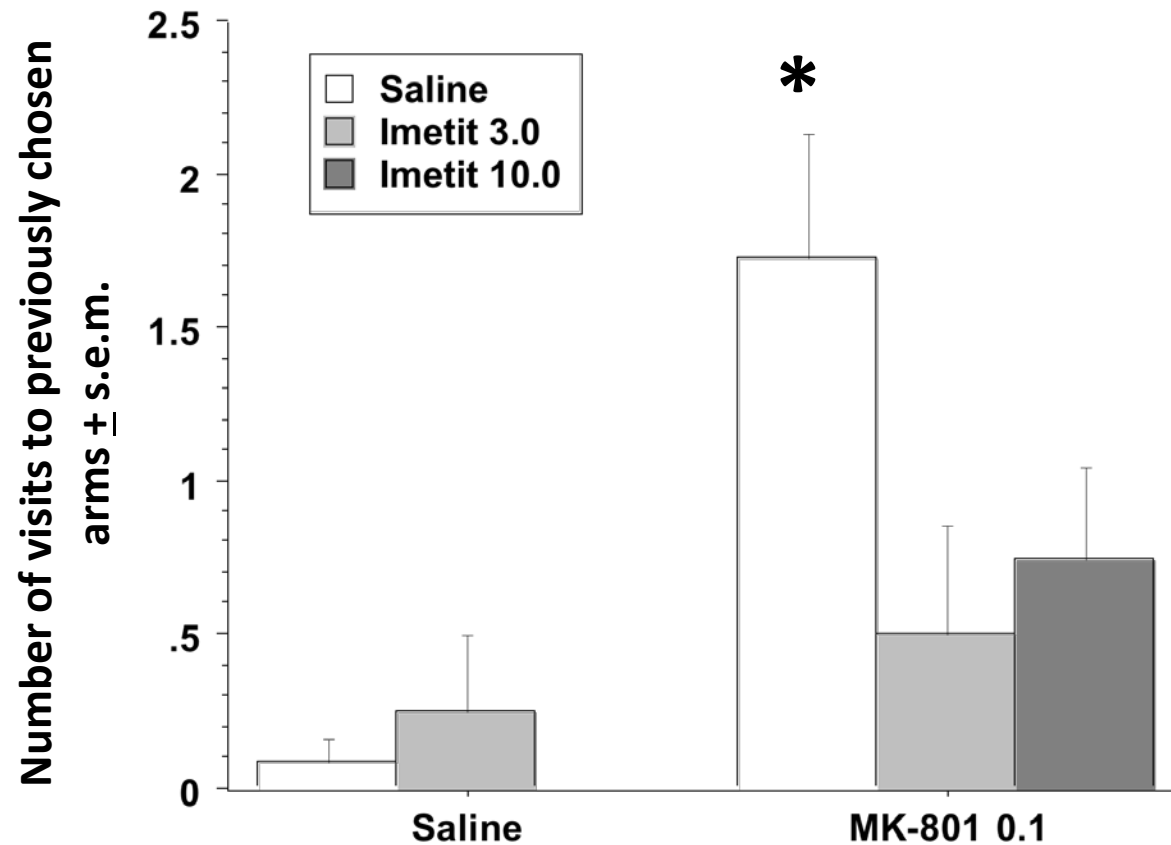
# Imetit reverses the effect on MK-801 on the first four arms selected during the free choice run.



# Imetit reduces the number of retroactive errors produced by MK-801 on the free choice run.



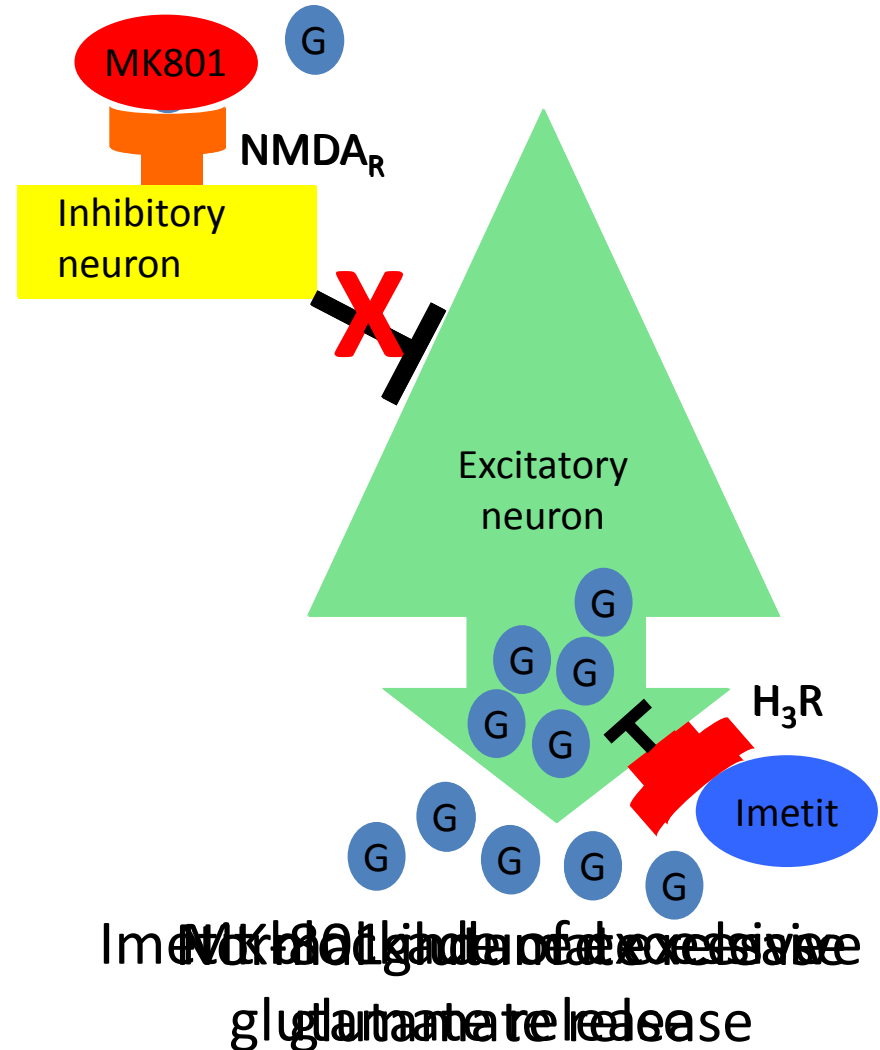
# Imetit reduces the number of revisit errors on the free choice run produced by MK-801.



Imetit x MK-801 interaction:  $F(1, 64) = 3.3, p < .04$ ; \* indicates difference from all other groups,  $p < .02-.0001$ .

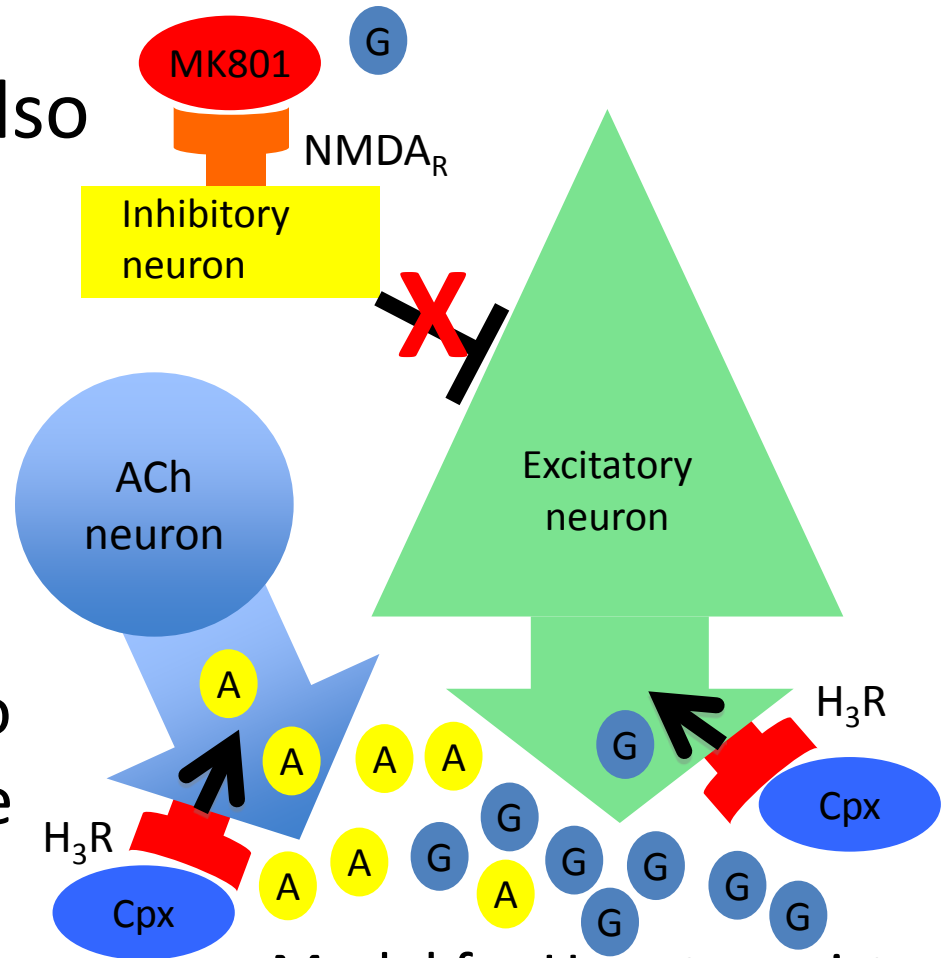
# Conclusions

- An H<sub>3</sub> agonist *alleviated* memory impairments in the NRH model.
  - By blocking excessive glutamate release induced by MK-801?



# Conclusions

- But H<sub>3</sub> antagonists also alleviate memory impairments in the NRH model.
  - By elevating acetylcholine and dopamine release to counteract excessive glutamate release?



Model for H<sub>3</sub> antagonist improvement of memory

# Conclusions

- The complex interaction between H<sub>3</sub> and NMDA receptors deserves much greater empirical attention.
  - Such work may lead to better treatments for memory deficits in schizophrenia and Alzheimer's disease.



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Fellowship

**AWARDEE**