

# Neurotoxicity of Methamphetamine

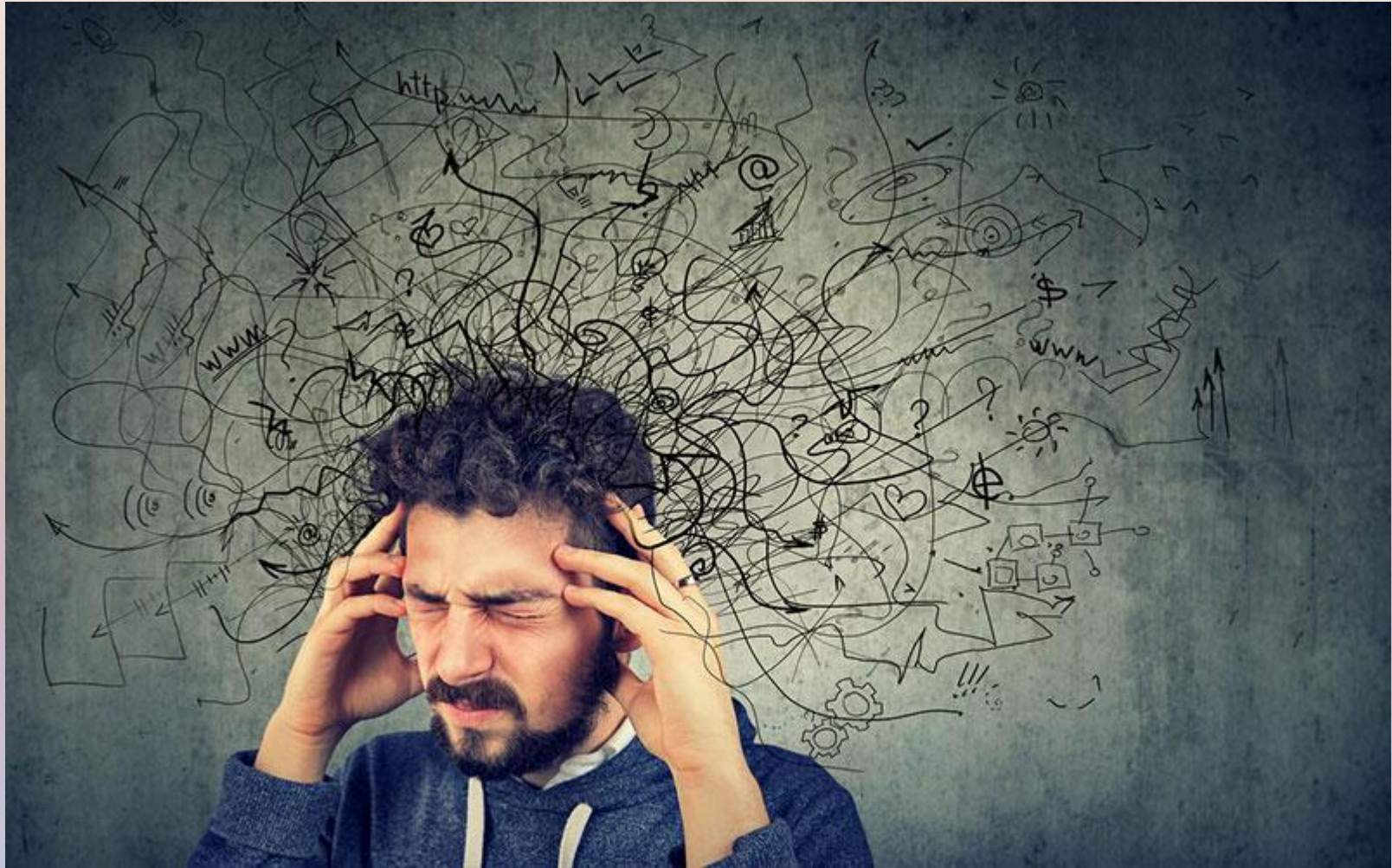
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# Neurotoxicity

- Side effects of Methamphetamine abuse that persist in periods of abstinence
  - Psychosis
  - Tremors and other movement problems
  - Cognitive changes

# Psychosis



# Psychosis

- Occurs in perhaps half of methamphetamine users
- Generally is limited to time immediately following use
- Persistent psychosis may occur in ~15% of patients
- Usually requires time to develop- usually over a year of use

# Psychosis

- Imaging, such as PET-CT and MRI show similarities between methamphetamine associated psychosis and schizophrenia
- Similar cognitive impairments are grossly seen in Methamphetamine associated psychosis as are seen in Schizophrenia
- Substance Induced Psychosis is practically indistinguishable from Schizophrenia

# Psychosis

- Generally patients seem to improve with antipsychotic use
- Increased risk of extra-pyramidal side effects in patients both with Schizophrenia who use methamphetamine and patients with Methamphetamine Associated Psychosis

# Movement Disorders



# Movement Disorders

- Chorea, athetosis, tremor, dystonia, ataxia and bruxism are all associated with Methamphetamine and Amphetamine use
- The above can occur immediately following use, during withdrawal, or chronically in periods of abstinence
- Syndromes resembling Neuroleptic Malignant Syndrome are thought to have occurred during periods of withdrawal and induced withdrawal (when neuroleptics are given) from amphetamines



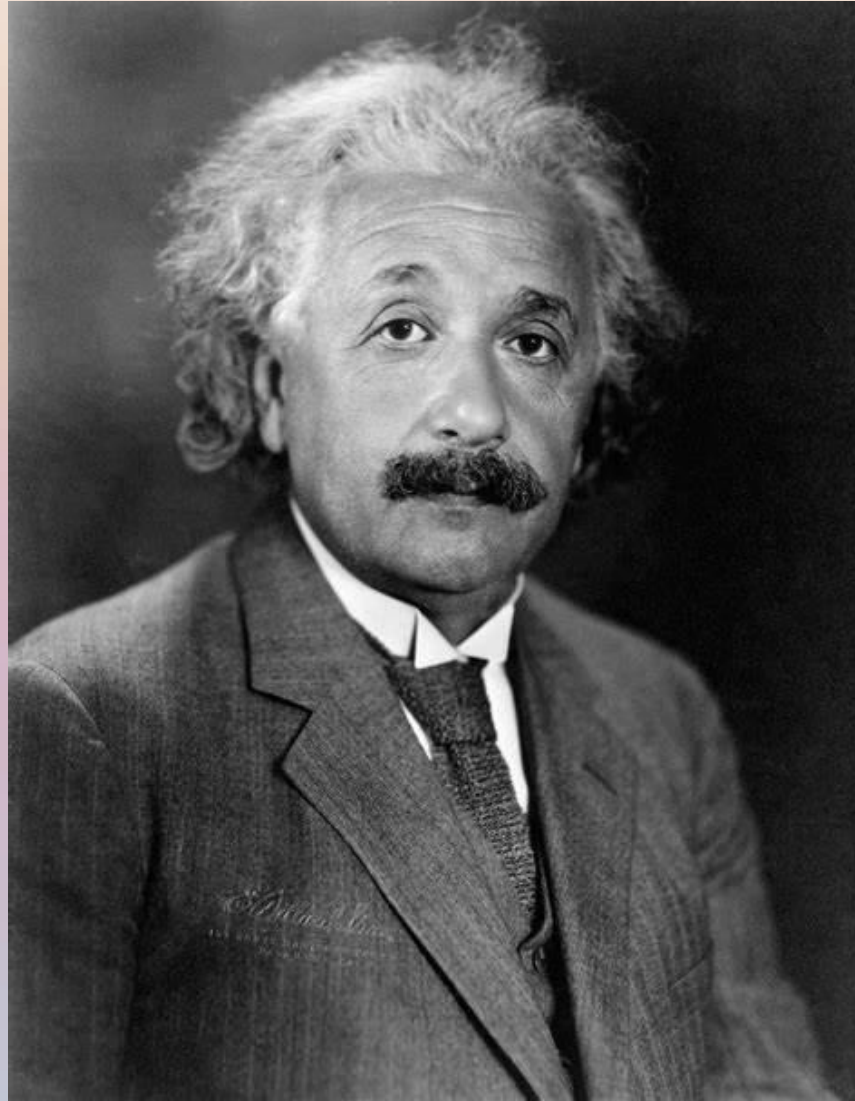
# Movement Disorders

- Recent increasing interest in association with Parkinson's disease
- Callaghan 2012- Nearly two-fold increase in Parkinson's disease among individuals with history of hospitalization for methamphetamine abuse
- Curtin 2014- Three-fold increase in Parkinson's disease in abusers of methamphetamine or amphetamine. No increase in risk in abusers of cocaine
- Methamphetamine users more typically have mild deficits in fine motor coordination (for example, manipulating a peg board) as opposed to Parkinsonian traits

# Movement Disorders

- Syndromes resembling Neuroleptic Malignant Syndrome are thought to have occurred during periods of withdrawal and induced withdrawal (when antipsychotics are given) from amphetamines

# Cognitive Changes



# Cognitive Changes

- Executive function
- Memory
- Social Cognition
- Anhedonia

# Executive Function



# Executive Function

- Arguably the most evidence for impairment exists for this category
- 'Mild' to 'Severe' impairments in Working Memory and Inhibitory Control in various studies when compared to controls

# Executive Function

- Some question as to whether methamphetamine is causative:
  - Very high prevalence of childhood ADHD symptoms in methamphetamine users.
  - Executive deficits are known to precede and be predictive of schizophrenia, which also has a high comorbidity with stimulant abuse.

# Memory





# Memory

- Multiple studies show mild impairments in multiple memory and learning categories.
- This impairment may be permanent (one study showed similar impairments ~2 years after initial evaluation)

# Memory

- Prospective Memory is thought to be particularly affected
- Prospective memory is needed for remembering future tasks, such as appointments.

# Social Cognition



# Social Cognition

- Methamphetamine users score poorly on emotional facial recognition tests
- Suggestive of difficulty with theory of mind and empathy

# Social Cognition

- There is evidence that they may not recognize threats as quickly but then overreact to threats once recognized
- Associated with vocational impairment

# Social Cognition

- Social cognition effects may fade.
- A longitudinal study found no difference between individuals in recovery and controls after 7 years of abstinence

# Anhedonia

- Leventhal 2010- Cross sectional study looking at depression and anhedonia in lifetime use of stimulants and those dependent upon stimulants (both cocaine and meth/amphetamine)
- Anhedonia alone (not depression) was found to be associated with both lifetime use as well as dependence
- Suggestive of either anhedonia leading to both sampling of stimulants as well as subsequent dependence or anhedonia being a result of their use.
- The results were similar when cocaine and amphetamines were separated.

# Why Neurotoxicity Occurs

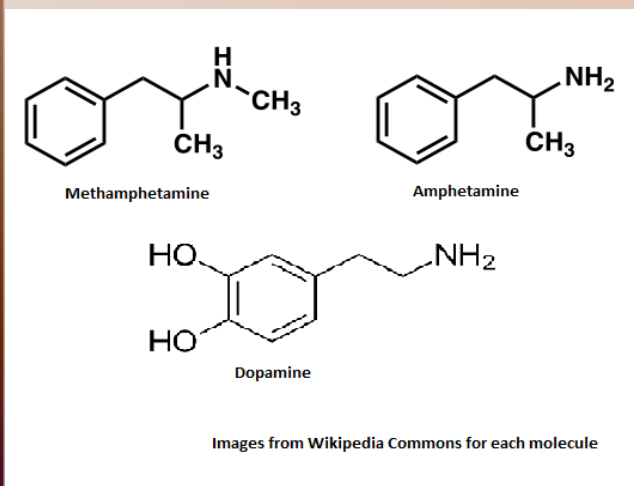




# How Methamphetamine (and Amphetamine) Work

- It does more than ‘increases dopamine’
- Two main binding sites for therapeutic effects:
  - TAAR-1
  - VMAT

# Trace Amine Associated Receptor (TAAR-1)

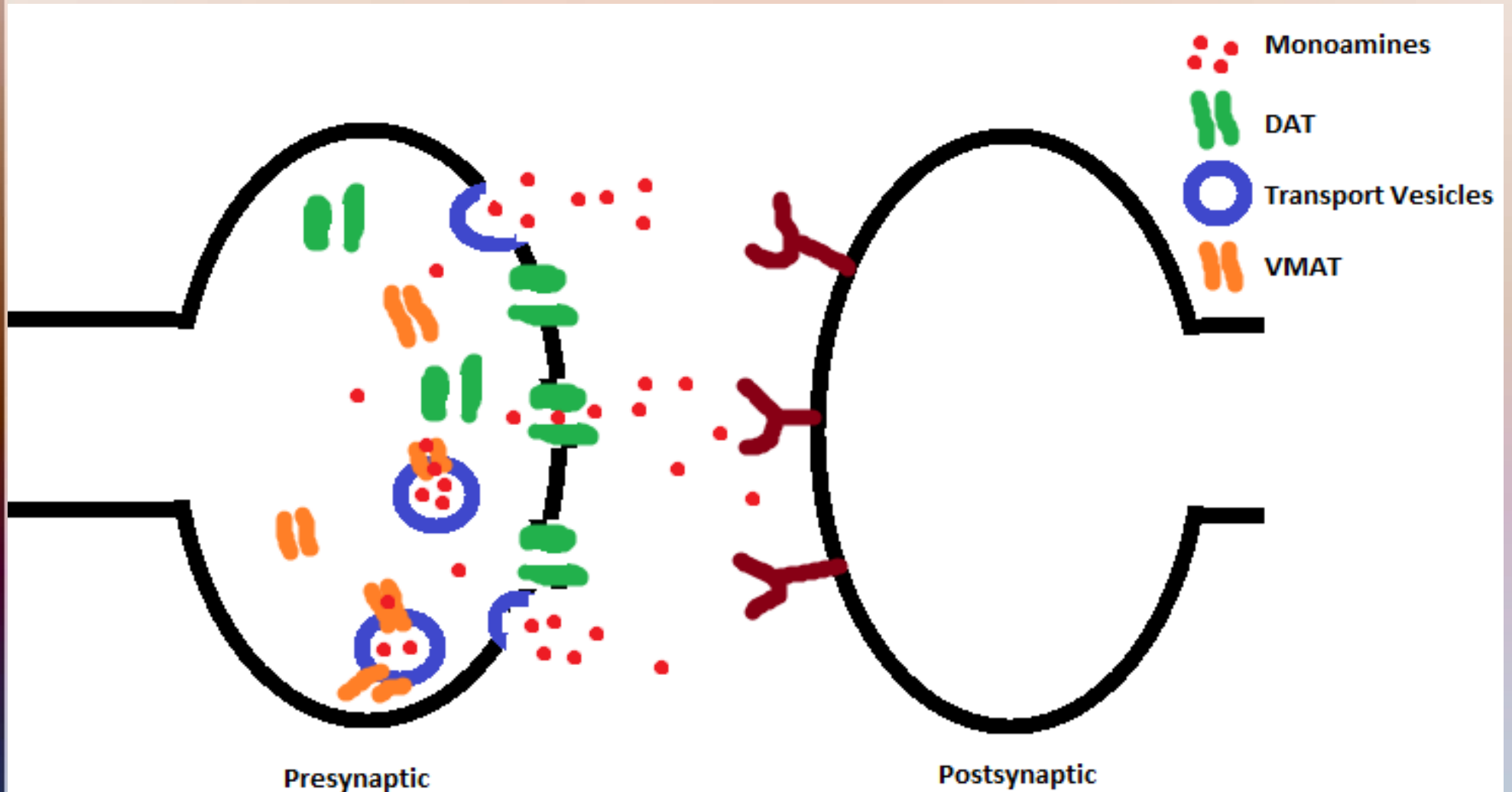


Agonistic TAAR1 ligands	
ADRB1/2 ligands	
antagonistic	agonistic
<p>Tyramine</p> <p><chem>NCCc1ccc(O)cc1</chem></p>	<p>(-) Isoprenaline</p> <p><chem>CC(C)NCC(O)c1cc(O)c(O)cc1</chem></p>
<p><math>\beta</math>-Phenylethylamine</p> <p><chem>NCCc1ccccc1</chem></p>	<p>(-) Adrenaline</p> <p><chem>CNCC(O)c1cc(O)c(O)cc1</chem></p>
<p>(+/-) Octopamine</p> <p><chem>NCC(O)c1ccc(O)cc1</chem></p>	<p>(-) Noradrenaline</p> <p><chem>NCC(O)c1cc(O)c(O)cc1</chem></p>

# Trace Amine Associated Receptor (TAAR-1)

- Normally binds *Trace Amines* (eg. Tryptamine, Phenethylamine)
  - Metabolic relatives of monoamine neurotransmitters like S, D, NE
- TAAR is *presynaptic* and *intracellular* (cytoplasm)
- Agonism of TAAR results in DAT (Dopamine transporter) either being turned off or reversing its flow
- Results in decrease in monoamine reuptake from synaptic cleft and an increase in monoamine release into the cleft
- Amphetamine, Methamphetamine, and MDMA, Phentermine are all TAAR-1 agonists
- Presynaptic Alpha 2 and 5HT1A have opposite effect as TAAR-1

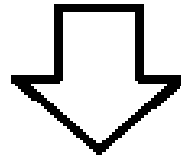
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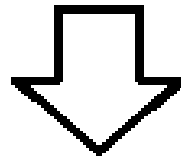
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**TAAR-1 Activation by Amphetamine**



**DAT (Dopamine Reuptake Transporter) turns off. With further TAAR activation, it pumps in opposite direction.**



**More monoamines (mostly dopamine) outside of the cell, in the synaptic cleft.**

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**\*\*\*Cocaine, Methylphenidate, Bupropion just directly block the DAT (or SERT or NET)**

**They therefore do not cause retrograde flow through the transporters**

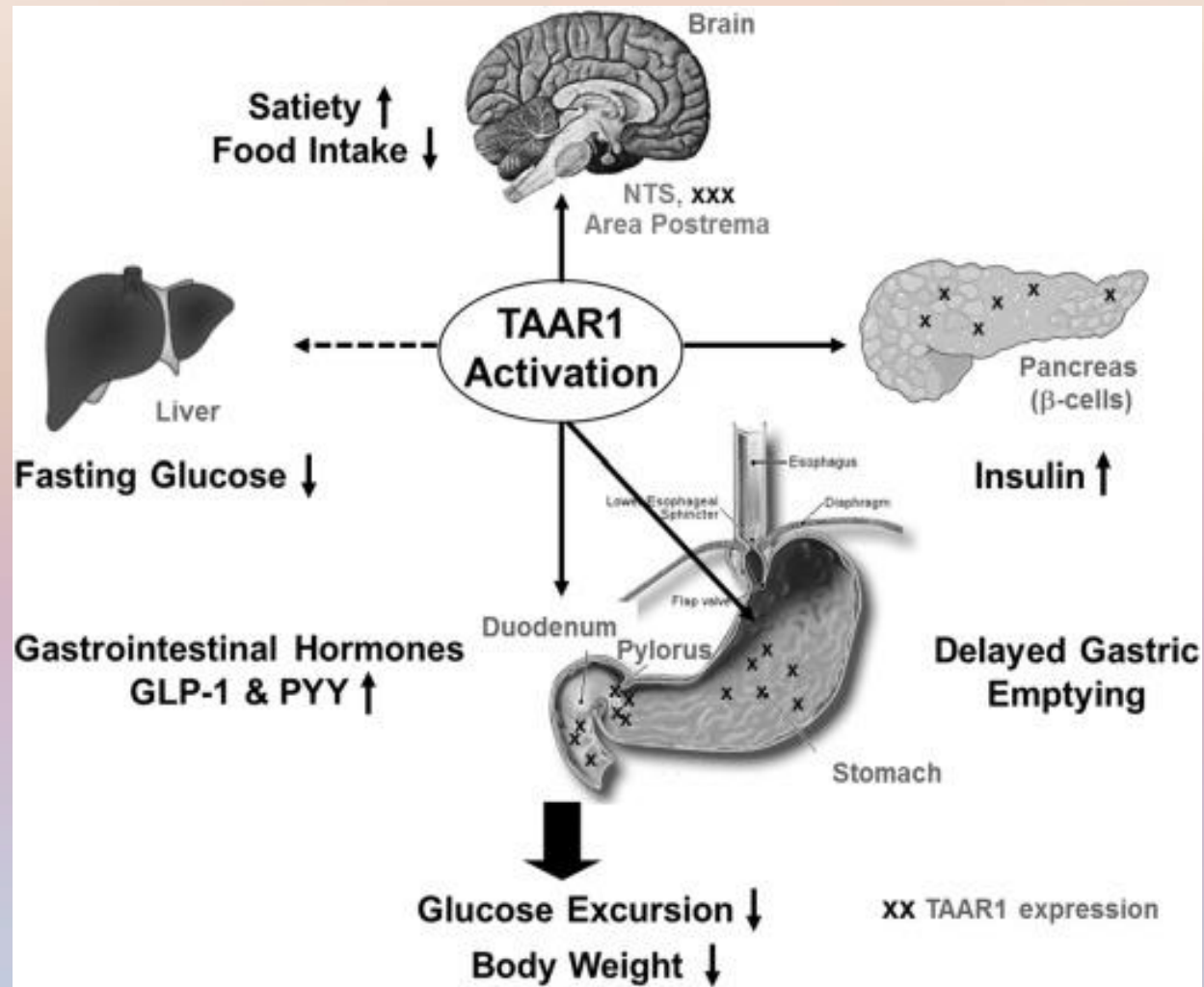
## Let me say that again

- Cocaine, Bupropion, Methylphenidate are not the same thing
- These are reuptake inhibitors (DAT). They do not bind TAAR.

# Overall Effects of TAAR agonism

- Increases monoamine neurotransmission. Especially NE and D
- Euphoria, wakefulness, increased sex interest, improved cognitive control
- Increased physical endurance, delays fatigue, allows higher tolerable core temperatures
- Releases GLP-1 from intestines, lowers appetite
- Hypertension, Raynaud's, movement disorders, increased respiration
- Psychosis, compulsive behavior, addiction, irritability and agitation at increasing doses

# Overall Effects





## Vesicular Monoamine Transporter (VMAT-2)

- Transporter responsible for loading monoamines from the cytoplasm into vesicles for expulsion into the synaptic cleft

# Vesicular Monoamine Transporter (VMAT-2)

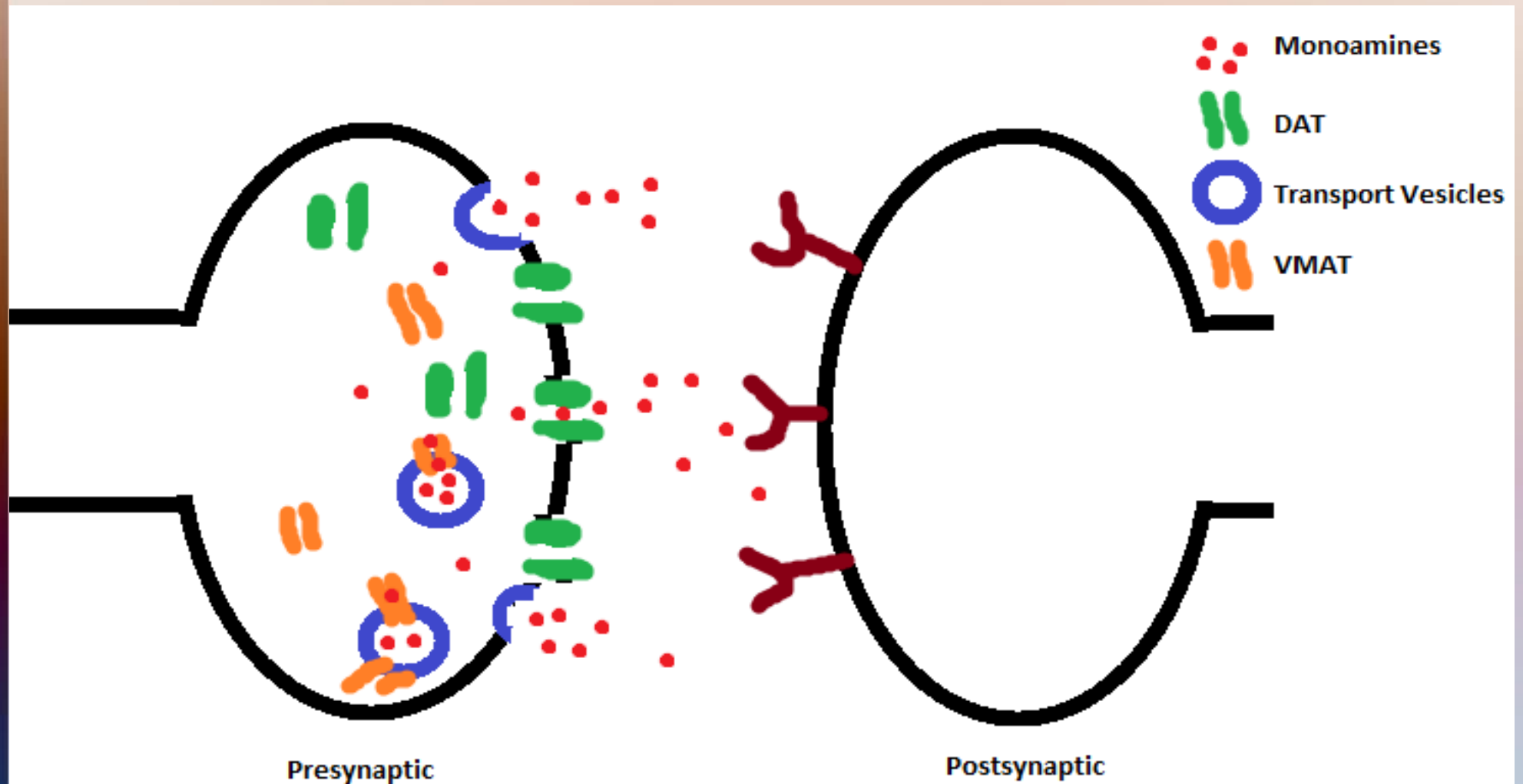
- Methamphetamine does two things to this transporter
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# Vesicular Monoamine Transporter (VMAT-2)

- Methamphetamine does two things to this transporter
  - It is a competitive antagonist
  - It triggers removal of the transporters from vesicle membranes
- Methylphenidate, Bupropion, and Cocaine all increase the number of VMAT proteins located in vesicle membranes

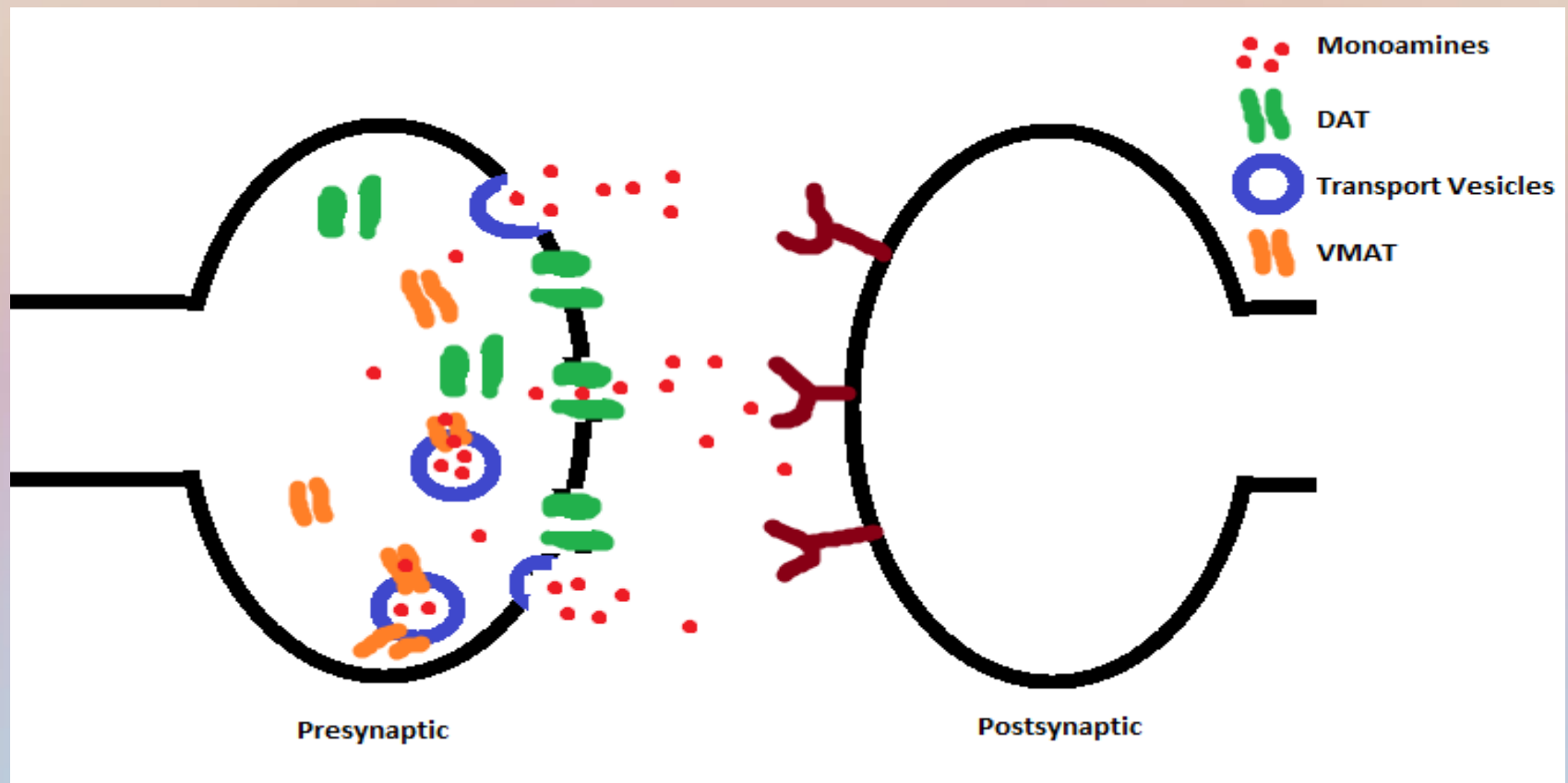
Methamphetamine does two things to VMAT-2:

- It is a competitive antagonist
- It triggers removal of the transporters from vesicle membranes



# Mechanisms of Injury

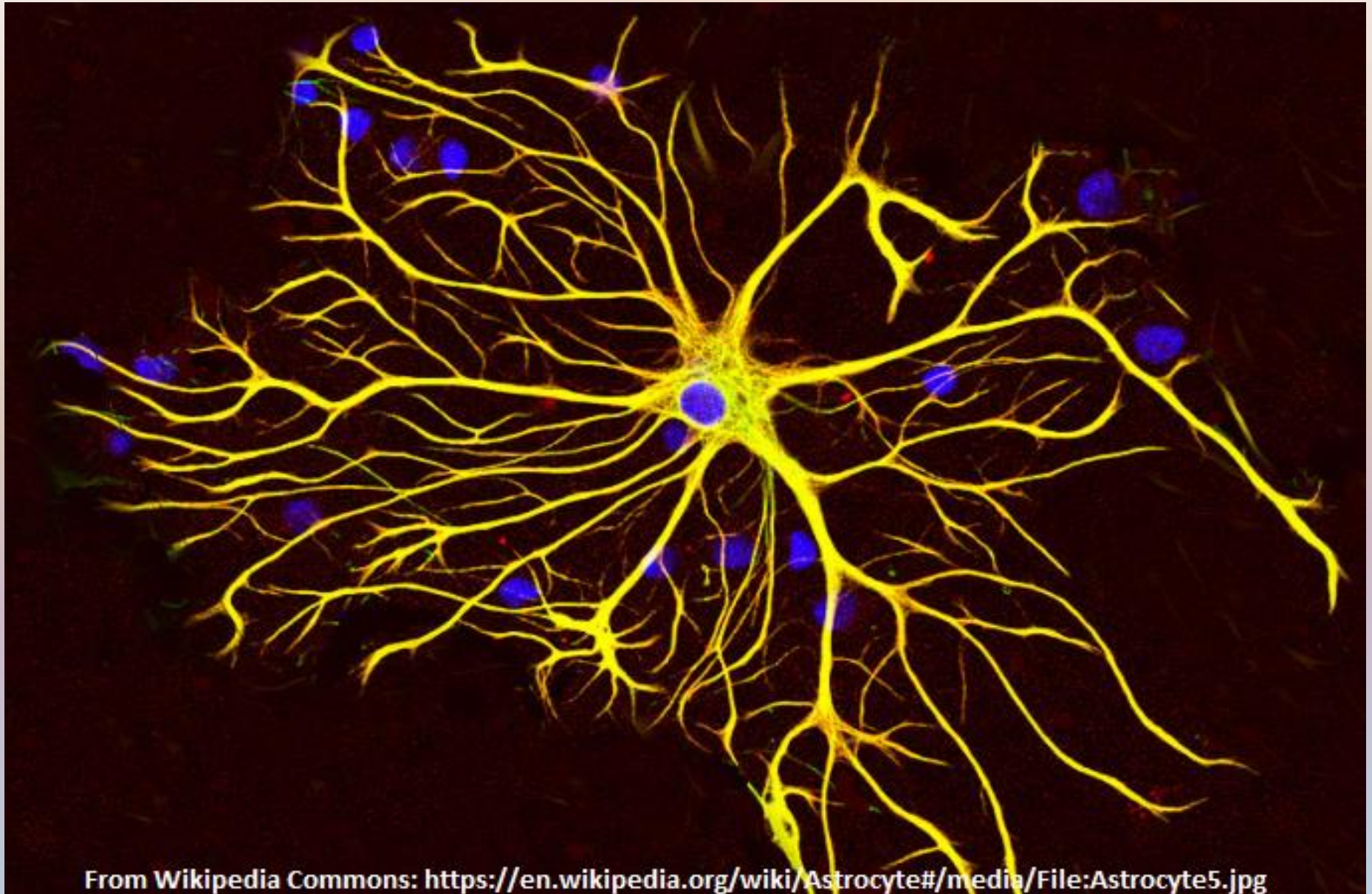
- DAT and VMAT get turned off and stay off.
- Cells make much less dopamine
- Results in hypodopaminergic state



# Neurologic Injury

- Extensive publications confirming decreases in dopamine and other monoamine levels (Serotonin as well as NE) following methamphetamine exposure
- Similar data showing long term decreases in DAT and VMAT proteins
- Similar patterns in mice, rats, monkeys and humans
- Studies include cellular assays from animals as well as PET and postmortem studies in humans
- Injury seems dose dependent
- Most of the studies use high dose Methamphetamine or Methamphetamine abusers (unclear what low dose amphetamines do)

# Additional Mechanisms of Injury



From Wikipedia Commons: <https://en.wikipedia.org/wiki/Astrocyte#/media/File:Astrocyte5.jpg>

# Sigma-1

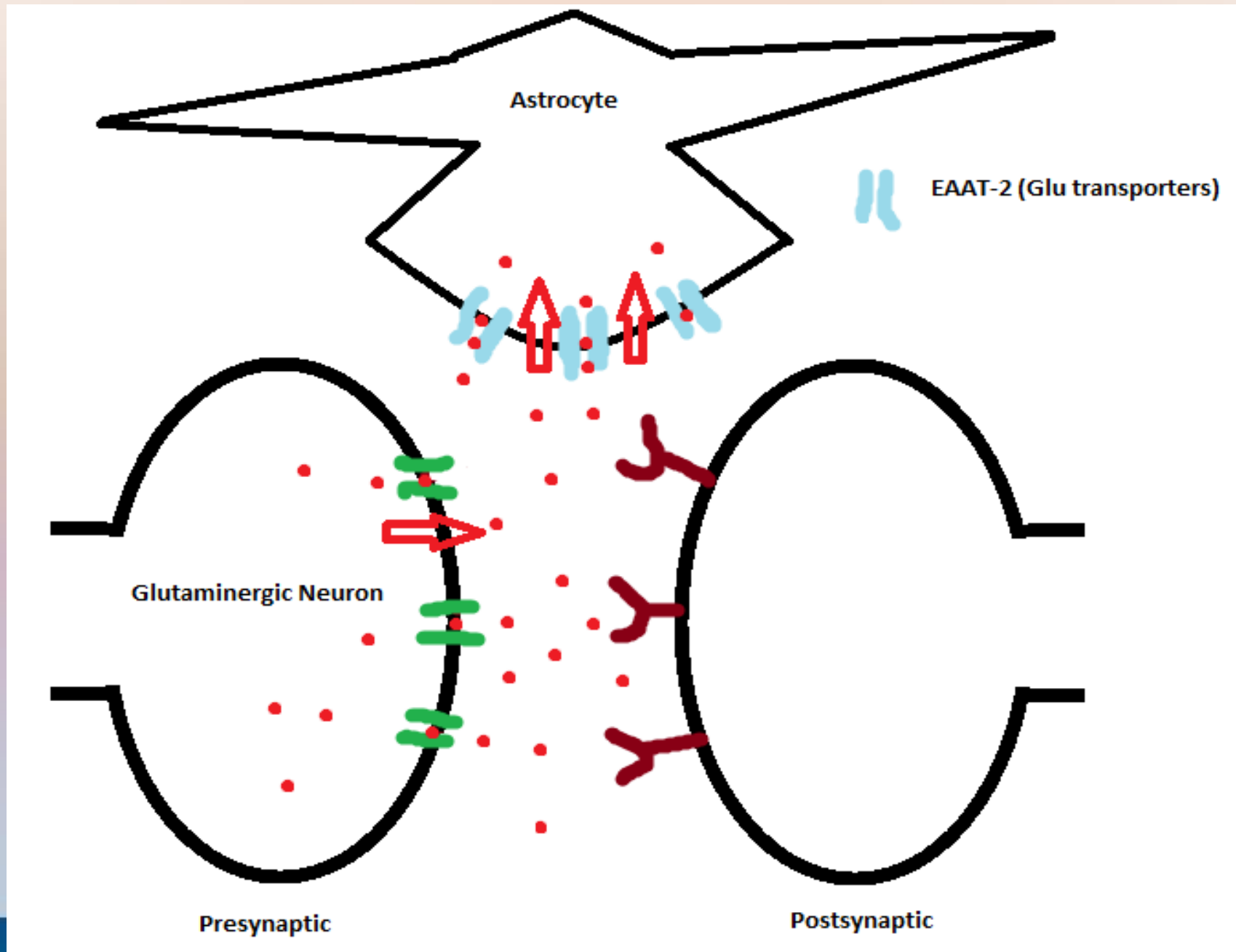
- Methamphetamine is an agonist for Sigma-1 ( $\sigma$ 1R)
- Sigma-1 is located in both microglia as well as neurons
- Binding of Sigma-1 by Methamphetamine may activate microglia, resulting in neuronal injury
- Binding of Sigma-1 by MA may be the signal that leads to reduction in VMAT expression in neurons
- Sigma-1 may also have something to do with addiction. Antagonists of Sigma-1 seem protective from addictive behaviors in mice
- Pridopidine is a Sigma-1 agonist (Huntingtons Disease)



## EAAT-2

- Excitatory Amino Acid Transporter (basically Glutamate reuptake transporter)
- Located on astrocytes. They are responsible for absorbing 90% of the glutamate secreted in the brain
- Astrocytes have TAAR-1 receptor too
- When Methamphetamine activates TAAR, EAAT-2 is downregulated
- EAAT-2 downregulation is correlated with compulsive behavior
- Interestingly, upregulation of EAAT-2 is associated with schizophrenia (glutaminergic antagonism)
- EAAT-2 is the suspected target of N-acetyl cysteine for substance use disorders

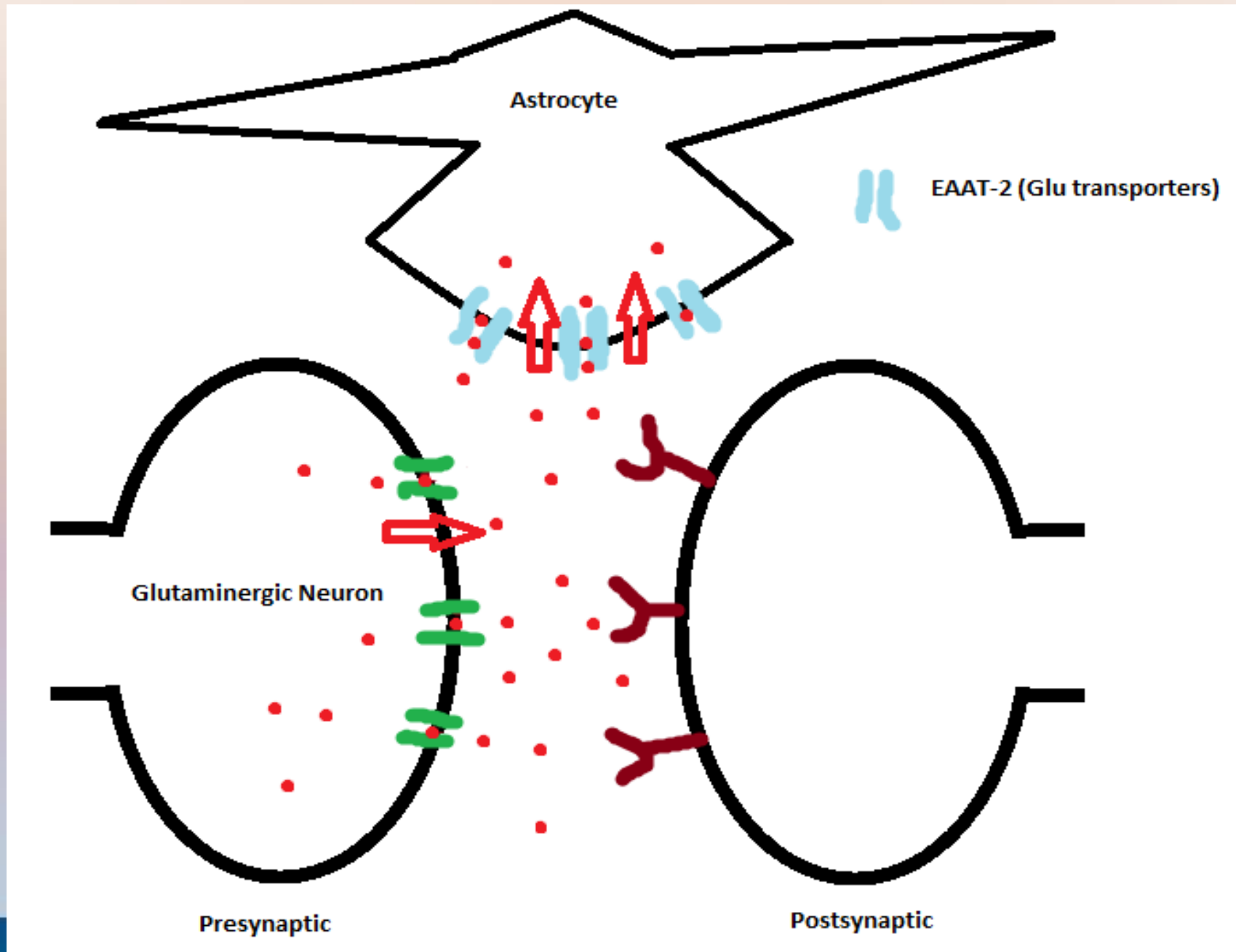
# Additional Mechanisms of Injury- EAAT-2



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# Methamphetamine vs Reuptake Inhibitors (eg Cocaine)

- Both affect D and NE neurotransmission
- Methamphetamine works inside cells resulting in additional effects
- Methamphetamine has additional receptor effects: Sigma, EAAT

# Macro Injuries

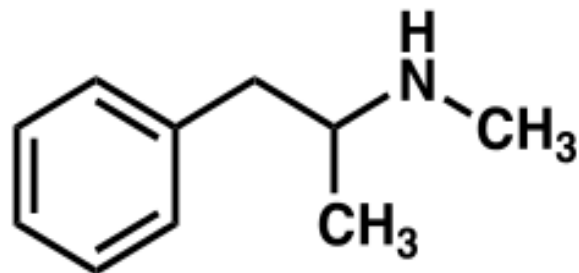
- Stimulant use increases the risk for stroke
- Hyperthermia is associated with neurologic injury
- Poor impulse control can make injuries such as TBI more likely
- HIV in combination with methamphetamine use increases the incidence of HIV Associated Neurocognitive Disorder- possibly from immunologic modification of astrocyte function by methamphetamine
- Poor nutrition
- Drug dependence of any type seems to result in neurologic changes

# Permanent injury?

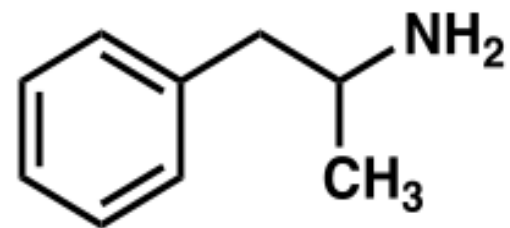
- Cell death generally does not occur (but it does sometimes)
- Cell bodies remain intact while the morphology of the synapses change
- Some changes may reverse with time (months to years)
- Many changes seem to be permanent- at least in time frames of years
- Recovery is slow to happen when it does (minimum of 3 months in some studies after cessation of use)
- Recovery has been seen both in imaging (PET) and in functional assessments in humans (motor and verbal processing, for example)



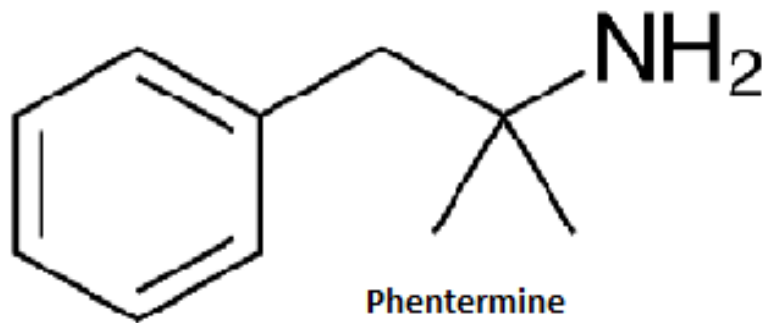
# How are Meth and Amphetamine different?



Methamphetamine



Amphetamine



Phentermine

Images from Wikipedia Commons for each molecule

# How are Meth and Amphetamine different?

- We are a bit unsure
- Methamphetamine is more lipid soluble than Amphetamine. It enters the brain easier and stays longer
- Methamphetamine seems to be much more potent outside of its ease at crossing into the brain: Goodwin 2008 showed twice as much Ca influx in rat cells when exposed to Methamphetamine vs Amphetamine. Interestingly, this difference was in the Nucleus Accumbens only, not the Dorsal Striatum
- Goodwin noted that another study showed greater prolongation of dopamine pulses with equivalent doses of Amphetamine Salts and Dextroamphetamine

## Other Stimulants

- Many other stimulants have similar effects to Amphetamines but different mechanisms
- They tend to simply block reuptake transporters, like DAT, as opposed to binding to TAAR. They do not cause reversal in transporter function, VMAT downregulation, or (generally) the abnormal astrocyte response
- Data does not show associations between Cocaine and Methylphenidate and Parkinson's Disease

# Is Amphetamine Safe?

- Baumeister 2021. “Is ADHD a Risk Syndrome for Parkinson's Disease”. Harvard Psychiatry Review.
- Notes an increase in incidence of Parkinson's Disease and a recent retrospective study showing correlation between PD and ADHD.
- ADHD alone may be a risk factor for PD
- Treatment of ADHD with amphetamines creates a further 6-fold increase in incidence of PD in the study
- Methylphenidate may be a preferable agent to Amphetamine

# Treatment?

- Limited studies

# Treatment of Executive Dysfunction

- Should this be treated like ADHD?

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- What about the issues with Anhedonia?

# Treatment of Executive Dysfunction

- Should this be treated like ADHD?
- What about the issues with Anhedonia?
- Some evidence for use of Methylphenidate and Adderall
- Evidence for use of Bupropion
- Amitriptyline, Atomoxetine etc?
- Evidence for use of Mirtazapine
- Role of psychotherapy



# Treatment of Movement Disorders

- Limited and small studies
- Propranolol
- Mirtazapine
- Anticholinergics
- Benzodiazepines
- Dopamine Agonists (Ropinirole) or Stimulants

- The system modified by these drugs is a common target of many other psychotropic drugs. Consider: SSRIs, SNRIs, Antipsychotics

# History of Neurotoxicity

- Case reports of psychosis induced by amphetamine in 1935
- Experiments in 1970s producing psychosis with amphetamine and methamphetamine
- Evidence from animal models in 1980s showing persistent changes in monoamine levels and morphological changes in dopaminergic neurons in rodents following MA use
- PET abnormalities in stimulant abusers in 2000s and correlations between stimulant use and Parkinson's Disease.
- Discovery of TAAR in 2001
- In last 10 years, exploration of Sigma-1, EAAT-2, astrocyte activation and glutamate regulation

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