

Pharmacological Studies of Effort- related Motivational Function in Rodents: Relation to Fatigue/ Anergia/Avolition

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Disclaimer

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure

This certifies that I, John Salamone, have no financial relationship that is relevant to the subject matter of this presentation.

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Behavioral Activation and Effort-related Aspects of Motivation

- Motivated behavior is *directed* towards or away from stimuli, but it also is characterized by *activational* aspects
 - i.e., *Vigor, speed, or persistence of work output*
- *Activational aspects* enable organisms to *initiate and sustain the effort* necessary for overcoming *response costs* or constraints and obtain access to reinforcing stimuli



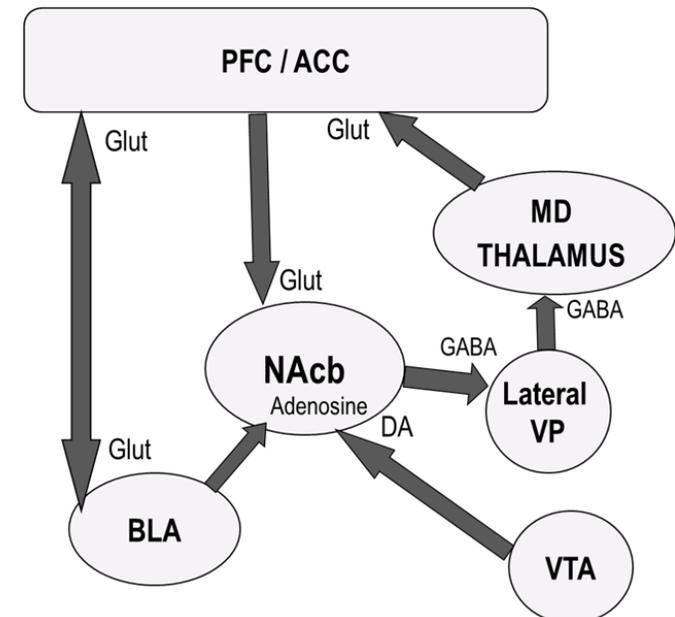
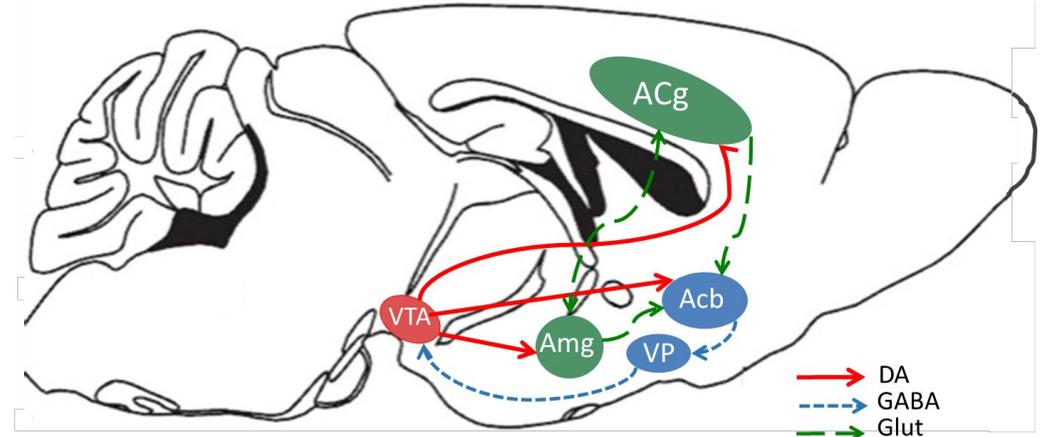
Behavioral Activation and Effort-related Aspects of Motivation: Clinical Implications

- Dysfunctions of behavioral activation seen in psychopathology: symptoms include – ***fatigue***; *central fatigue defined as “the failure to initiate and/or sustain attentional tasks (mental fatigue) and physical activities (physical fatigue) requiring self motivation” (Chaudhury & Behan (2000))*
- Other commonly used terms: *avolition, anergia, apathy, psychomotor retardation, lassitude, amotivation.*
- Seen in depression, schizophrenia, Parkinsonism, TBI, multiple sclerosis and other disorders.
- Symptoms such as anergia & fatigue not treated well with SSRIs (Targum & Fava 2011; Fava et al. 2014; Cooper et al. 2014; Rothschild et al. 2014; Ferguson et al. 2014).
- Evidence indicates that drugs that stimulate DA transmission, including bupropion (Wellbutrin), methylphenidate (Ritalin) and modafinil, can have positive effects on motivational symptoms in humans (Stotz et al. 1999; Papakostas et al. 2006; Friedman et al. 2007; Targum & Fava 2011; Bell et al. 2013; Muller et al. 2013; Cooper et al. 2014)

Effort-Related Motivational Function: Neural Circuitry in Humans & Rodents

- **Basal ganglia areas** including caudate, putamen, ventral striatum (nucleus accumbens), pallidal areas
- **Frontal cortical areas** including ventromedial prefrontal cortex, anterior cingulate cortex (PFC/ACC)
- **Limbic system areas** (basolateral amygdala).
- **DA systems** projecting to prefrontal cortex and *nucleus accumbens/ventral striatum*.

(Salamone et al. 2007, 2010, 2016, 2018; Farrar et al. 2008; Mingote et al. 2008; Nunes et al. 2013; Suzuki et al. 2020; Strasser et al. 2020)



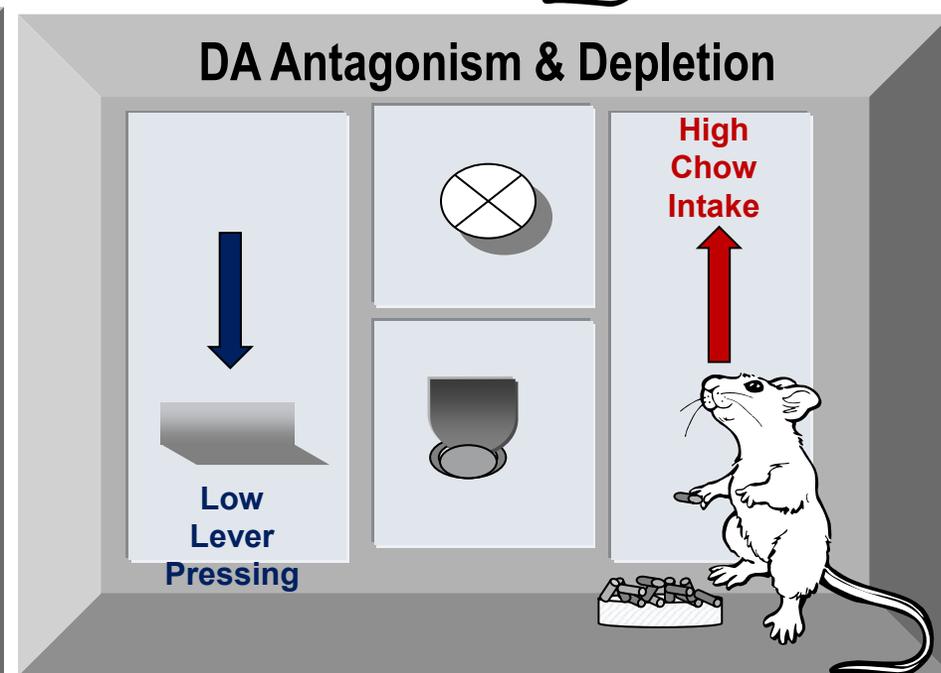
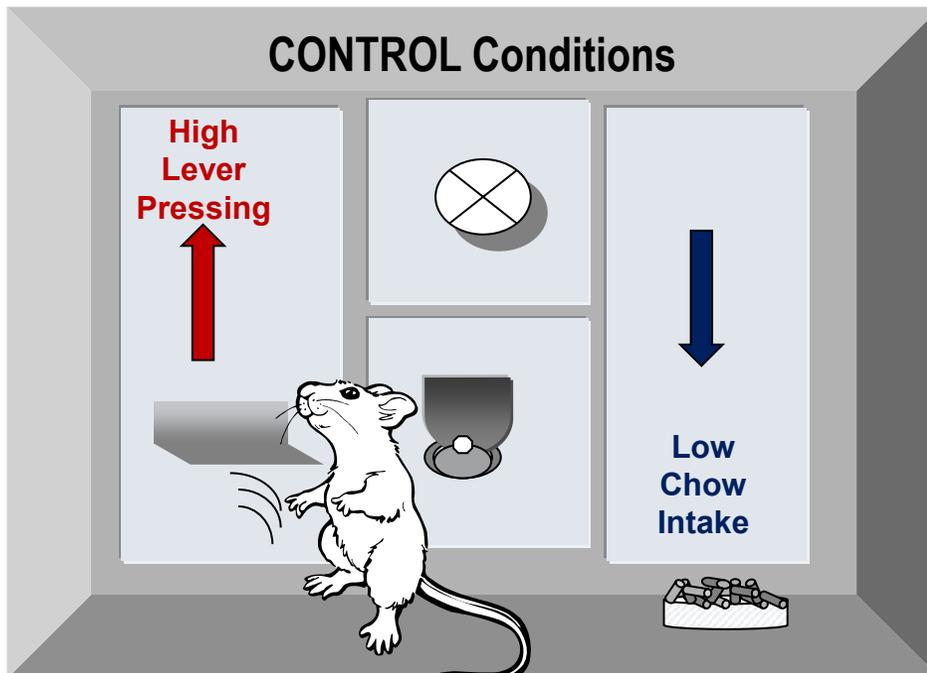
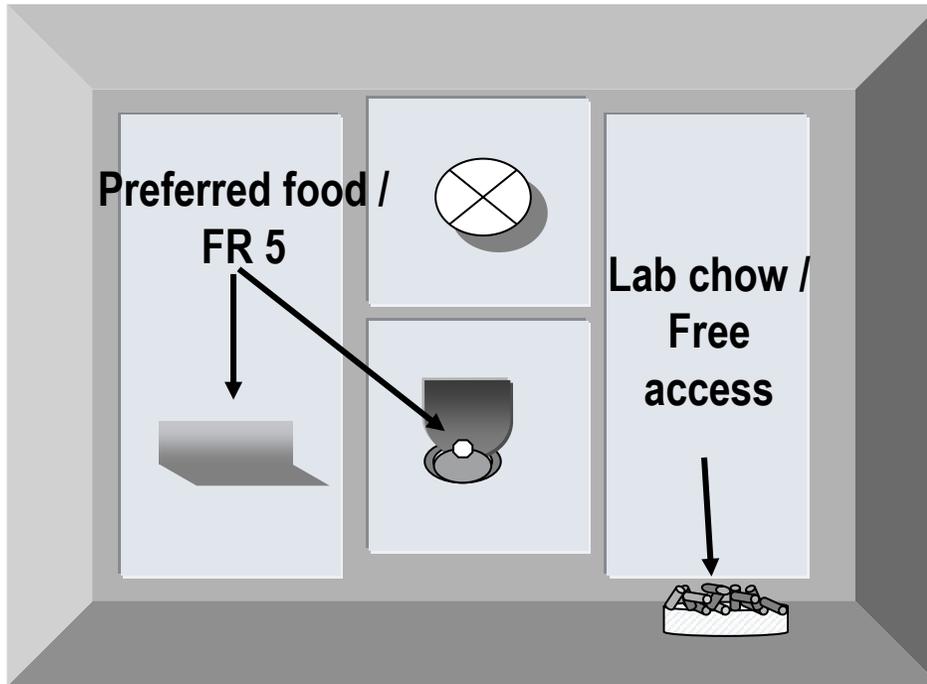
Dopamine and Motivation

- Common descriptions of the role of dopamine (DA) in motivation are often oversimplified
 - Inaccurate to say that DA is the “pleasure chemical”; DA also is involved in responsiveness to *stress, aversive motivation*; DA neuron activity & release also occurs in response to *aversive stimuli* (Salamone et al. 2007).
 - DA antagonism or depletion do not block hedonic reactivity to food (Berridge, Robinson & colleagues)
 - DA antagonism does not blunt the euphoria induced by drugs of abuse in humans (Gawin 1986; Brauer & DeWit 1998; Haney et al. 2001; Nann-Vernotica et al. 2001; Evans et al. 2001; Venugopalan et al. 2011)
- Basic Neuroscience Research: interference with mesolimbic *DA transmission produces effects that are selective and dissociative in nature*, with strong effects on activational aspects of motivation, but leaving other aspects intact (Salamone et al. 1991, 1997, 2002, 2007, 2016, 2017, 2018).
- Interference with ventral striatal DA reduces exertion of effort and ***alters effort-related decision making*** (Salamone et al. 2007, 2018, 2019)

Effort-Related Decision Making

- Organisms continually make effort-related choices **based upon cost/benefit analyses of reinforcement preference vs. costs and effort** (Salamone et al. 2007; Treadway and Zald 2011)
- Animals have a choice between a ...
 - High effort/preferred reward option vs.
 - low effort/less preferred reward option
- Several tasks in rodents have been developed for assessing effort-based decision making based upon physical effort
 - Fixed Ratio 5 (FR5)/Chow feeding choice (Salamone et al. 1991)
 - T-maze Barrier Choice (Salamone et al. 1994; Cousins et al. 1996)
 - Mouse Touch Screen FR/Pellet Choice (Yang et al. 2020)
 - Progressive Ratio (PROG)/Chow feeding Choice Task (Randall et al. 2012, 2014, 2015)
 - Running Wheel vs. Food choice (Correa et al. 2015)
 - Physical or Cognitive Effort Discounting (Floresco et al. 2008; Hosking et al. 2015)

CONCURRENT FR5 LEVER PRESSING/FEEDING TASK

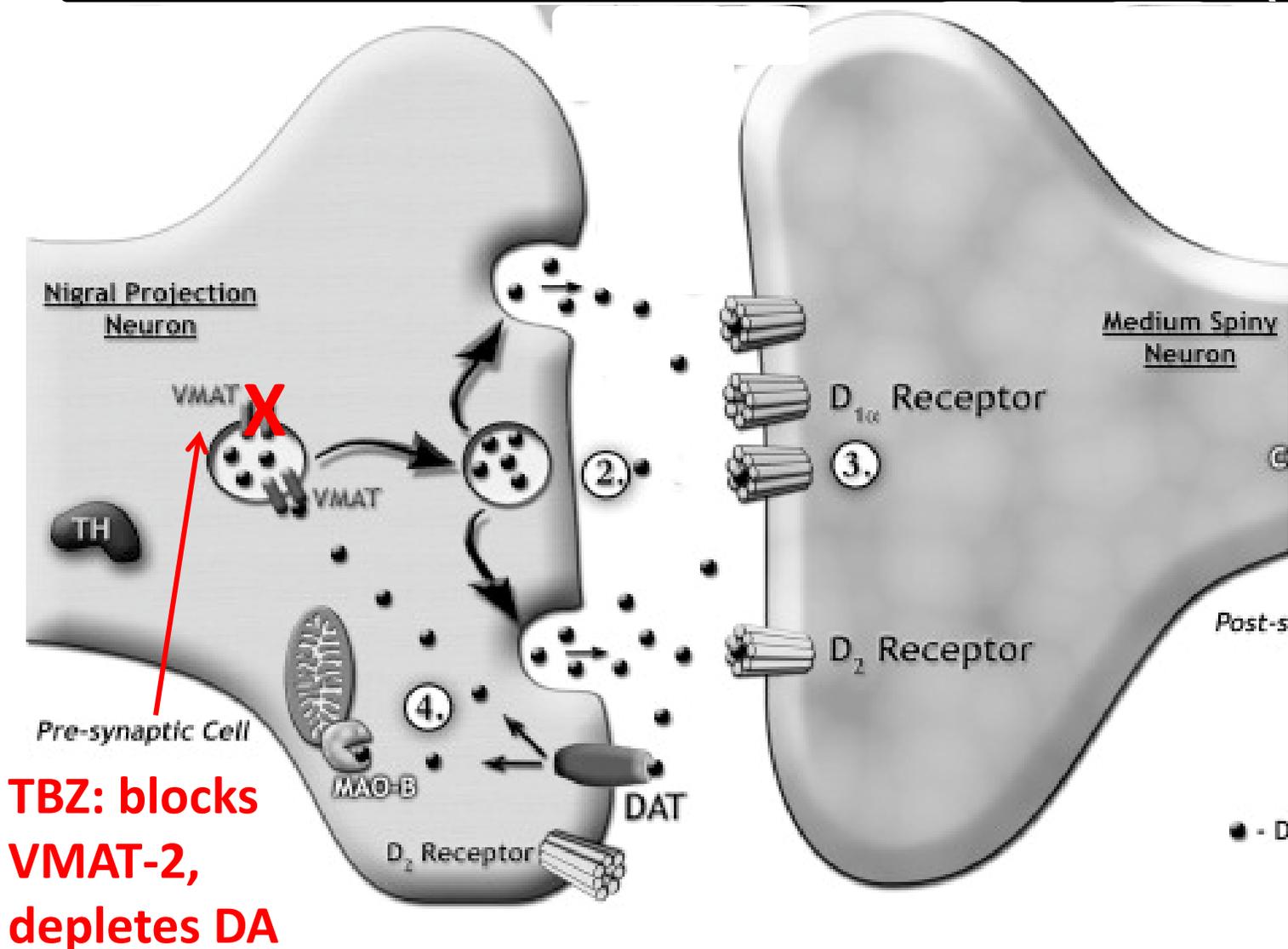


Dopaminergic Manipulations that Induce a Low-Effort Bias

Several DAergic manipulations shift effort-based choice from high-effort lever pressing to low-effort chow consumption (i.e., a *low-effort bias*)

- Systemic administration of low doses of DA D1 & D2 receptor antagonists
(Salamone et al. 1991, 2002; Sink et al. 2008)
- Local infusion of DA D1 & D2 antagonists into nucleus accumbens (Nowend et al. 2001; Farrar et al. 2010)
- Neurotoxic depletion of DA in nucleus accumbens but not caudate/putamen
(Salamone et al. 1991, 1994; Cousins et al. 1993, 1996; Cousins and Salamone 1994; Sokolowski et al. 1998)
- Tetrabenazine (Nunes et al. 2013; Randall et al. 2014, 2015; Yohn et al. 2015a,b 2016a,b,c,d)

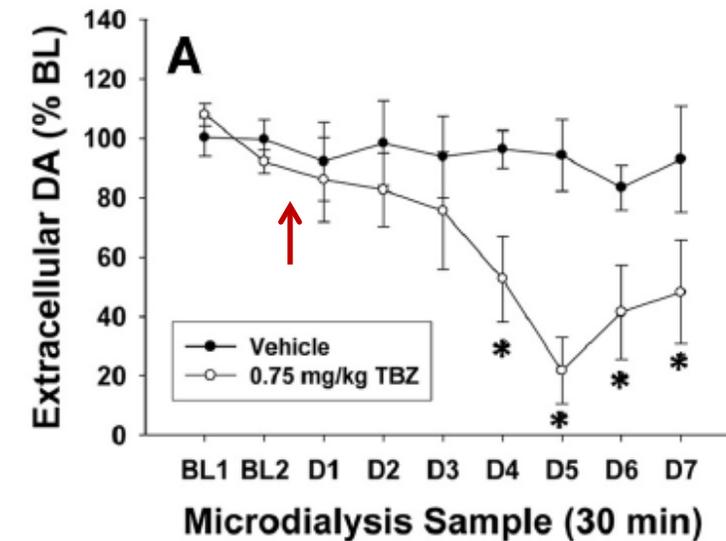
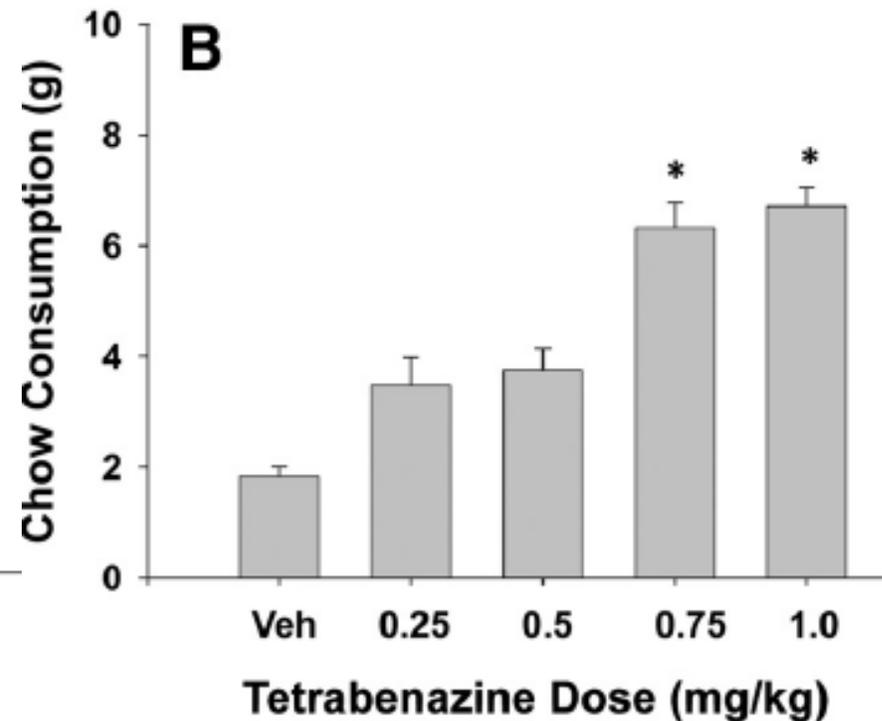
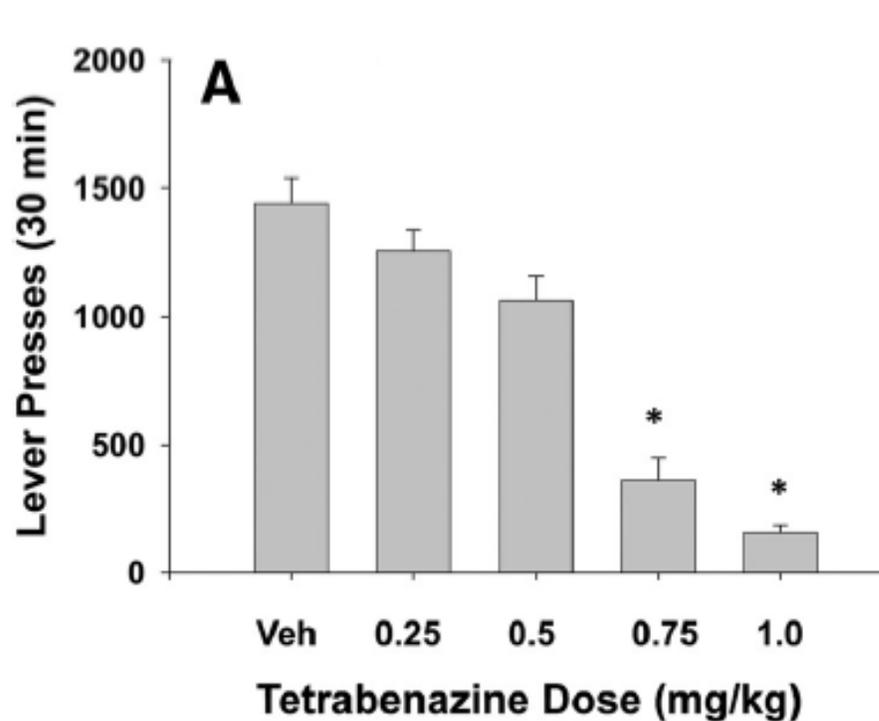
Modeling Effort-related Symptoms with Tetrabemazine (TBZ)



- TBZ reversibly and selectively inhibits the vesicular monoamine transporter-2 (VMAT-2), blocking vesicular storage (Meyer et al. 2011; Owesson-White et al. 2012; Guay 2010; Henry and Scherman, 1989)
- TBZ is used to treat Huntington's disease; common side effects in humans including fatigue, apathy, depression (Frank 2009, 2010; Guay 2010; Chen et al. 2012)

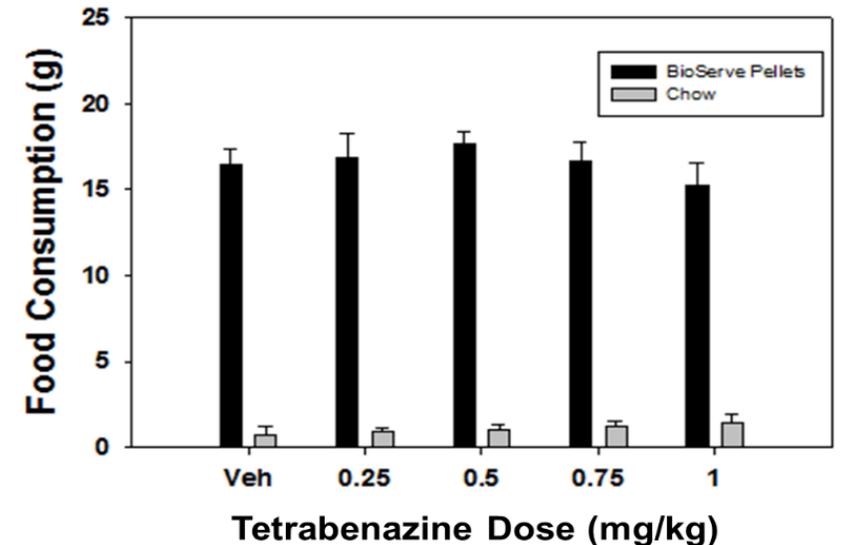
Motivational Aspects of Depression: TBZ Model

VMAT-2 inhibitor tetrabenazine (TBZ) reduces extracellular DA, shifts choice behavior, reducing FR5 lever pressing & increasing chow intake (low effort bias)



TBZ Model: Not deficit in primary food motivation or 'reward'

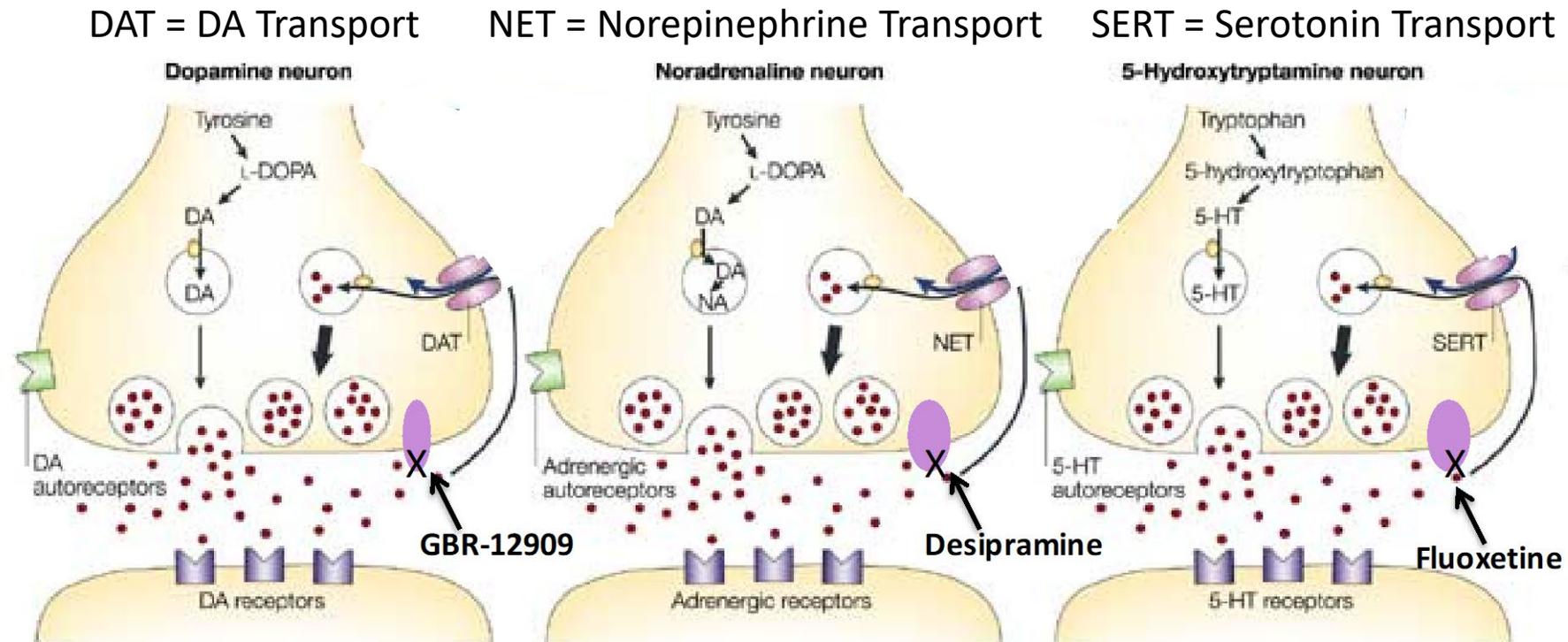
- Effect of TBZ on lever pressing is not a “reward” or “anhedonia” deficit *per se*.
- Effects of TBZ do not resemble effects of reinforcer devaluation or appetite suppressant drugs.
- TBZ does not alter sucrose preference or hedonic reactivity.
- TBZ does not change preference for the two foods or amount consumed in free feeding preference tests.
- **TBZ makes animals less likely to work for food**



Tetrabenazine Produces a Low-Effort Bias Across Multiple Tasks

- Tetrabenazine Induces a low-effort bias in rats and mice tested on:
 - Fixed Ratio 5 (FR5)/Chow feeding choice (Nunes et al. 2013; Yohn et al. 2016a,b,c,d; Rotolo et al. 2019, 2020, 2021)
 - T-maze Barrier Climbing Choice (Yohn et al. 2015a,b)
 - Mouse Touch Screen FR/Pellet Choice (Yang et al. 2020)
 - Progressive Ratio (PROG)/Chow feeding Choice Task (Randall et al. 2014)
- **PHYSICAL ACTIVITY CHOICE:** Tetrabenazine shifts behavior from wheel running to sucrose intake in mice (Carratala-Ros et al. 2019)

Are the TBZ-induced effects reversible with monoamine transport inhibitors?



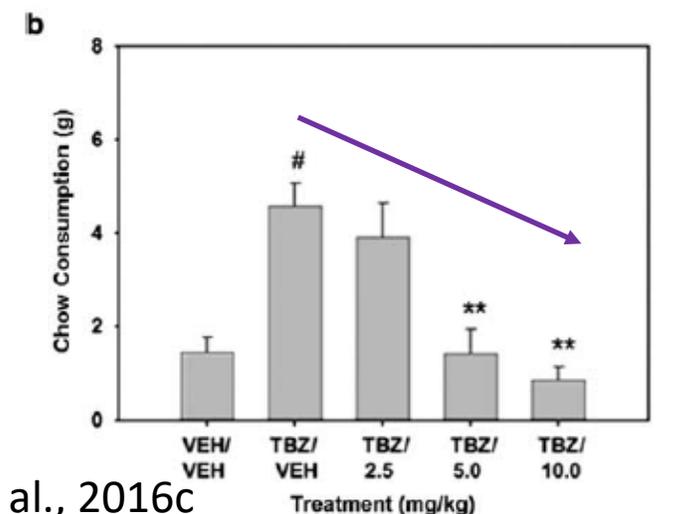
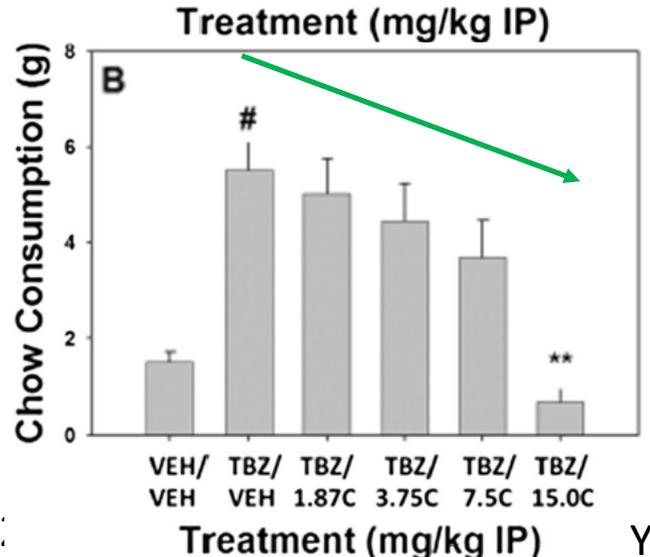
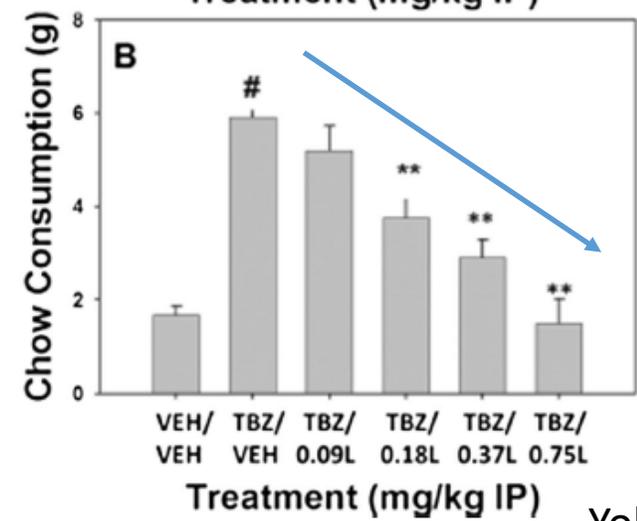
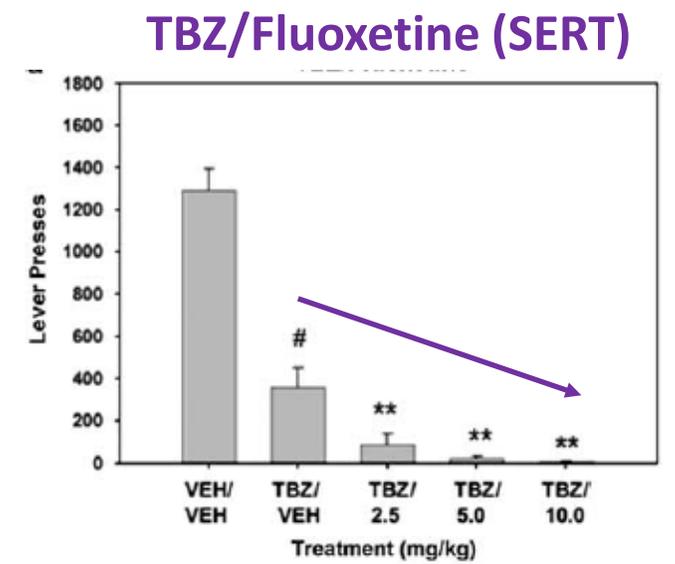
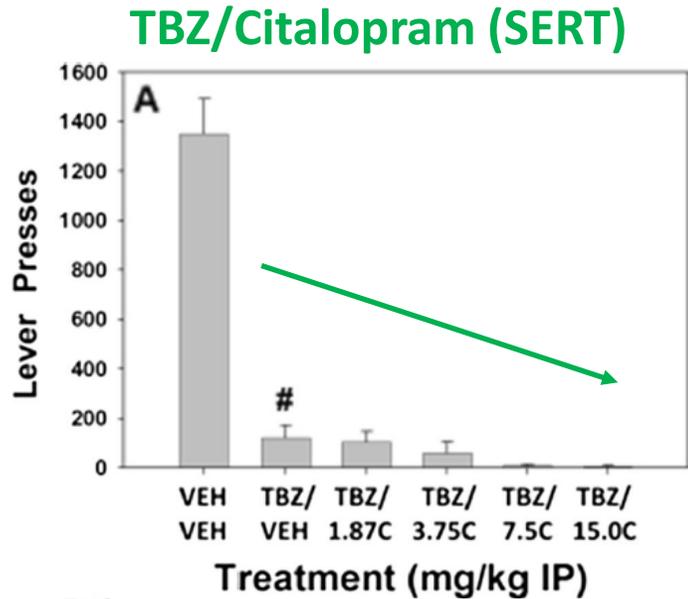
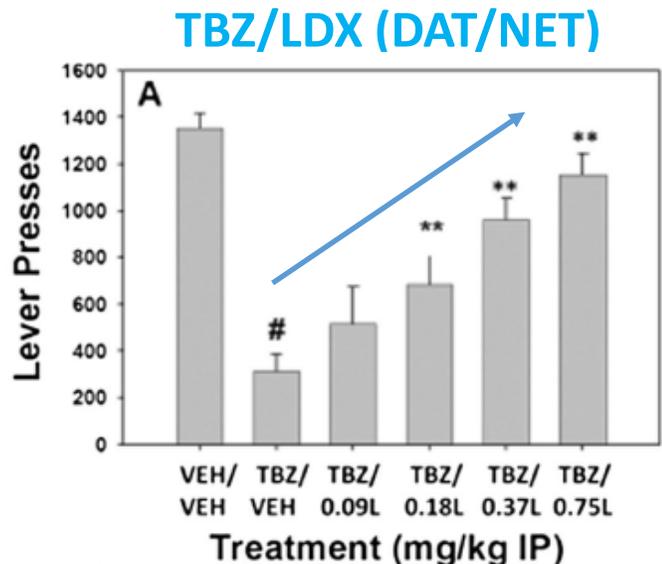
DAT INHIBITORS:
increases DA in
synaptic cleft

NET INHIBITORS:
inhibits NET, NE is
increased in synapse

SERT INHIBITORS:
inhibits SERT,
increasing 5-HT

Lisdexamfetamine (LDX, Vyvanse) reverses the effects of DA depleting agent Tetrabenazine (TBZ) on the FR5/Choice task...

while Citalopram and Fluoxetine worsen the effects of TBZ

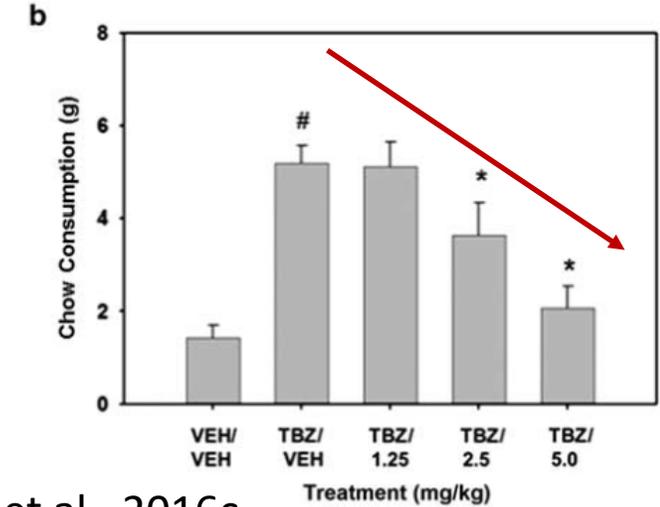
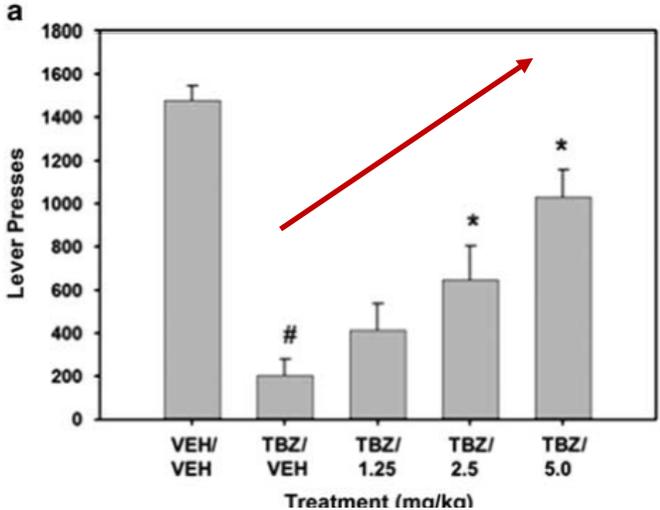


Yohn et al.,

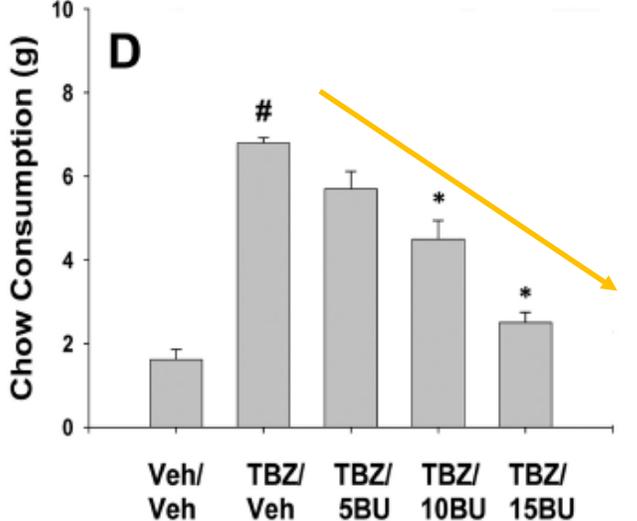
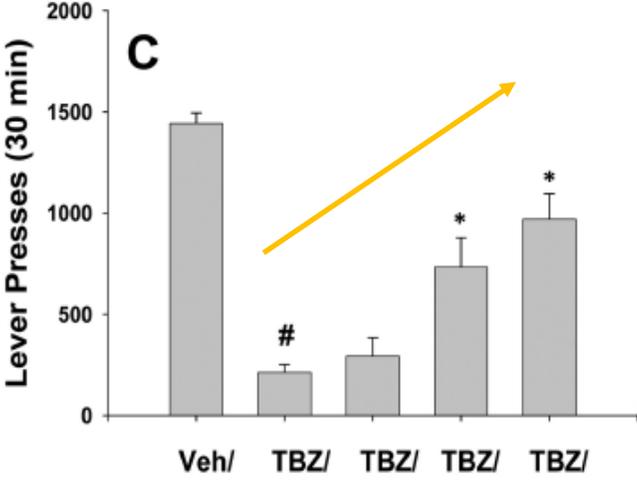
Yohn et al., 2016c

GBR12909 and **Bupropion** reverse the effects of DA depleting agent Tetrabenazine (TBZ) on the FR5/Choice task...
 while *Desipramine* worsens the effects of TBZ

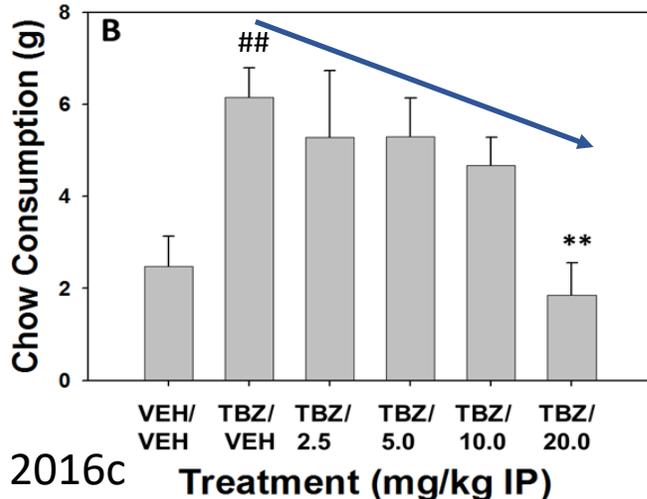
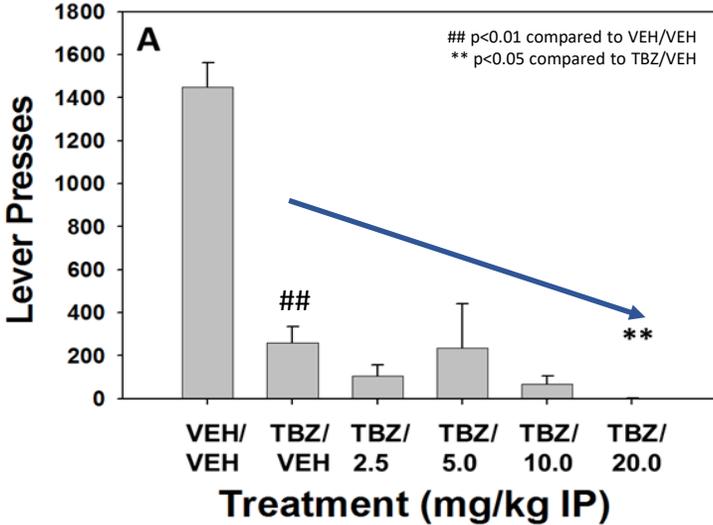
TBZ/GBR12909 (DAT)



TBZ/Bupropion (DAT/NET)



TBZ/Desipramine (NET)



Yohn et al., 2016c

Nunes et al. 2013 **Drug Treatment**

Yohn et al., 2016c

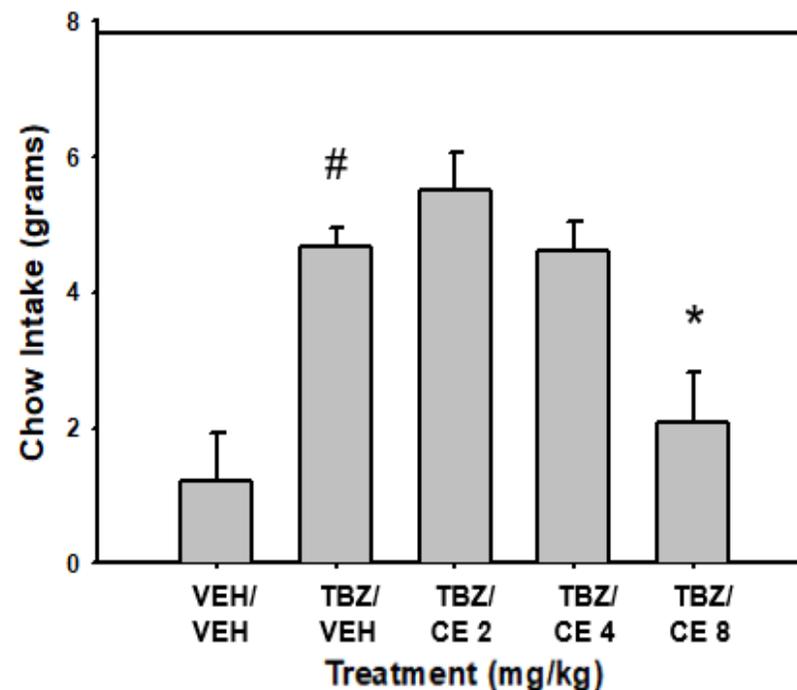
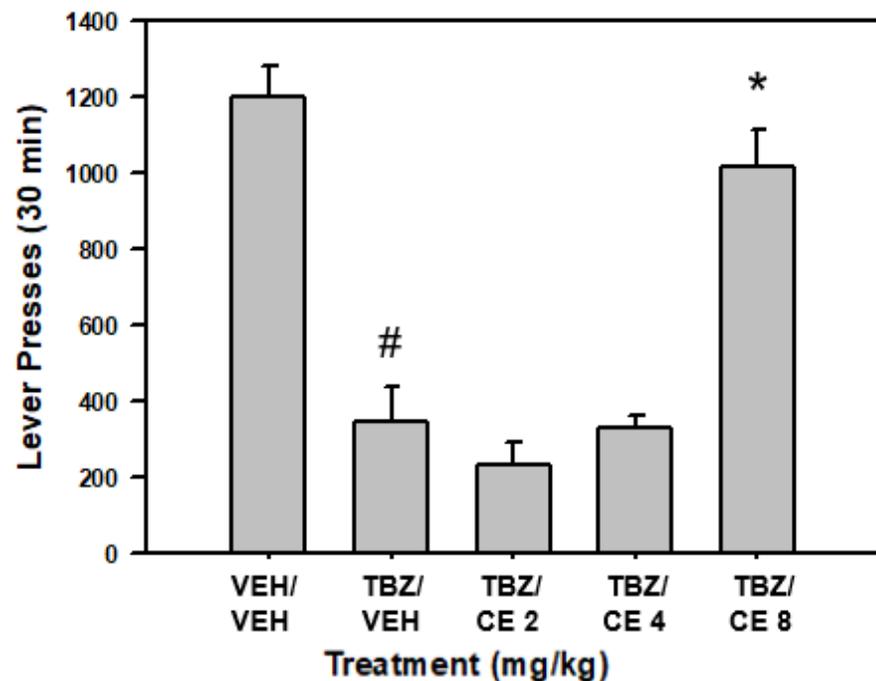
Treatment (mg/kg IP)

New Drug Targets: Assessment of Novel Atypical DAT Inhibitors

- Most classical DAT inhibitors have a well characterized abuse liability or may induce psychotic symptoms, limiting therapeutic utility
- Not all DAT blockers bind to the same binding site, or with the same kinetic characteristics as cocaine. Researchers at NIDA are interested in these drugs because of low abuse liability, possibility of blocking cocaine effects (Schmitt et al. 2008; Schmitt et al. 2013; Kohut et al. 2014)
- A new generation of ***atypical DAT blockers*** is being developed, including analogs of benztropine, modafinil and vanoxerine (GBR12909) (Schmidt & Reith 2008, 2011; Reith et al. 2015; Lubec et al. 2017)
- We have tested... CT-5404 (Chronos UK), JJC8-088, JJC8-091 (NIDA Laboratories, Amy Newman) & S-CE-123 & CE-158, modafinil analogs from Gert Lubec's lab (Austria)

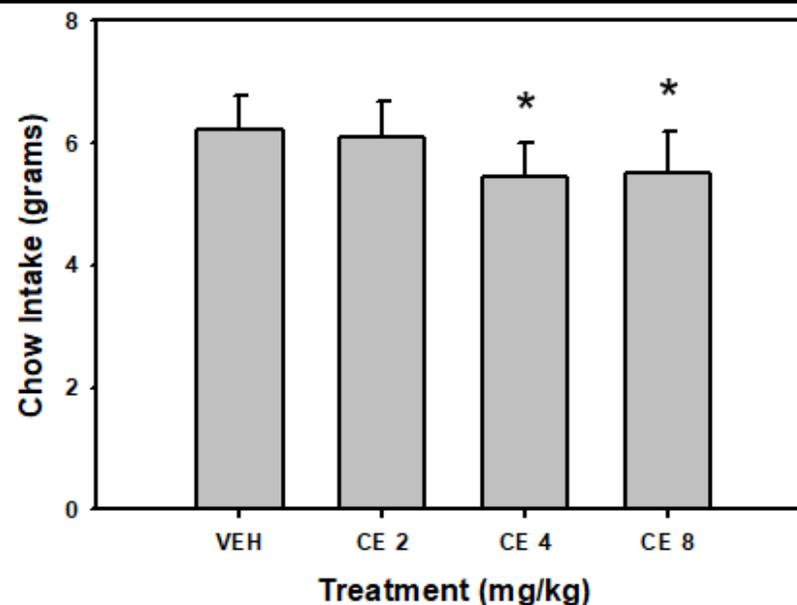
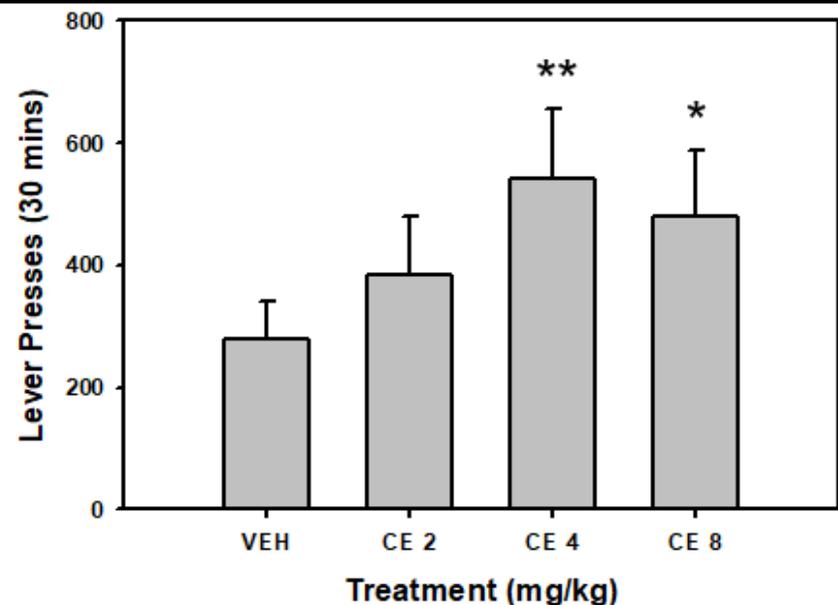
EFFECTS OF CE-158

FR5/CHOW TASK



CE-158 significantly reverses effort-related effects of TBZ on the concurrent FR5/chow feeding choice task

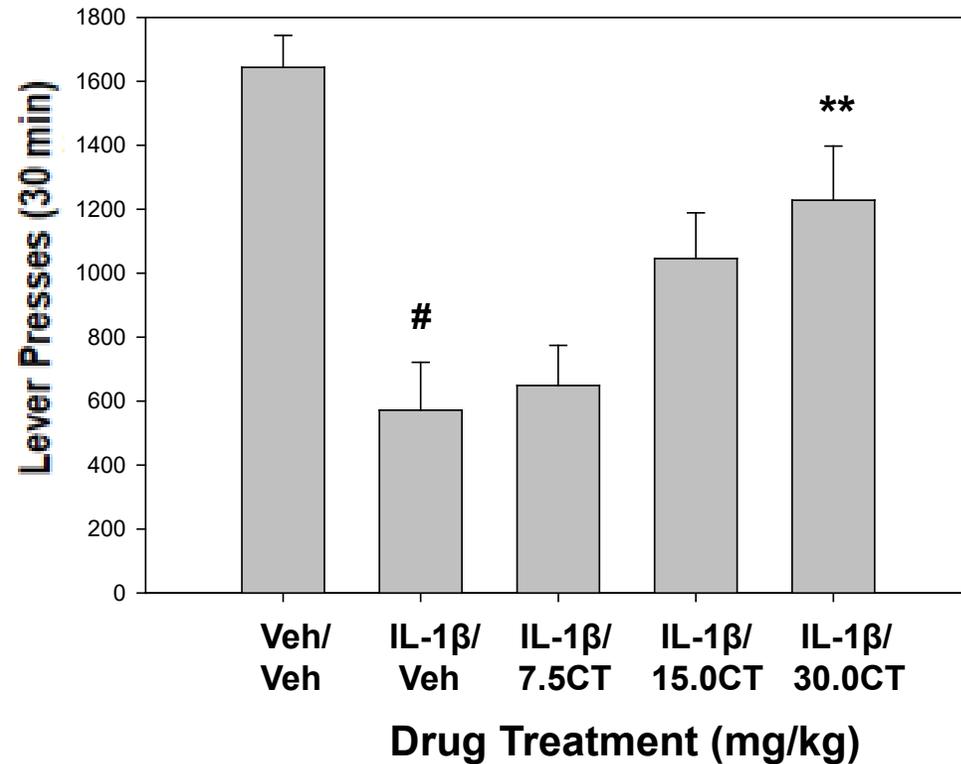
PROG/CHOW TASK



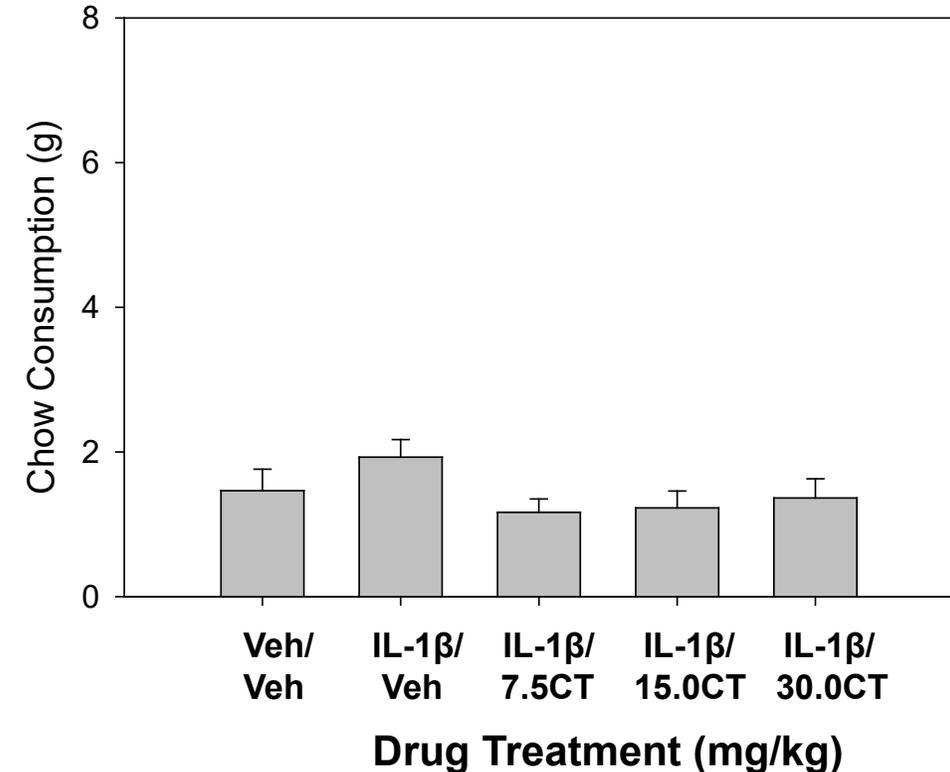
CE-158 on its own significantly increases lever pressing and decreases chow intake on the concurrent PROG/chow feeding choice task

CT-5404 Reverses the Effects of Pro-Inflammatory Cytokine Interleukin-1 β (IL-1 β)

Lever Presses

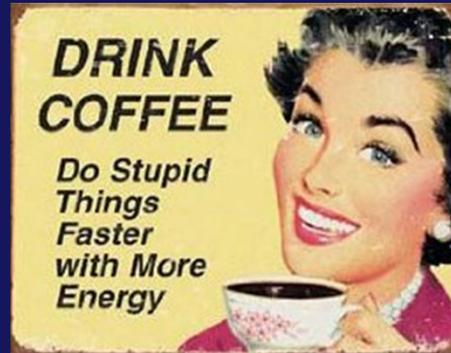


Chow Intake



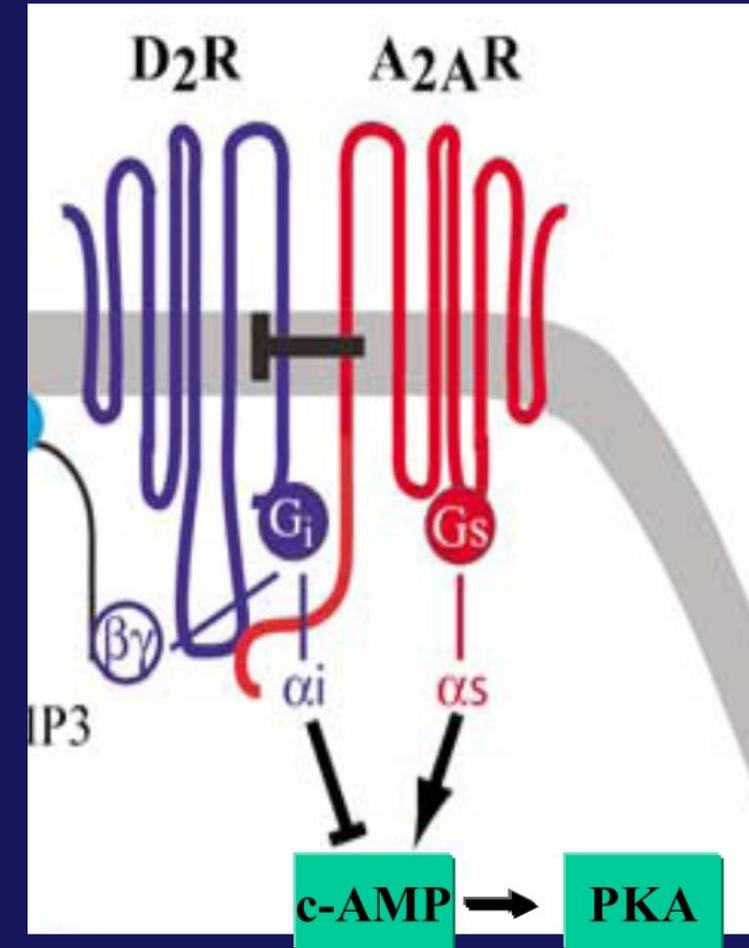
NEW DRUG TARGETS: ADENOSINE ANTAGONISTS

- Non-selective adenosine antagonists are minor stimulants: caffeine, theophylline, theobromine, in “energy” drinks



- Selective adenosine A2A antagonists used to treat Parkinson's disease (e.g. istradefylline), have effects of fatigue and apathy; A2A & DA D2 receptors co-localized →
- Adenosine A2A antagonists *reverse the effects of TBZ and pro-inflammatory cytokines* on effort-related choice (Nunes et al. 2014; Yohn et al. 2016)

(Azad et al. 2009)



Conclusions

- DA exerts a bi-directional regulation over effort-related motivational functions related to fatigue, avolition & anergia
- Enhanced DA transmission reverses effects of TBZ and increases selection of high-effort alternatives, in contrast to drugs that block SERT or NET, which have not been effective
- Effort-related models are useful for assessing various manipulations (e.g. DA-related, stress, inflammation, genetic variants) and developing pharmacological targets
 - *novel DAT inhibitors*
 - *A2A antagonists*
 - *D1 agonists*
 - *triple uptake inhibitors*

Thank you!

Principal Investigators:

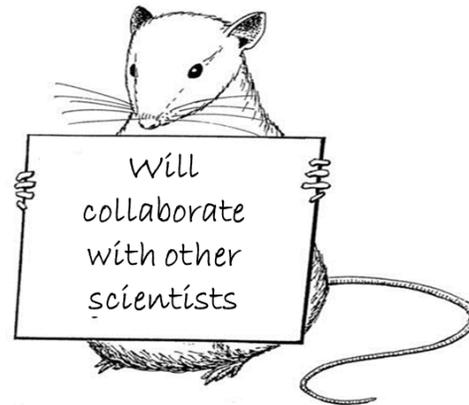
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Gayle Edelstein, Niki Meka, Sonya Srinath

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