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Trace Amine-Associated Receptor 1 (TAAR1): A Potential New Target For The Treatment of Schizophrenia

November 2022 US.PSY.D.22.00020

This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)

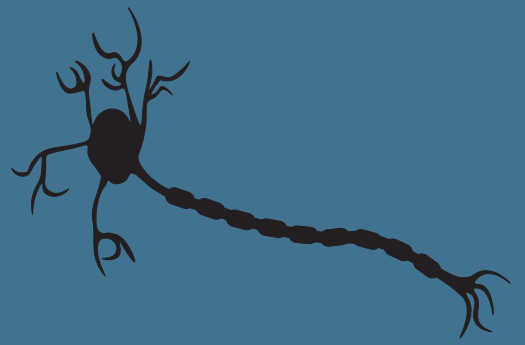
Speakers are paid consultants for Otsuka Pharmaceutical Development & Commercialization, Inc.

Objectives

Summarize the Unmet Needs of Schizophrenia as it Relates to Neural Circuitry

Introduce Trace Amines (TAs) and Trace Amine-Associated Receptors (TAARs) and Their Potential Relationship to Schizophrenia

Discuss TAAR1 Agonists in the Potential Treatment of Schizophrenia



Question 1

What is your current knowledge of TAAR1?

A. No knowledge
B. Basic knowledge
C. Adequate knowledge
D. Expert knowledge

Question 2

What does TAAR1 stand for?

A. Trace amino-acid receptor 1
B. Trace amine-associated receptor 1
C. Tyramine associated-amine receptor 1
D. Trace associated-amine receptor 1

Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.

Question 3

Besides the brain, TAAR1 is expressed peripherally in the:

A. Stomach and intestines
B. Pancreatic β-cells and leukocytes
C. None of the above
D. A + B

Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.

Question 4

TAAR1 may play a role in neuropsychiatric disorders such as schizophrenia, due to its ability to regulate[1,2]:

A. Dopamine, serotonin, and glutamate
B. Norepinephrine
C. Acetylcholine
D. Endorphins

1. Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.
2. Gainetdinov RR et al. *Pharmacol Rev*. 2018;70(3):549–620.

Question 5

Why are they called “trace” amines?

A. Because they disappear without a trace once activated
B. Because they are identical in structure to monoamines
C. Because they are expressed at extremely low or “trace” levels
D. Because they were named after the person who discovered them, Tracey McAmine

Gainetdinov RR et al. *Pharmacol Rev.* 2018;70(3):549–620.

Question 6

True or False: TAAR1 can be found both pre- and postsynaptically.

A. True
B. False

Gainetdinov RR et al. *Pharmacol Rev.* 2018;70(3):549–620.

Schizophrenia: Linking Neural Circuits to Unmet Needs

Schizophrenia Affects Both the Brain and Body[1–3]

In psychosis, abnormalities in multiple organ systems in addition to the central nervous system play a role in excess and premature mortality[1]

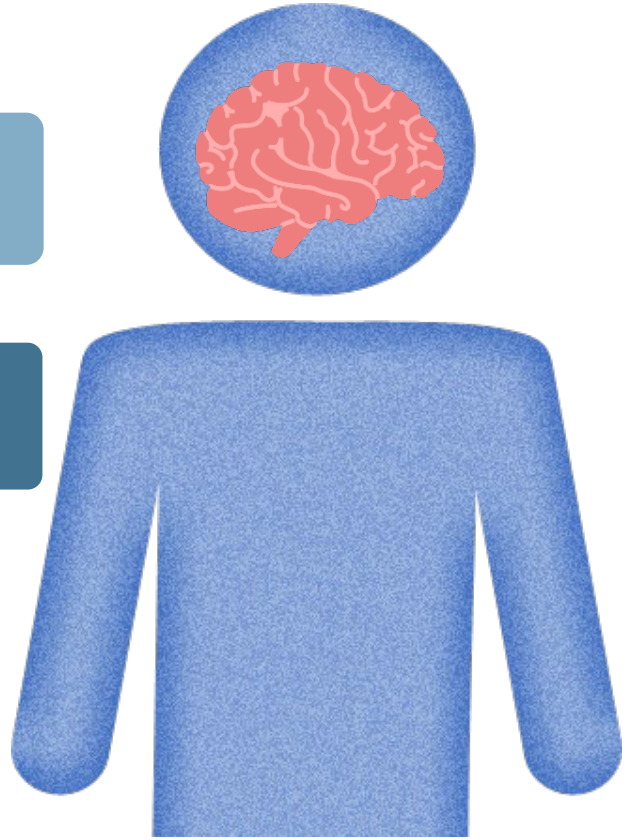
Positive symptoms

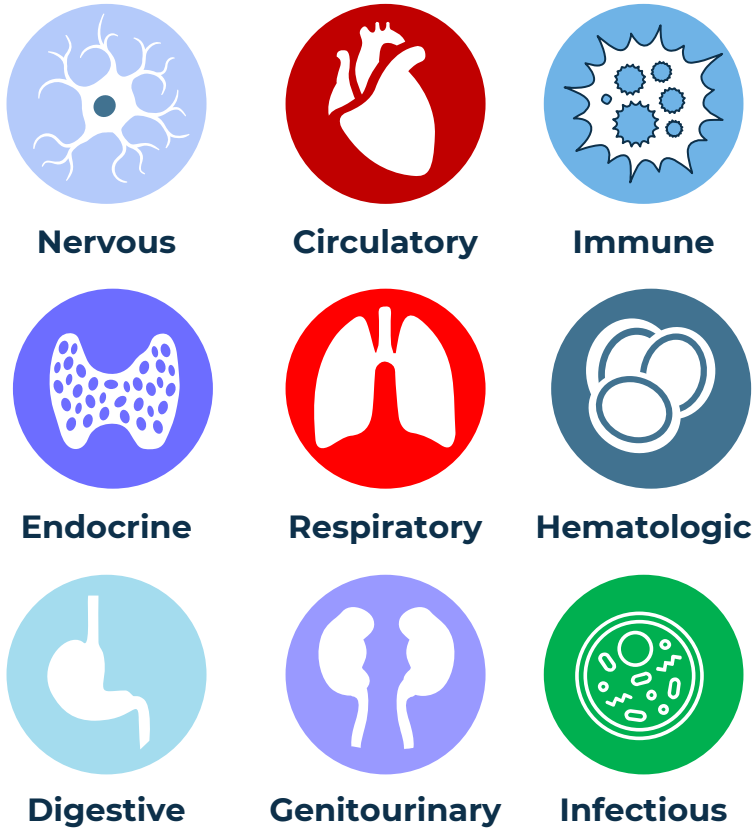
Cognitive dysfunction

Negative symptoms

Mood symptoms

Physical comorbidities across many categories





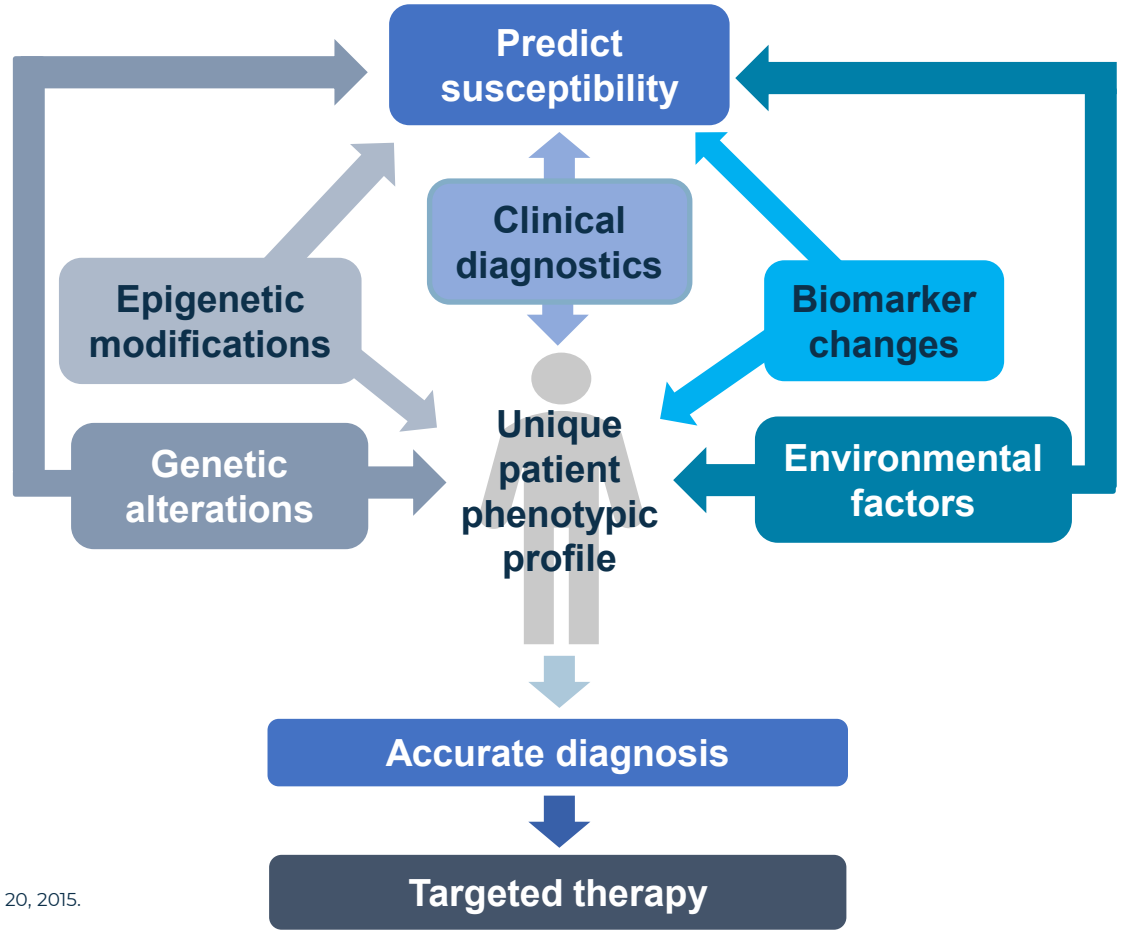
A 2017 study identified patients with SMI, including schizophrenia and bipolar disorder, had ***>1.5 times the odds for comorbidities across several disease categories***[3]

SMI, serious mental illness.

1. Pillinger T et al. *Mol Psych*. 2019; 24:776–794.
2. Maguire GA. *Am J Health Syst Pharm*. 2002;59(17 Suppl 5):S4–11.
3. Bahorik AL et al. *J Psychosom Res*. 2017;100:35–45.

Schizophrenia is Highly Heterogeneous In Terms of Symptoms, Brain Structure, and Chemistry

- Multiple factors contribute to individual phenotypes[1]
- Patients are unique in presentation, response to treatment, and clinical course[1–4]
  - Neurobiological basis of clinical heterogeneity is likely multifactorial[2]
- Heterogeneity requires individualized approaches to therapy[3]
  - There is a need to better understand subgroups of patients who are non-responsive to treatment[4]



Adapted from Ozomaro U et al. *BMC Medicine*. 2013;11:132–142. https://creativecommons.org/licenses/by/4.0/

1. National Institute of Mental Health. Schizophrenia. https://www.nimh.nih.gov/health/topics/schizophrenia. Accessed July 20, 2015.
2. Ozomaro U et al. *BMC Medicine*. 2013;11:132–142.
3. Case M et al. *Psychol Med*. 2011;41(6):1291–1300.
4. Kane JM. *JCP*. 2022; 42: S1–S13.

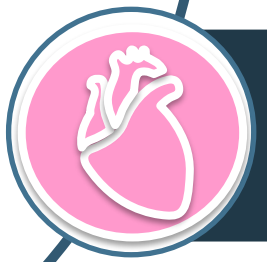
Unmet Needs in Schizophrenia

Despite advancements in medicine and our understanding of schizophrenia, treatment has relied on the same MOA for 70 years: dopamine D_2 receptor blockade[1]

- Antipsychotics have different receptor affinities and the benefits/risks can vary[2]
- Though indicated for schizophrenia, antipsychotics may not address all symptoms, may worsen others, and may cause side effects as well as long-term risks (eg, tardive dyskinesia)[2]

Despite the large number of current treatments[2]:

- Approximately 1 out of every 3 patients does not respond to standard-of-care antipsychotics
- Negative and cognitive symptoms may persist despite antipsychotic treatment



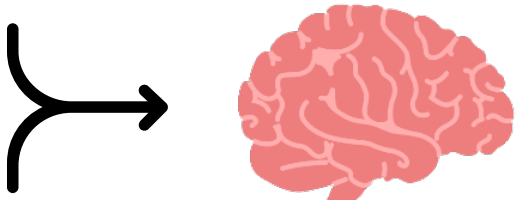
- 78% of individuals with schizophrenia experience disability and life expectancy is shortened by an average of 14.5 years[3,4]
- Incomplete efficacy and intolerable side effects may contribute to negative attitudes toward medication and poor adherence[2,5]

D_2, dopamine receptor type 2; MOA, mechanism of action.

1. Kane JM. JCP. 2022; 42: S1–S13.
2. Correll CU et al. J Clin Psychiatry. 2022;83(1):SU21204IP1.
3. Fakorede OO et al. *Int J Soc Psychiatry*. 2020;66(2):179–187.
4. Hjorthøj C et al. *Lancet Psychiatry*. 2017;4(4):295–301.
5. Dibonaventura M et al. *BMC Psychiatry*. 2012;12:20.

Current Understanding of Neurotransmitter Systems Linked to Schizophrenia

Neurodevelopmental and **genetic** factors alter the neural circuitry between several brain areas[1–6]



Dopamine Theory[2,3,4]
Hyperactive dopamine at D_2 receptors

GABA/Glutamate Theory[4,5]
NMDA receptor hypofunction

Serotonin Theory[4,5]
5-HT_{2A} receptor hyperfunction in the cortex

D_2, dopamine receptor type 2; GABA, γ-Aminobutyric acid; NMDA; N-Methyl-D-Aspartate; 5-HT_{2A}, serotonin receptor type 2A.

1. Lewis DA, Lieberman JA. *Neuron*. 2000;28:325–334.
2. Howes OD, Kapur S. *Schizophr Bull*. 2009;35:549–562.
3. Brunelin J et al. *Curr Med Chem*. 2013;20:397–404.
4. Brisch R et al. *Front Psychiatry*. 2014;5:47.
5. Yang AC, Tsai S-J. *Int J Mol Sci*. 2017;18:1689.
6. Stepnicki P et al. *Molecules*. 2018;23:2087.

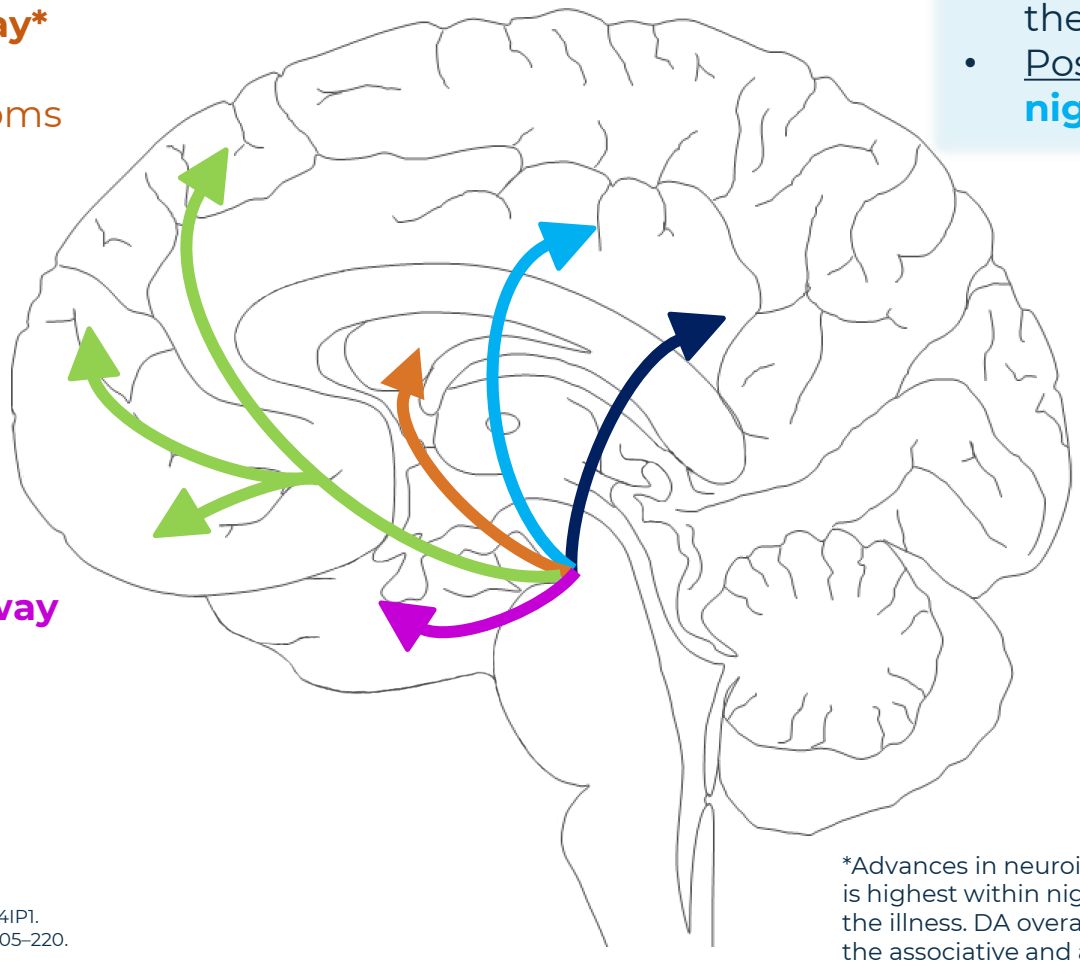
Disruption of DA Pathways in Schizophrenia Lead to Changes in other Circuits[1,2]

- Negative symptoms: **underactivity** in the **mesolimbic** and **mesocortical** pathways
- Cognitive dysfunction: **underactivity** in the **mesocortical** pathway
- Positive symptoms: **overactivity** in the **nigrostriatal** pathway

Mesolimbic Pathway*
(Limbic Striatum)
- Negative symptoms

Mesocortical Pathway
- Negative symptoms
- Cognitive symptoms
- Depression

Tuberoinfundibular Hypothalamic Pathway



Nigrostriatal Pathway
(Associative Striatum)
- Psychosis

Nigrostriatal Pathway
(Sensorimotor Striatum)
- Dystonia
- Akinesia
- Rigidity
- Tremor
- Dyskinesia

*Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is highest within nigrostriatal pathways, indicating the dorsal striatum is involved in the illness. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive symptoms.[2]

DA, dopamine.

1. Correll CU et al. *J Clin Psychiatry*. 2022;83(1):SU21204IP1.
2. McCutcheon RA et al. *Trends Neurosci*. 2019;42(3):205–220.

Effect of D2 Receptor Blockade on Neural Circuits[1,2]

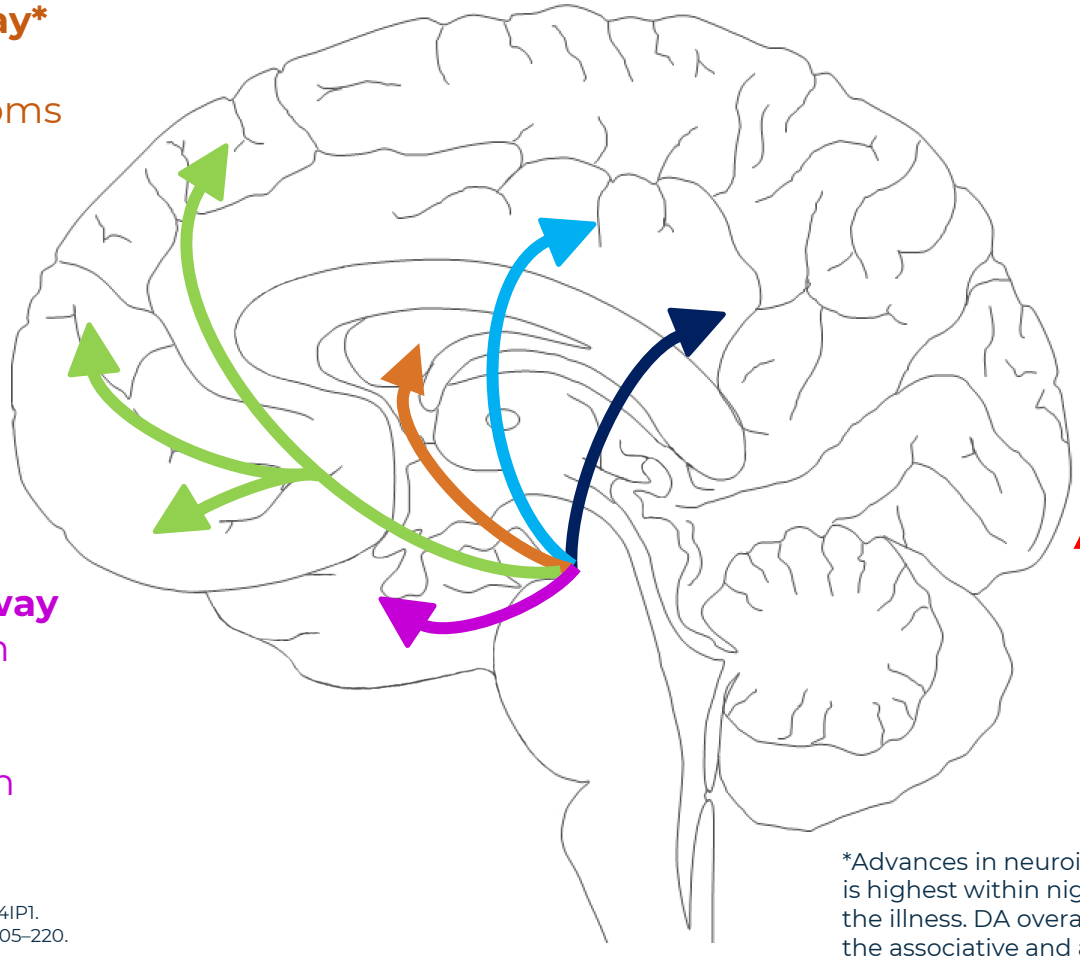
Underactivity of these circuits is associated with schizophrenia; the goal is to increase the activity

Overactivity of this circuit is associated with schizophrenia; the goal is to reduce the hyperactivity

Mesolimbic Pathway* (*Limbic Striatum*)
- Negative symptoms

Mesocortical Pathway
- Negative symptoms
- Cognitive symptoms
- Depression

Tuberoinfundibular Hypothalamic Pathway
- Prolactin elevation
- Amenorrhea
- Galactorrhea
- Sexual dysfunction



Nigrostriatal Pathway (*Associative Striatum*)
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Nigrostriatal Pathway (*Sensorimotor Striatum*)
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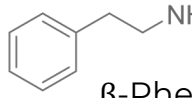
Trace Amines (TA) and Trace Amine-Associated Receptors (TAARs) and Their Potential Relationship to Schizophrenia

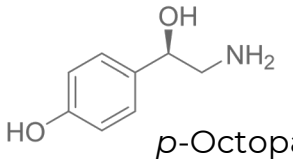
TAs & TAARs

- TAs are:
  - Endogenous chemical messengers[1]
  - Structurally similar to monoamine[1–3] neurotransmitters, DA, NE, and 5-HT
  - Expressed at **levels at least 100-fold lower** than corresponding neurotransmitters[2]
- TAARs[1]
  - In 2001, TAs were found to selectively activate a family of receptors called TAARs[1]
  - TAAR1 modulates monoaminergic and glutamatergic neurotransmission, making it a candidate for targeting to treat neuropsychiatric disorders[3,4]

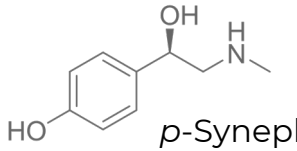
Traditional TAs



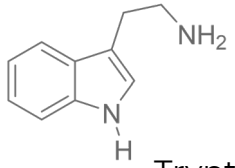
β-Phenethylamine



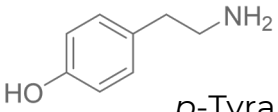
p-Octopamine



p-Synephrine

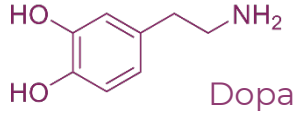


Tryptamine

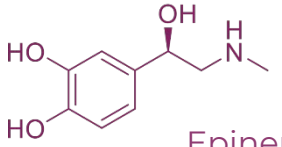


p-Tyramine

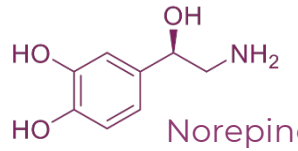
Monoamine Neurotransmitters



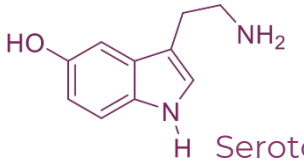
Dopamine



Epinephrine



Norepinephrine



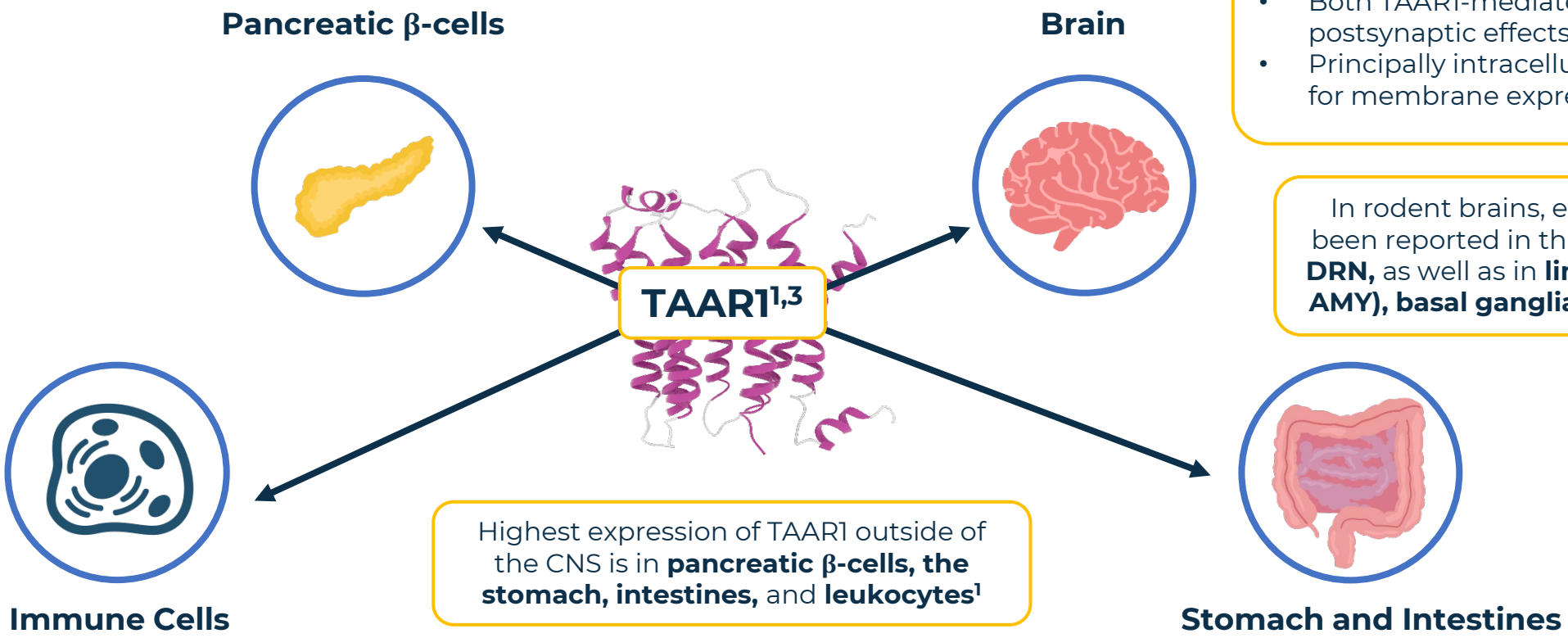
Serotonin

Adapted from Dedic N et al. *Int J Mol Sci.* 2021;22(24):13185.

DA, dopaine; NE, Norepinephrine; TAs, trace amines; TAARs, trace amine-associated receptors; TAAR1, trace amine-associated receptor 1; 5-HT, 5-hydroxytryptamine (serotonin).

1. Nair PC et al. *Mol Psychiatry*. 2021;27(1):88–94.
2. Gainetdinov RR et al. *Pharmacol Rev*. 2018;70(3):549–620.
3. Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.
4. Dodd S et al. *Neurosci Biobehav Rev*. 2021;120:537–541.

TAAR1 is Expressed in the Brain and Peripheral Tissues[1–3]



Precise synaptic/cellular localization is not clear[1]

- Low expression/lack of tools makes determination of localization challenging
- Both TAAR1-mediated pre- and postsynaptic effects observed
- Principally intracellular, evidence for membrane expression

In rodent brains, expression has been reported in the **VTA, SN, and DRN,** as well as in **limbic areas (eg, AMY), basal ganglia, and the PFC[1]**

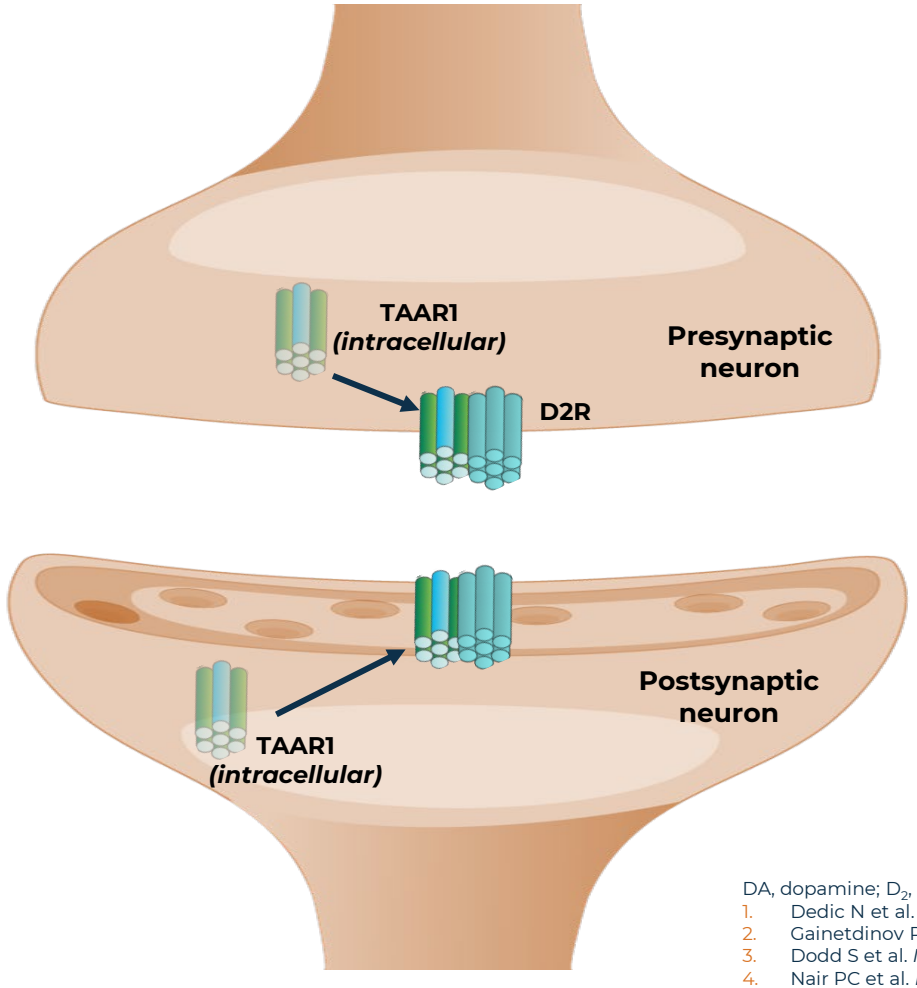
Highest expression of TAAR1 outside of the CNS is in **pancreatic β-cells, the stomach, intestines,** and **leukocytes[1]**

AMY, amygdala; DRN, dorsal raphe nucleus; PFC, prefrontal cortex; SN, substantia nigra; TAAR1, trace amine-associated receptor 1; VTA, ventral tegmental area.

1. Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.
2. Nair PC et al. *Mol Psychiatry*. 2022 Jan;27(1):88–94.
3. Dodd S et al. *Neurosci Biobehav Rev*. 2021;120:537–541.

Adapted from Dodd S et al. Neurosci Biobehav Rev. 2021;120:537–541.

Cellular Localization of TAAR1



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- **TAAR1 is primarily intracellular**, but **can move to the membrane** (and back in)[1,2]
- Can be found both **pre-** and **postsynaptically**[2]
- Can form heterodimers with other receptors[1,2]
  - Eg, can interact with D_2 receptors presynaptically and postsynaptically to affect DA signaling and promote preferential inhibitory signaling

DA, dopamine; D_2, dopamine receptor type 2; D2R, D2-like dopamine receptor 2; TAAR1, trace amine-associated receptor 1.

1. Dedic N et al. *J Pharmacol Exp Ther*. 2019;371(1):1–14.
2. Gainetdinov RR et al. *Pharmacol Rev*. 2018;70(3):549–620.
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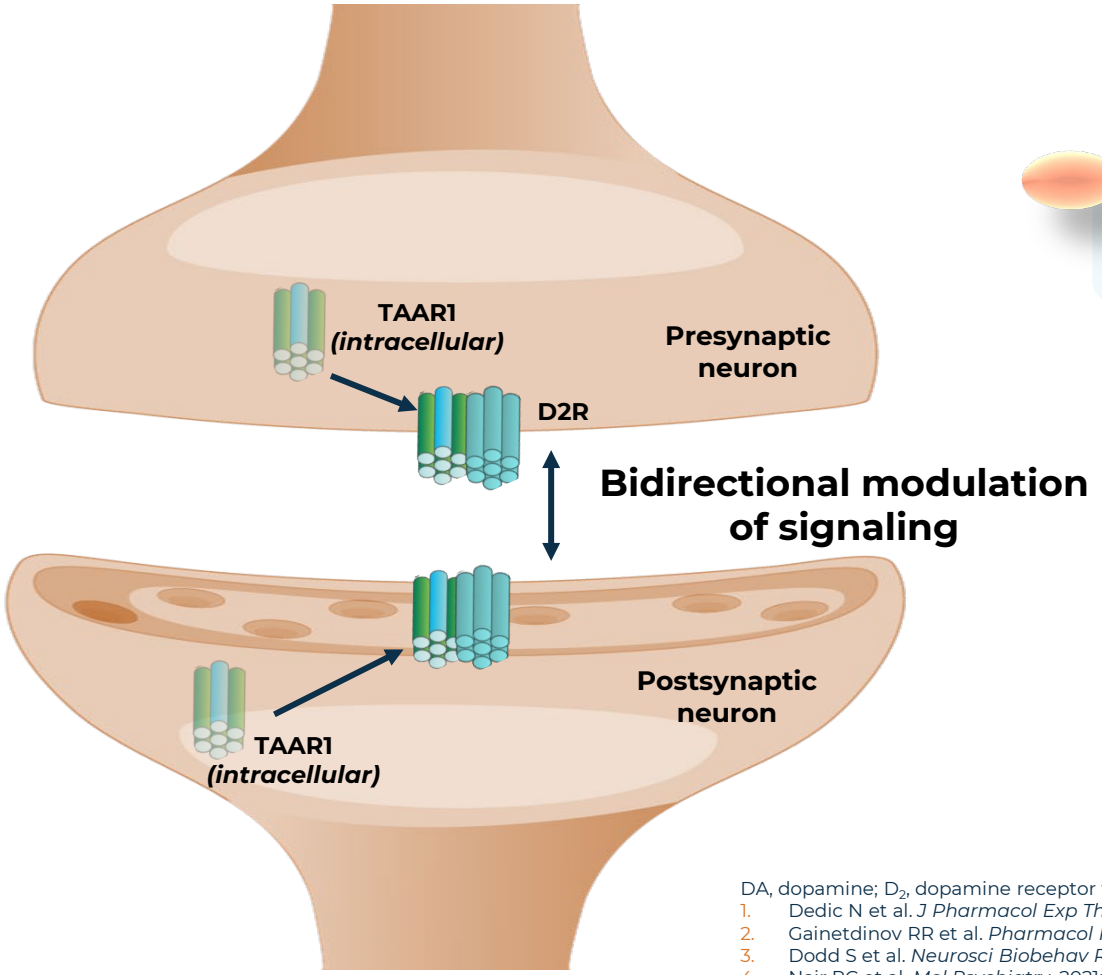
6. Revel FG et al. *Proc Natl Acad Sci U S A*. 2011;108(20):8485–8490.

Cellular Localization of TAAR1



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Modulation of DA[3,4]

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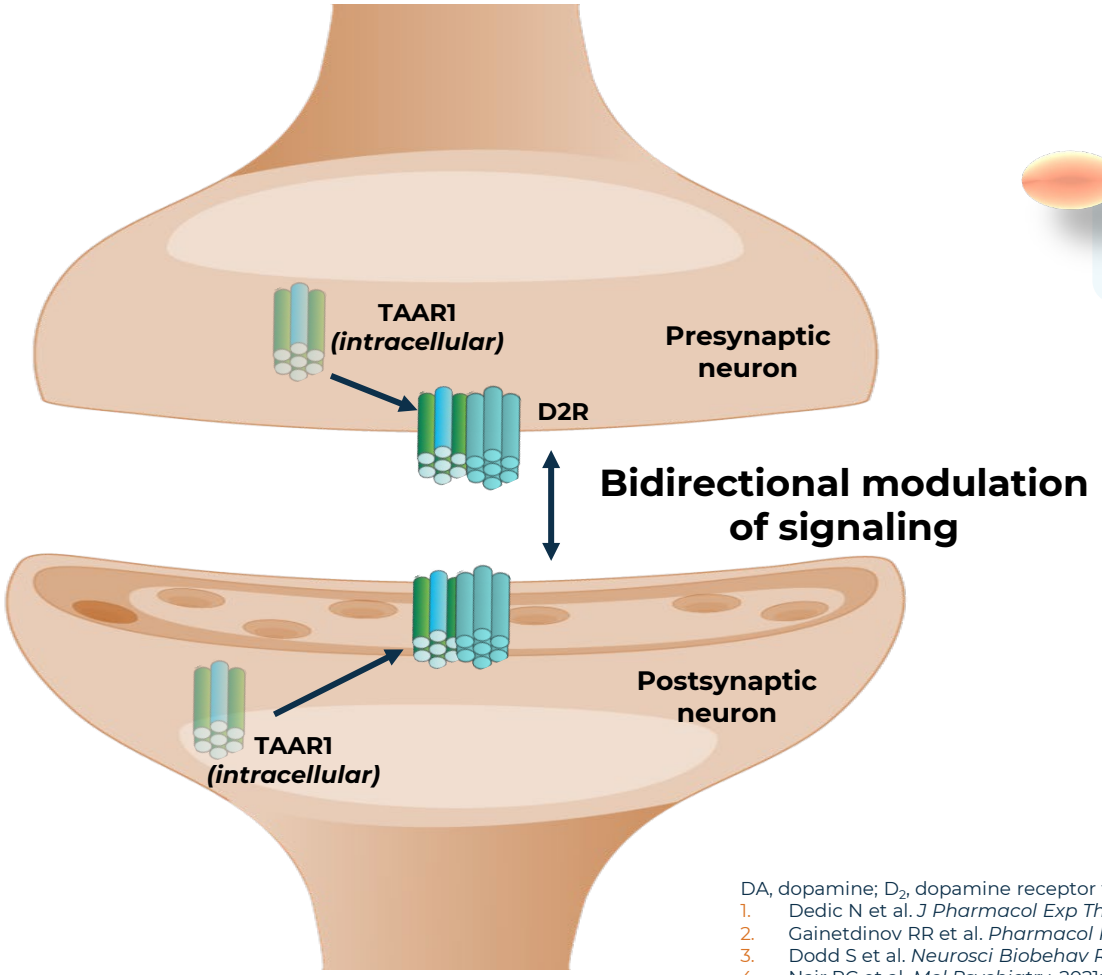

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Modulation of DA[3,4]

Regulation of Glu Circuits[1,4]

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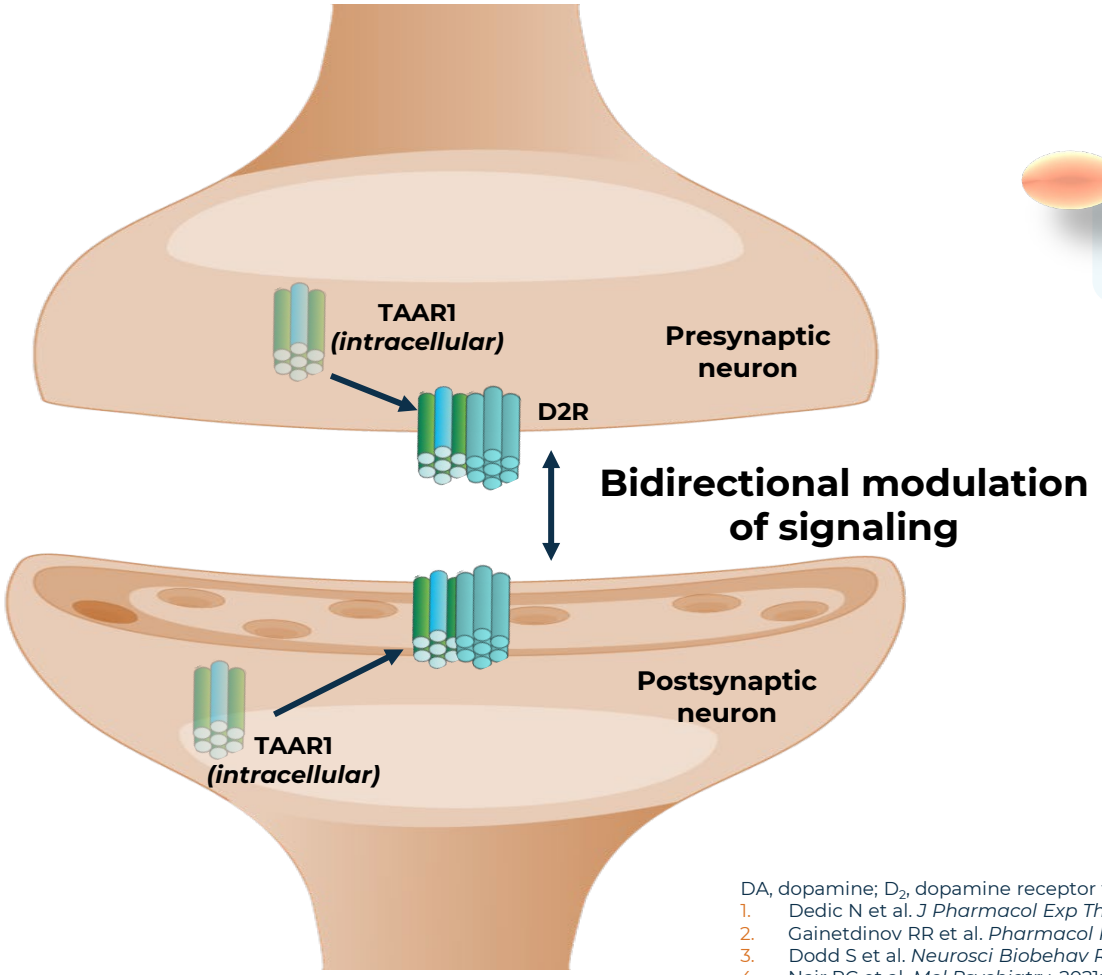

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Modulation of DA[3,4]

Regulation of Glu Circuits[1,4]

Modulation of 5-HT Activity[1,2,4–6]

DA, dopamine; D_2, dopamine receptor type 2; D2R, D2-like dopamine receptor 2; Glu, glutamate; TAAR1, trace amine-associated receptor 1; 5-HT, 5-hydroxytryptamine (serotonin).

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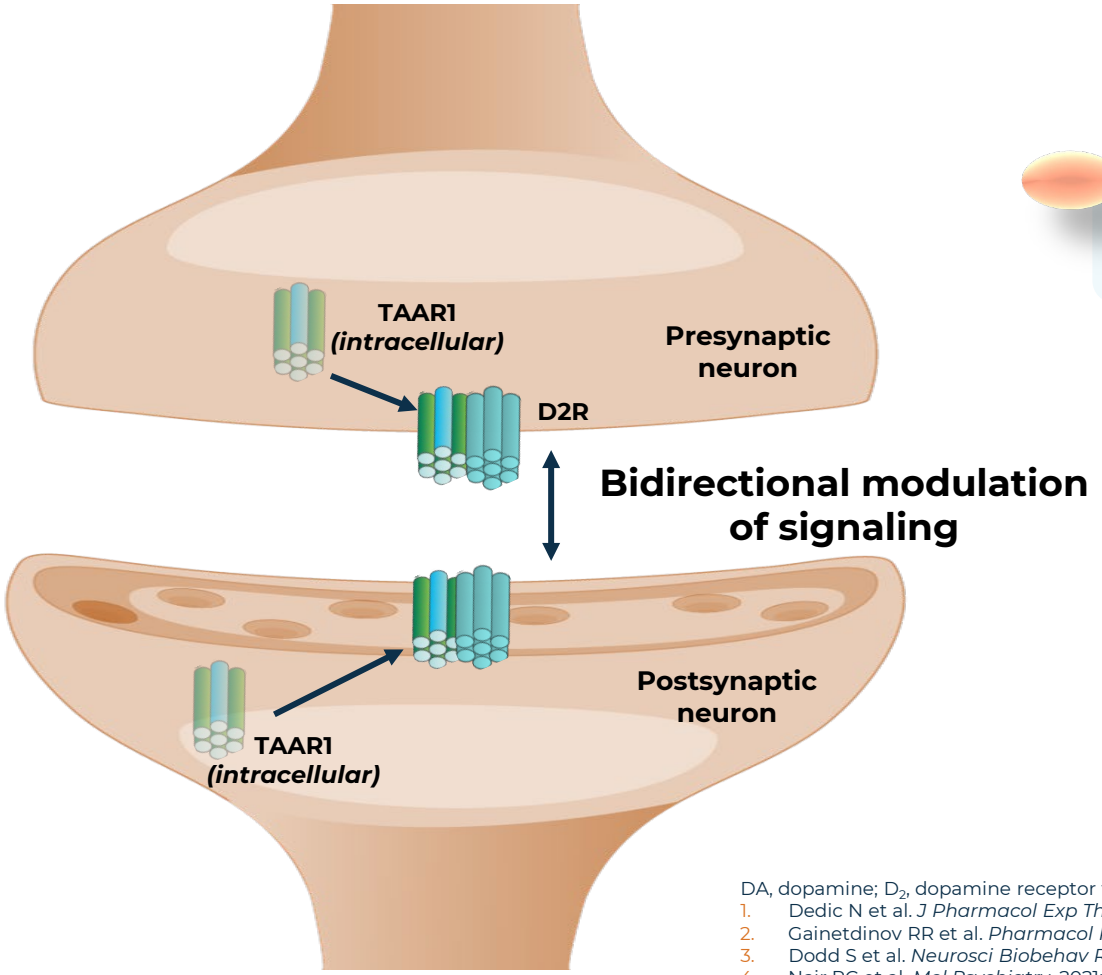

Adapted from Gainetdinov, R.R. 2018 and Berry M.D., 2018,

Suggests a role for TAAR1 in reward circuits, cognitive processes, mood, & other symptoms relevant to schizophrenia[1,3,4]

Modulation of DA[3,4]

Regulation of Glu Circuits[1,4]

Modulation of 5-HT Activity[1,2,4–6]

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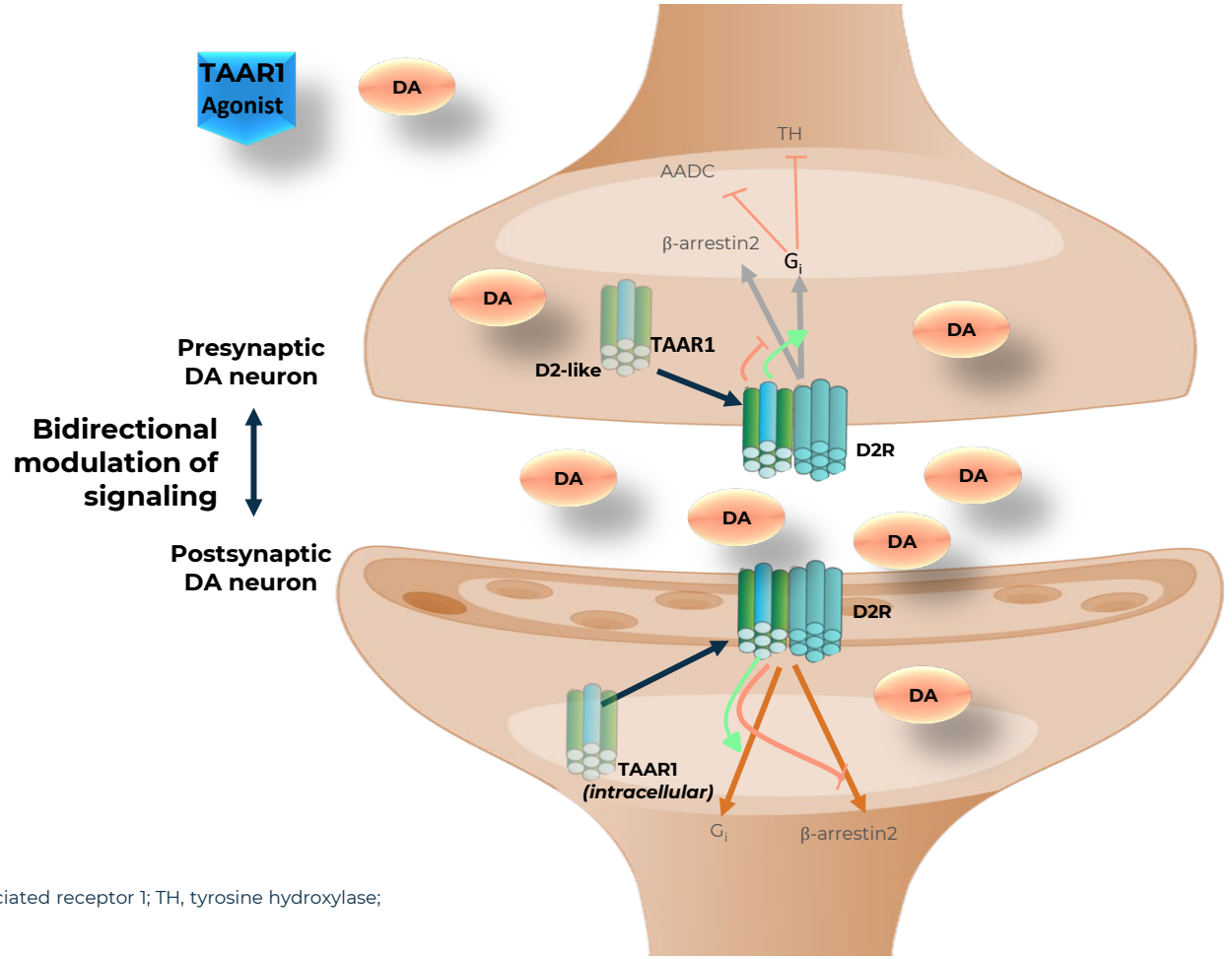
What Happens When you Stimulate TAAR1?

TAAR1 Mediates Allostasis[1,2]

Example: what happens when there is too much DA signaling?

- TAAR1 agonists *decrease* the firing rate in midbrain VTA DA neurons[3]
- TAAR1 agonists *increase* inactivation of the presynaptic D_2 autoreceptor[1]
- TAAR1 agonists act to reduce DA-driven behaviors[1]



AADC, aromatic L-amino acid decarboxylase; DA, dopamine; D2R, D2-like dopamine receptor 2; TAAR1, trace amine-associated receptor 1; TH, tyrosine hydroxylase; VTA, ventral tegmental area.

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2. McEwen BS, Wingfield JC. Horm Behav. 2010;57(2):105–11.
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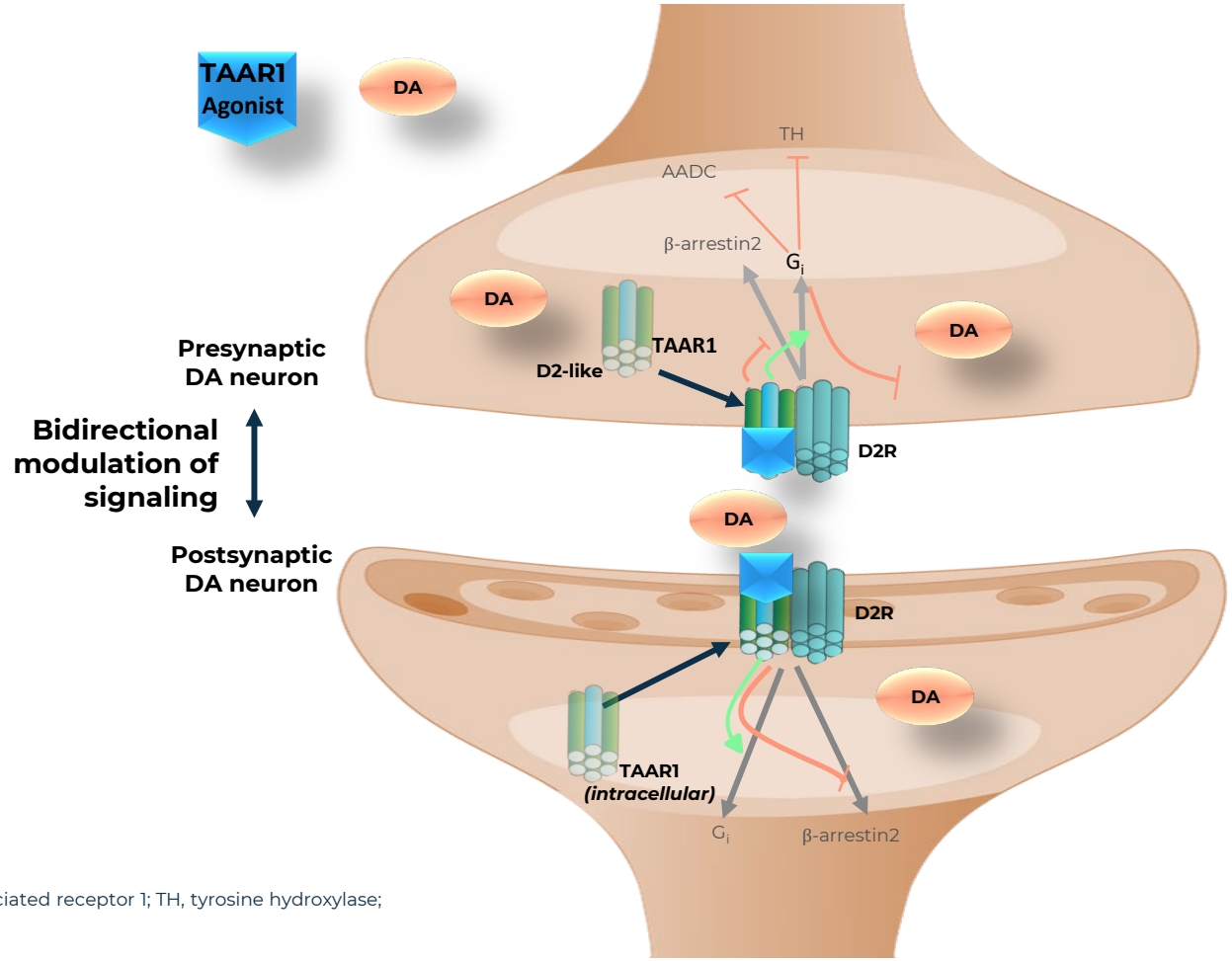
Adapted from Gainetdinov, R.R. 2018 and Berry M.D., 2018,

What Happens When you Stimulate TAAR1?

TAAR1 Mediates Allostasis[1,2]

Example: what happens when there is too much DA signaling?

- TAAR1 agonists *decrease* the firing rate in midbrain VTA DA neurons[3]
- TAAR1 agonists *increase* inactivation of the presynaptic D_2 autoreceptor[1]
- TAAR1 agonists act to reduce DA-driven behaviors[1]



AADC, aromatic L-amino acid decarboxylase; DA, dopamine; D2R, D2-like dopamine receptor 2; TAAR1, trace amine-associated receptor 1; TH, tyrosine hydroxylase; VTA, ventral tegmental area.

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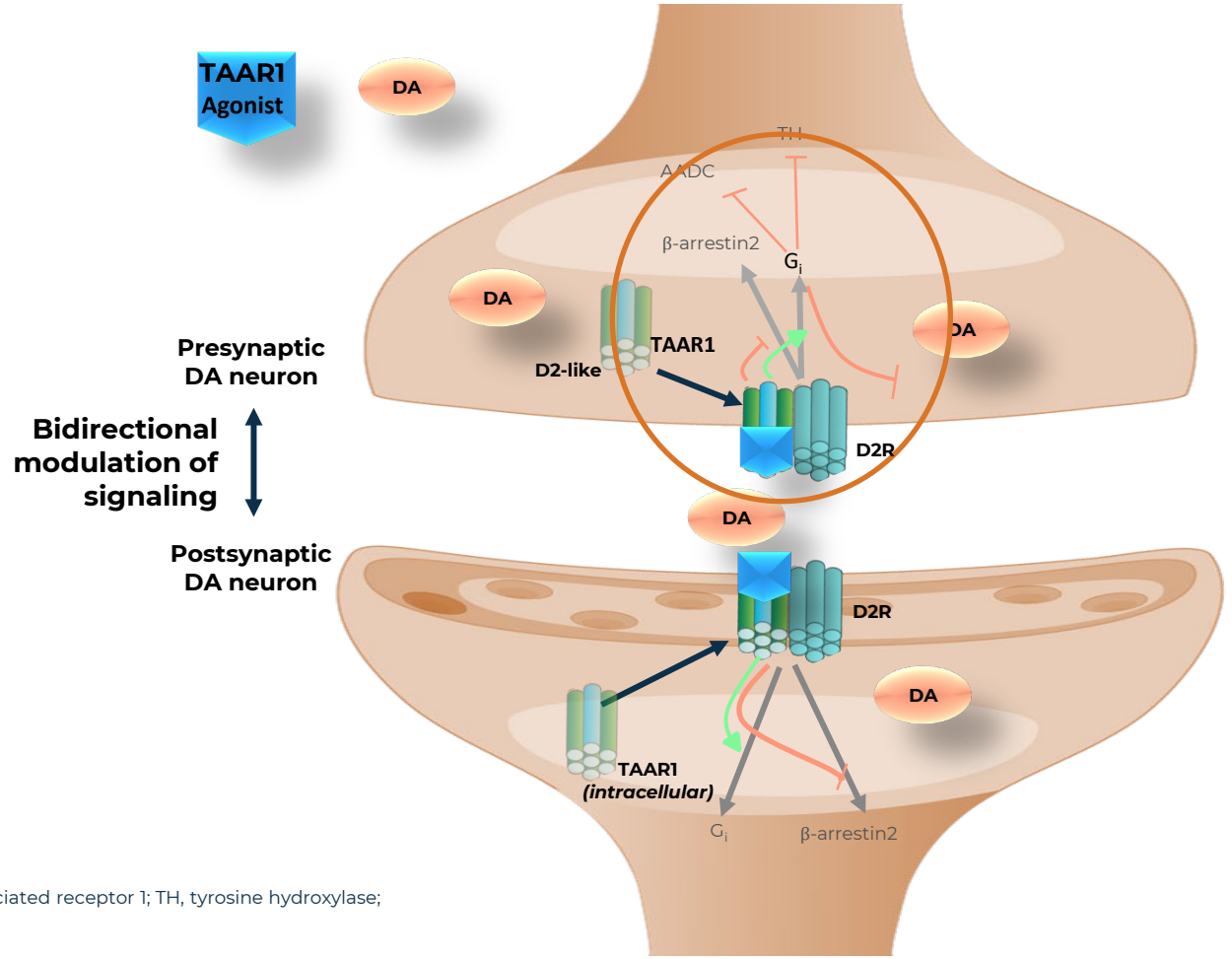

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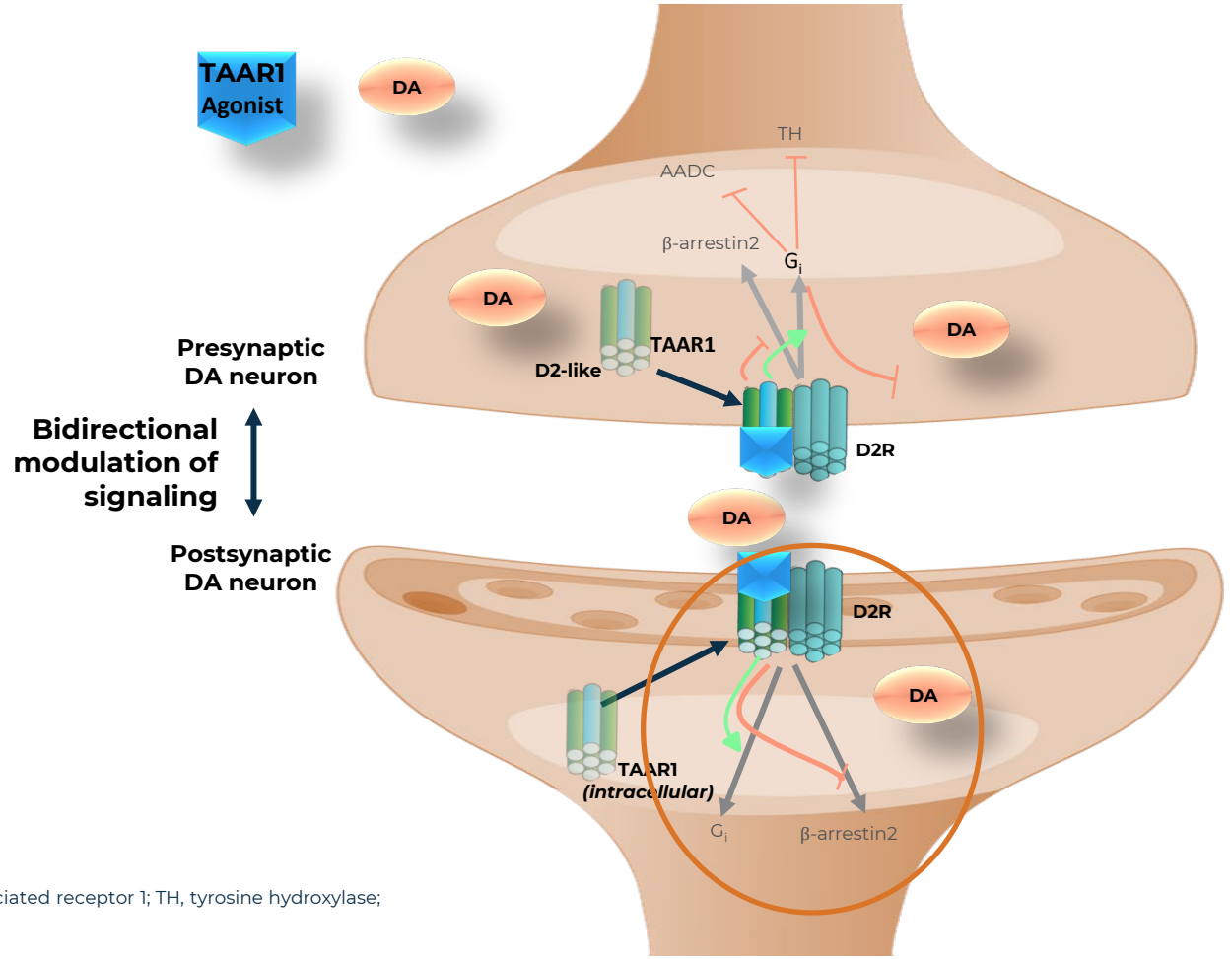

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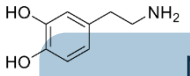
Potential Modulating Effects of TAAR1 on Neurotransmitter Signaling Associated with Schizophrenia Pathophysiology

Preclinical Evidence for TAAR1 in Schizophrenia

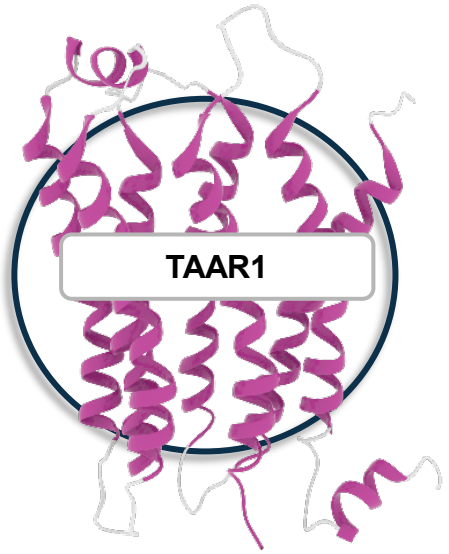
Genetic links + TAAR1-KO mice show association with schizophrenia[1–5]



Modulation of DA, 5-HT, and Glu, neurotransmitters important to schizophrenia[1–3, 6]

Expression in brain regions associated with schizophrenia[1–3,5]

Functional physical interaction between TAAR1 and D_2 receptors[1–3]



Potential role in positive, negative, and cognitive symptoms observed in animal models[6]

Evidence for pro-cognitive, antidepressant-like, and antipsychotic-like effects of TAAR1 agonists in animal models[1,3]

Evidence for prevention of atypical antipsychotic-related weight gain and fat accumulation in animal metabolic models[3,6]

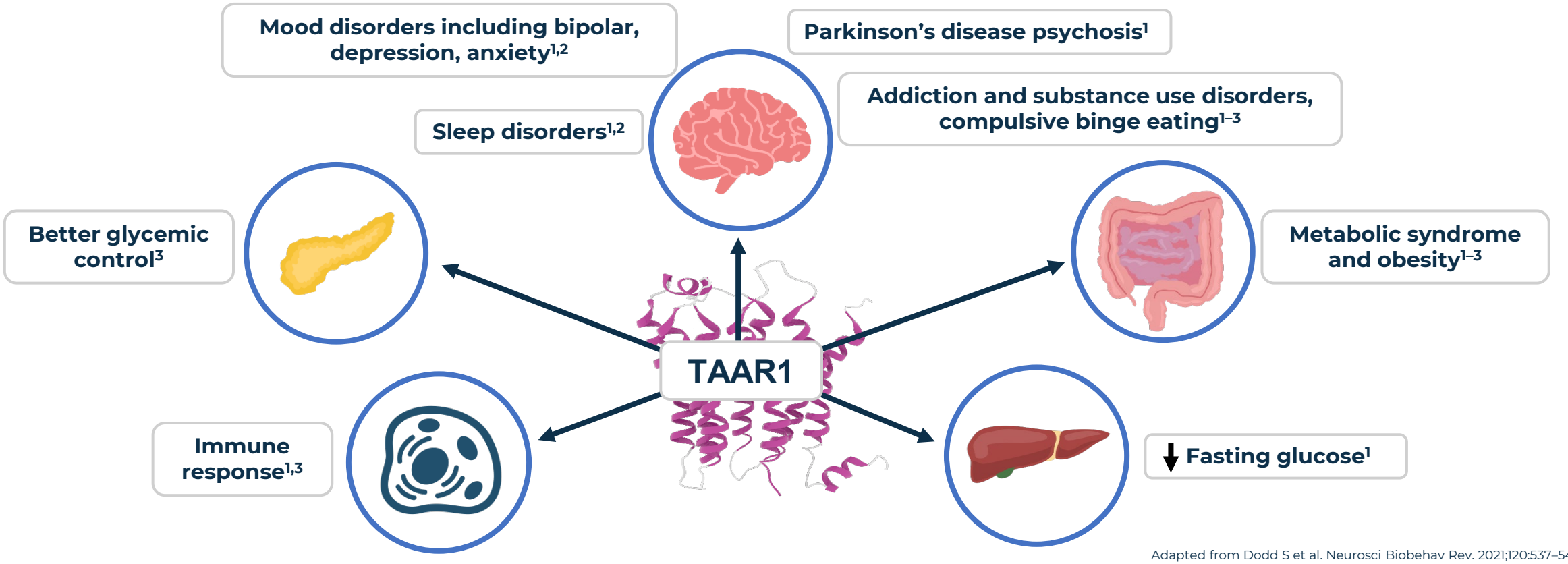
Potential utility in disorders associated with schizophrenia, such as mood disorders, substance use disorders, metabolic syndrome, and obesity[1–3]

The safety and efficacy of TAAR1 agents have not been reviewed or approved by the US Food and Drug Administration.

DA, dopamine; D_2, dopamine receptor type 2; Glu, glutamate; KO, knockout; TAAR1, trace amine-associated receptor 1.; US, United States; 5-HT, 5-hydroxytryptamine (serotonin).

1. Nair PC et al. Mol Psychiatry. 2021;27(1):88–94.
2. Dodd S et al. *Neurosci Biobehav Rev*. 2021;120:537–541.
3. Revel FG et al. *Mol Psychiatry*. 2013;18(5):543–556.
4. Rutigliano G et al. *Cell Mol Neurobiol*. 2020;40(2):239–255.
5. Rutigliano G et al. *Front Pharmacol*. 2019;10:1027.
6. Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.

Potential for TAAR1 Agonists Beyond Schizophrenia: Preclinical Evidence



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TAAR1, trace amine-associated receptor 1; US, United States.

1. Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.
2. Nair PC et al. Mol Psychiatry. 2021;27(1):88–94.
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TAAR1 Agonists in Development

- The development of selective TAAR1 antagonists has been challenging—so far only 1 compound has been identified and characterized[1]
- However, new **TAAR1 agonists** are in clinical development[1]
- Preclinical data indicate[1–3]:
  - Effects across a broad range of animal models/assays of schizophrenia
  - Antidepressant- and anxiolytic-like effects in rodent models
  - Preclinical safety profile demonstrated no catalepsy, no prolactin-related effects
  - Lacks APD-induced metabolic liabilities; improved metabolic parameters in rodent models
- Further research is needed[1]

APD, antipsychotic drug; TAAR1, trace amine-associated receptor 1.

1. Dedic N et al. *Int J Mol Sci.* 2021;22(24):13185. doi:10.3390/ijms222413185.
2. Dedic N et al. *J Pharmacol Exp Ther*. 2019;371(1):1-14.
3. Dedic N et al. SIRS 2022. Florence, Italy.

Investigational TAAR1 Agonists in Phase 2/3 Clinical Trials

TAAR1 partial agonist

One active Phase 2 study in patients with schizophrenia or schizoaffective disorder and negative symptoms (ages 18-55) –currently recruiting, with estimated completion May 2023[1]

One Phase 2 study recently terminated (in a preliminary analysis, the primary endpoint was negative)[2]

TAAR1 agonist with 5-HT_{1A} agonist activity[3]

Phase 2 studies complete in patients with schizophrenia (ages 18-40)[4]

Currently in Phase 3 development for the treatment of schizophrenia (ages 13-65)[5]

FDA Breakthrough Therapy Designation for the treatment of schizophrenia[3]

FDA, Food and Drug Administration; TAAR1, trace amine-associated receptor 1; 5-HT_{1A}, serotonin 1A receptor.

1. ClinicalTrials.gov identifier: NCT03669640. Updated October 13, 2022. Accessed October 21, 2022. https://clinicaltrials.gov/ct2/show/NCT03669640.
2. ClinicalTrials.gov identifier: NCT04512066. Updated July 15, 2022. Accessed October 21, 2022. https://clinicaltrials.gov/ct2/show/NCT04512066.
3. Heffernan MLR et al. *ACS Med Chem Lett*. 2021;13(1):92–98.
4. ClinicalTrials.gov identifier: NCT02970929. Updated February 9, 2022. Accessed October 25, 2022. https://clinicaltrials.gov/ct2/show/study/NCT02970929.
5. ClinicalTrials.gov identifier: NCT04109950. Updated October 3, 2022. Accessed October 21, 2022. https://clinicaltrials.gov/ct2/show/NCT04109950.

Summary

1. Schizophrenia is a chronic, heterogenous, and disabling disease affecting both the brain and body[1]
2. Current treatments for schizophrenia (antipsychotics) involve direct D_2 (+/- 5-HT_{2A}) receptor modulation[2]
3. Current antipsychotics have varying risk/benefit profiles and heterogeneous treatment response[3]
4. TAAR1 is a potential novel receptor target for psychiatric disorders including schizophrenia as well as other disorders[4,5]
5. Two TAAR1 agonists are currently in clinical development for patients with schizophrenia[4]

D_2, dopamine receptor type 2; TAAR1, trace amine-associated receptor 1; 5-HT_{2A}, serotonin receptor type 2A.

1. Maguire GA. *Am J Health Syst Pharm*. 2002;59(17 Suppl 5):S4–11.
2. Kane JM. *JCP*. 2022; 42: S1–S13.
3. Ozomaro U et al. *BMC Medicine*. 2013;11:132–142.
4. Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.
5. Dodd S et al. *Neurosci Biobehav Rev*. 2021;120:537–541.

Question 1

What is your current knowledge of TAAR1?

A. No knowledge
B. Basic knowledge
C. Adequate knowledge
D. Expert knowledge

Question 2

What does TAAR1 stand for?

A. Trace amino-acid receptor 1
B. Trace amine-associated receptor 1
C. Tyramine associated-amine receptor 1
D. Trace associated-amine receptor 1

Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.

Question 3

Besides the brain, TAAR1 is expressed peripherally in the:

A. Stomach and intestines
B. Pancreatic β-cells and leukocytes
C. None of the above
D. A + B

Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.

Question 4

TAAR1 may play a role in neuropsychiatric disorders such as schizophrenia, due to its ability to regulate[1,2]:

A. Dopamine, serotonin, and glutamate
B. Norepinephrine
C. Acetylcholine
D. Endorphins

1. Dedic N et al. *Int J Mol Sci*. 2021;22(24):13185.
2. Gainetdinov RR et al. *Pharmacol Rev*. 2018;70(3):549–620.

Question 5

Why are they called “trace” amines?

A. Because they disappear without a trace once activated
B. Because they are identical in structure to monoamines
C. Because they are expressed at extremely low or “trace” levels
D. Because they were named after the person who discovered them, Tracey McAmine

Gainetdinov RR et al. *Pharmacol Rev.* 2018;70(3):549–620.

Question 6

True or False: TAAR1 can be found both pre- and postsynaptically.

A. True
B. False

Gainetdinov RR et al. *Pharmacol Rev.* 2018;70(3):549–620.

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Trace Amine-Associated Receptor 1 (TAAR1): A Potential New Target For The Treatment of Schizophrenia

November 2022 US.PSY.D.22.00020