Babol University
Of Medical Sciences

IJMCM, Autumn 2025, VOL 14, NO 4

International Journal of Molecular and Cellular Medicine

Journal homepage: www.ijmcmed.org

IJMCM

REVIEW ARTICLE

Trace Amine-associated Receptor 1: Role in the Implementation of Neuroprotective Signaling Pathways

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ARTICLE INFO

Received: 2024/11/27
Revised: 2025/04/14
Accepted: 2025/05/16

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ABSTRACT

Trace amine-associated receptor 1 (TAAR1) is a classical representative of G-protein coupled receptors (GPCRs). It is widely distributed in the mammalian brain, potentially plays an important role in modulating neurotransmitter functions and may regulate synaptic transmission and neuronal activity. Studies on TAAR1 signaling pathways were reviewed to identify the potential of TAAR1 as a novel target for neuroprotection and neurorepair. TAAR1 realizes effects through binding to the G-protein subunits Gas or Ga13. The target of Gas is PKA and the target of Ga13 is RhoA. Among the RhoA-mediated effects of TAAR1, effects on MAPK/ERK pathway kinases, AMPA and NMDA glutamate receptors and CREB factor have been investigated. RhoA-mediated effects include effects on the internalization of DAT and EAAT3, neuronal transporters of dopamine and glutamate. A G-protein independent pathway is mediated by β-arrestin and is probably related to the formation of the TAAR1-D2R heterodimer. The modulatory effect of TAAR1 on neurotransmitter systems allows us to consider TAAR1 agonists as potential therapeutic agents for the treatment of neurodegenerative diseases and psychiatric disorders, as well as neuroprotectors in ischemic brain damage.

***Keywords*:** Trace amine-associated receptors, Signal transduction, Neuroprotection, Neurotransmitter agents, Cyclic AMP-dependent protein kinases

Cite this article: Voevoda M, et al. Trace Amine-associated Receptor 1: Role in the Implementation of Neuroprotective Signaling Pathways. 2025; 14 (4): 980-993. DOI: 10.22088/IJMCM.BUMS.14.4.980

[Downloaded from ijmcmed.org on 2026-11-07]

[DOI: 10.22088/IJMCM.BUMS.14.4.980]

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Introduction

Different types of cell membrane receptors are widely represented in the nervous system (NS). They receive external regulatory signals and transmit this information inside the cell. One of the largest families of transmembrane proteins is G protein-coupled receptors (GPCRs). To date, approximately 200 receptors of this family have been described. They are capable of interacting with various stimuli such as neurotransmitters, nucleotides, amines, peptides, cytokines and hormones in the extracellular environment (1, 2). There are two modulators of signal transduction involving GPCRs: heterotrimeric G-proteins and arrestins. Characterization of the physiological functions of GPCRs in the NS and pathological mechanisms in disease models may accelerate the development of drugs targeting this receptor family. Trace amine-associated receptor 1 (TAAR1) is a classical member of the GPCRs. It is widely distributed in the mammalian brain (3) and represents a highly conserved subtype of TAAR in all species studied (4). Active expression of the TAAR1 gene is found in brain structures associated with psychiatric disorders, particularly in key regions where modulation of signal transduction by dopamine (ventral pavement region) and serotonin (dorsal suture nuclei) occurs, and the presence of TAAR1 variants is associated with schizophrenia (3). TAAR1 can specifically respond to endogenous trace amines in the central nervous system (CNS) and peripheral tissues and potentially play an important role in modulating neurotransmitter functions. In addition, TAAR1 may regulate synaptic transmission and neuronal activity. TAAR1 agonists also exhibit antidepressant/stress-reducing activity, procognitive, vigilance-promoting, antinociceptive, anti-narcoleptic and anticataleptic effects (4-8). Because of the close relationship between TAAR1 and dopamine D2 receptors (D2R), as well as involvement in overlapping brain neuronal networks relevant to schizophrenia and the reward system, there has been considerable interest in the development of TAAR1 agonists as potential drug agents for the treatment of psychiatric disorders.

Numerous psychotropic drugs, including amphetamines, methamphetamine and methylenedioxymethamphetamine are potent TAAR1 agonists in humans, leading to the consideration of TAAR1 ligands as agents aimed at alleviating addictive behaviors (8, 9). In this context, it is of interest to prescribe TAAR1 agonists to patients with schizophrenia and co-occurring substance abuse (10, 11). According to recent studies, TAAR1 has exerted its functions by regulating signaling pathways and substrate phosphorylation. We conducted a detailed review of studies on TAAR1 signaling pathways to identify the potential of TAAR1 as a novel therapeutic target for neuroprotection and neuroreparation.

Signal generation by TAAR1 receptors

High-affinity endogenous TAAR1 agonists include hormone metabolite 3-iodothyronamine (3-T1AM). The 3-T1AM molecule contains b-phenylethylamine, which is responsible for the molecule's ability to recognize GPCRs in cells. In 2021, we studied the effect on hypothermia of a water-soluble synthetic analog of thyronamine T0AM ((4-(4-(4-(2-amino-ethoxy)-benzyl)-phenylethylamine dihydrochloride)). Intraperitoneal injection of this substance into rats at a dosage of 50 mg/kg resulted in a statistically significant sustained decrease in rectal temperature, indicating the affinity of the substance to target receptors. To enhance the water solubility of the investigated agent, we synthesized another thyroid hormone derivative, thyronamide, in which the ethylamine group was replaced by an amide group acting as a hydrogen bond acceptor. It was expected to provide additional binding sites for the receptor, however, the study showed reduced activity of this compound as a hypothermic agent. We hypothesized that this is due to the loss of an important fragment from the thyronamide molecule that is characteristic of 3-T1AM, T0AM and (4-(4-(4-(2-aminoethoxy)-benzyl)-phenylamine, which provides the configuration necessary for tight binding to the active site of TAAR1 (12).

TAAR1-activated receptors generate secondary signals via G-protein, which is inactive in its heterotrimeric form. Individual GPCRs may participate in the realization of different functions in various tissues due to preferential binding to one of the subclasses of G-proteins. A common function of the G_{as} subunit is to activate adenylate cyclase, which in turn produces cyclic adenosine monophosphate (cAMP) (13).

The signal from the ligand-stimulated GPCR is enhanced because the receptor can activate several heterotrimers of G_{as} before it is inactivated. Activation

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of Go protein-coupled TAAR1 was found to modulate the activity of potassium voltage-gated channel through the activation of protein kinase C-theta in trigeminal ganglion neurons (14). G-protein-dependent signaling is considered to be the major signaling pathway for GPCRs. However, β-arrestin (βArr) is able to modulate GPCR signaling by a G-protein-independent mechanism. β-arrestin (signal terminator) can use the receptor as a structural component to generate an intracellular signaling complex consisting of receptor and nonreceptor tyrosine kinases occupied by agonists (c-Src) (Figure 1) (15).

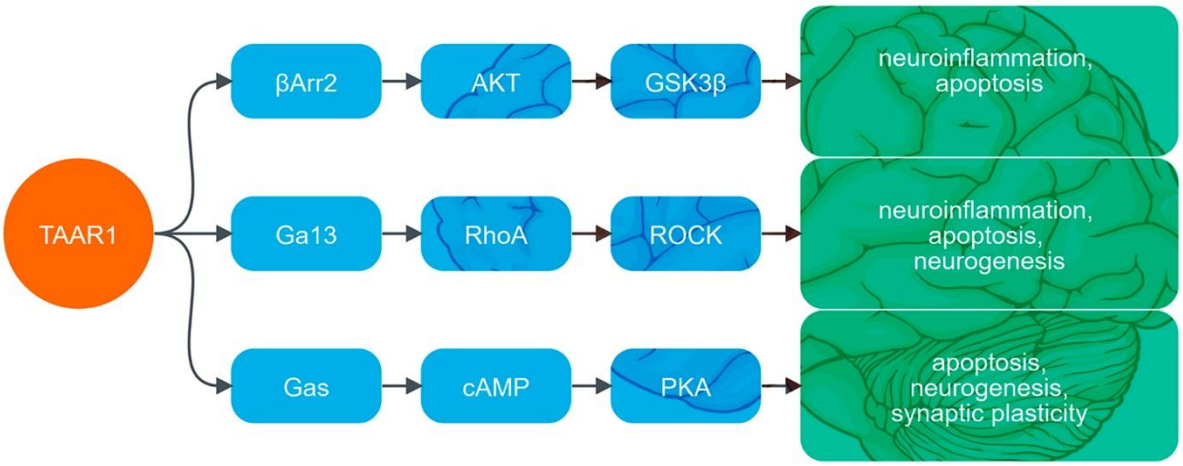


Figure 1. Pathways of signal transmission from the TAAR1 in the neuron Note: βArr2 - β-Arrestin2, AKT - Protein kinase B, GSK3β - Glycogen synthase kinase-3 beta, G_{a13} - G13 alpha subunits, RhoA - Ras homolog family member A, ROCK - Rho-associated protein kinase, G_{as} - Gs alpha subunits, cAMP - Cyclic adenosine monophosphate, PKA - protein kinase A.

Activation of protein kinases

As a G_{as}-related receptor, TAAR1 promotes the production of cAMP through stimulation of adenylate cyclase. This was confirmed after studying TAAR1 expression in different cell types and using different approaches to analyze cAMP concentrations. In fact, the study of cAMP is currently a central component of TAAR1 ligand screening programs (5). Elevated level of cAMP activates a number of cAMP-dependent protein kinases grouped under the name protein kinase A (PKA).

PKA is a multifunctional serine/threonine kinase that regulates a wide range of physiological processes, including gene transcription, metabolism and synaptic plasticity. It is thought to play a central role in the induction of both functional and structural changes in neurons, such as long-term potentiation and depression. In addition, the role of PKA is also important in neurodevelopmental processes (16). Inhibition of various G_a signaling pathways in cell lines and in vivo revealed that endogenous intracellular TAAR1 can also bind to G_{a13} and increase RhoA activity. This allowed to assume that there are several populations of TAAR1 receptors that differ in their binding to G-protein subunits, G_{as} or G_{a13}.

The target of G_{as} is PCA and the target of G_{a13} is a transforming protein RhoA (Ras homolog family member A, small GTPase protein (RhoA)). RhoA signaling is concentrated near the endoplasmic reticulum (EPR), while intracellular AMPH-mediated activation of PKA is more widely distributed throughout the cell. However, it remains unclear whether the two receptor populations are located apart or colocalized. The specificity of TAAR1 binding to G_{as} or G_{a13} is also unknown (17, 18). Interestingly, two processes occur in parallel in the cell simultaneously. Part of the intracellular TAAR1 receptors activate RhoA and another TAAR1 population activates the adenylate cyclase/cAMP/PKA pathway, which leads to inactivation of RhoA by direct PKA-mediated phosphorylation, which in turn limits RhoA-dependent effects.

MAP kinase cascade and related transcription factors

Recent studies have suggested that the mitogen-activated protein kinase cascade is involved in TAAR1 signaling (19, 20). Mitogen-activated protein kinases (MAPK) play an important role in the regulation of gene expression in all cellular activities. Classical

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MAP kinases MAPK-3 and MAPK-1 (according to the modern classification ERK1 and ERK2, respectively) are activated in response to growth factors, hormones, neurotransmitters, cytokines, transforming agents, carcinogens, viral infections and regulate cell proliferation and differentiation. Activation of the MAPK cascade requires four sequential events involving the activation of small guanosine triphosphate hydrolases (Ras and Rac proto-oncogenes), MAPK kinases (Raf or MEKK), MAPK kinases (MEK) and MAPK itself. Once activated, MAPKs become highly efficient signaling molecules that link various extracellular stimuli to cytoplasmic, intranuclear or synaptic responses to them.

The MAPK/ERK signaling pathway is regulated by PKA. Specifically, phosphorylation by PKA of the B-Raf protein in the Ser365 region inhibits ERK signaling by blocking B-Raf binding to Ras. In addition, PKA can stimulate ERK signaling by phosphorylating various proteins of the ERK signaling pathway (16). Another cAMP effector, guanine nucleotide exchange factor 3 (Epac), is a second possible activation pathway, which activates Rap1/B-Raf and downstream ERK1/2 in neuronal, endocrine and other cell types. In neurons, the effect of TAAR1 agonists on Epac activity has not been studied (20).

ERK signaling plays an important role in cell survival, and ERK activation inhibits apoptosis by regulating the expression of various apoptotic proteins. Inhibition of ERK1/2 phosphorylation prevents TAAR1-induced increase in Bcl-2 levels, and this indicates that TAAR1 activation of ERK1/2 pathway upregulates the anti-apoptotic protein Bcl-2 (21). The authors consider this as evidence of a mechanism by which TAAR1 plays a protective role against cell death.

CREB activation signaling pathway

CREB is a widely distributed transcription factor, normally bound to a region of DNA called CRE (cAMP response element). In the absence of stimulation, CREB is dephosphorylated and does not affect transcription. A variety of signal transduction pathways, including PKA and MARK, lead to CREB phosphorylation. ERK1/2 phosphorylates CREB at the Ser-133 region. Thus, as a result of phosphorylation, CREB is involved in activation of neuronal gene transcription, particularly in the expression of BDNF (22). CREB activation may play an important role in mediating drug addiction, anxiety behavior, insulin resistance, leukemia and other pathological processes. One of the target genes of CREB is brain-derived neurotrophic factor (BDNF) (Figure 2). The neuroprotective effect of 3-T1AM under oxygen-glucose deprivation may be related to this factor. Thus, inhibition of BDNF action on TrKB reduces the protective activity of 3-T1AM. The role of BDNF in 3-T1AM-induced neuroprotection was confirmed by the increased BDNF levels observed in 3-T1AM-treated slices, and this effect could be reversed by co-perfusion with the selective TAAR1 antagonist EPPTB (23).

BDNF plays an important role in several aspects of brain function, including neurogenesis, neuronal survival and maturation, synapse formation and synaptic plasticity. BDNF binds to its receptor tropomyosin receptor kinase B (TrkB), and phosphorylated TrkB is able to activate the Ras/ERK pathway. On the other hand, activated CREB factor can trigger BDNF expression. In addition, studies have shown that the CREB/BDNF signaling pathway is closely related to emotional and cognitive function in rats, and is also involved in oxidative stress (OS) and inflammatory responses in neurodegenerative diseases (24). Unbalanced accumulation of oxidized proteins in the brain enhances neurodegeneration and impairs cognitive functions. The accumulation of oxidative damage underlies the molecular basis of brain aging, neurodegenerative disorders (Parkinson's disease, Alzheimer's disease and Huntington's disease) and ischemic brain damage. In the experiment on modeling ischemic stroke by permanent occlusion of the middle cerebral artery (MCA) an increase in lipid peroxidation (LPO) was observed in the ischemia focus already after 24 hours.

LPO final products activate phospholipase A2, which hydrolyzes phospholipids of cell membranes, which, in turn, is accompanied by the release of proinflammatory mediators (25). Peroxidation products can also trigger the p53 signaling pathway, disrupting membrane structure and mitochondrial DNA function. Oxidative modification of proteins increases their antigenicity and changes the antigenic profile itself. In an experiment on an animal model of unilateral brain ischemia, we revealed a statistically significant decrease in malonic dialdehyde levels and an increase in superoxide dismutase activity in the ischemic hemisphere, as well as an increase in glutathione peroxidase activity in brain tissue in

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response to the administration of a synthetic analog of T0AM, which indicates a significant potential of thyronamines and their analogs in activation of antioxidant defense mechanisms in nervous tissue (26). The positive effect of thyronamine analogs on the recovery of behavioral and cognitive functions in rats after ischemia was also demonstrated by the authors (27), which suggests the intervention of thyronamines and their analogs in the implementation of the CREB/BDNF signaling pathway. Thus, the results of studies using various TAAR1 agonists demonstrate that part of their functions is realized through regulation of the cAMP/PKA/CREB pathway (28). This indicates the potential ability of TAAR1 agonists to improve synaptic plasticity of damaged neurons and increase the efficiency of signal transduction

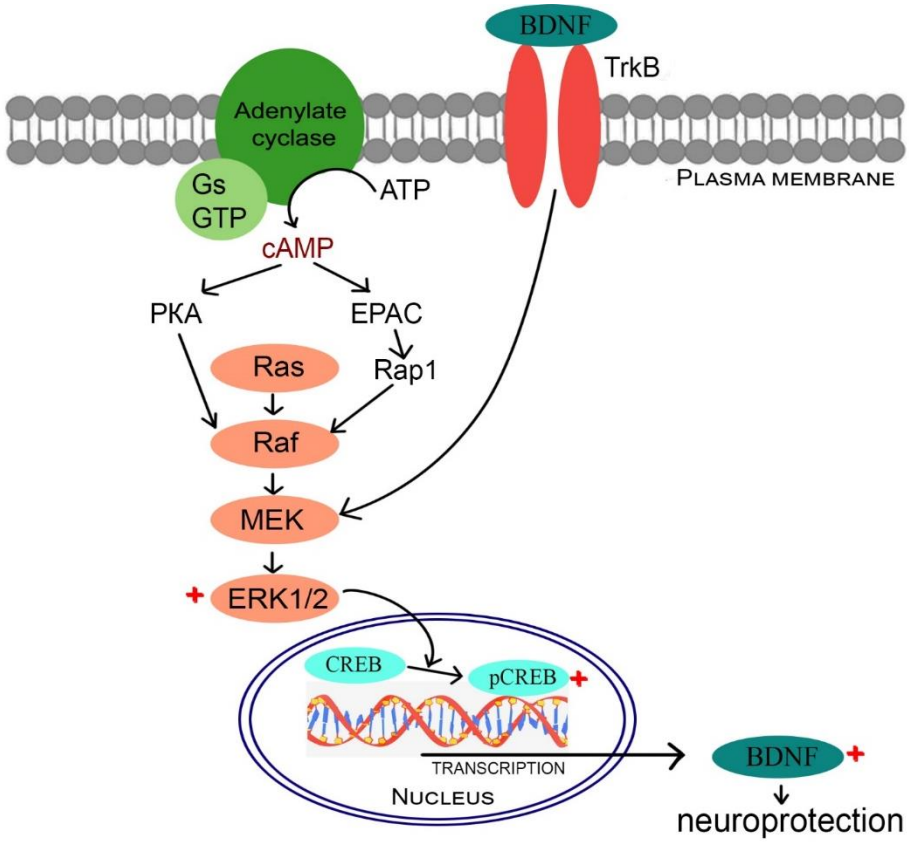


Figure 2. Effect of TAAR1 on the activation of the MAP kinase cascadeNote: "+" marks proteins which binding to TAAR1 was detected in the experiment. Gs - subunit of the heterotrimeric G protein, GTP - guanosine-triphosphate, ATP - adenosine triphosphate, cAMP - cyclic adenosine monophosphate, PKA - protein kinase A, EPAC - exchange protein directly activated by cAMP, Rap-1 - Ras-related protein, Raf - serine/threonine-specific protein kinases, MEK - mitogen-activated protein kinase, ERK1/2 - extracellular signal-regulated kinase, CREB - cAMP response element-binding protein, BDNF - brain-derived neurotrophic factor, TrkB - tropomyosin receptor kinase B.

Heterodimerization of TAAR1 and D2 receptors: implications for the dopaminergic system

Many studies have focused on the role of TAAR1 in modulating the dopaminergic system, and it is clear that, in general, TAAR1 has a negative effect on dopaminergic activity. Mice of the TAAR1-KO line show higher sensitivity to amphetamine and other psychostimulants and appear to possess a supersensitive dopaminergic system, making them an interesting model relevant to schizophrenia (29).The functional interaction between TAAR1 and D2R is likely mediated through their heterodimerization. Evidence that TAAR1 and D2R forms a heterodimer with unique functional properties has been found both in vitro and in vivo. The TAAR1-D2R interaction increases TAAR1 localization at the plasma membrane (30). D2R transmit signals via $G_{\alpha i}$ proteins, which leads to a decrease in intracellular cAMP. They can also activate signaling cascades in a G-protein-independent manner via βArr2, which forms a protein complex

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consisting of Akt, βArr2 and protein phosphatase 2A (PP2A). Once in the complex, PP2A dephosphorylates and deactivates Akt, activating glycogen synthase kinase 3β (GSK3b) (29, 30).

PI3K/AKT/GSK3β signaling pathway

Phosphatidylinositol 3-kinase/protein kinase B/glycogen synthase kinase-3β (PI3K/AKT/GSK3β) is an important pathway for maintaining neuronal and cell survival. GSK3β is involved in various biological functions such as neuroinflammation and apoptosis. GSK3β activation can induce NF-κB and NO production in microglia to generate proinflammatory cytokines. These processes promote microglia migration and mediate the development of neuroinflammation (31).

GSK3β promotes apoptosis under a variety of conditions, including DNA damage, hypoxia/ischemia, EPR stress (dysfunction), etc., by inhibiting survival-promoting transcription factors such as CREB and heat shock factor-1 and promoting the activation of pro-apoptotic transcription factors such as p53 (32).GSK3β activity can be reduced by Ser-9 phosphorylation. Protein kinase B (AKT), including Akt, is able to mediate this modification. Phospho-Akt exerts a protective effect in cerebral ischemia by inactivating GSK3β. The AKT/GSK3β pathway is closely related to the inhibition of inflammation and apoptosis as well as vascular endothelial protection. AKT/GSK3β activation promotes neuronal survival in the hippocampus, reduces glial inflammation and maintains blood-brain barrier (BBB) integrity after cerebral ischemia, demonstrating that the AKT/GSK3β pathway plays an essential role in neurovascular protection (33). Studies by Harmeier at al. showed that the TAAR1-D2R interaction leads to an attenuation of the cascade of cAMP signaling upon TAAR1 activation compared to homoreceptor. These results could be explained by the fact that TAAR1-D2R heteromerization shifts signaling from $G_{\alpha s}$ to $G_{\alpha i}$. The specific interaction of TAAR1 with βArr2 is enhanced in the presence of D2R.

In contrast, the affinity of βArr2 for activated D2R is reduced when co-expressed with TAAR1. In cells showing increased recruitment of βArr2 to TAAR1, one would expect decreased phosphorylation of Akt and GSK3β. Instead, the opposite was observed – inactivation of GSK3β signaling through increased phosphorylation. This is probably due to the fact that Akt, as a key signaling node, can be activated or deactivated through different pathways (30). Thus, TAAR1-D2R heteromerization generally leads to a decrease in cAMP accumulation and GSK3β inactivation (Figure 3).

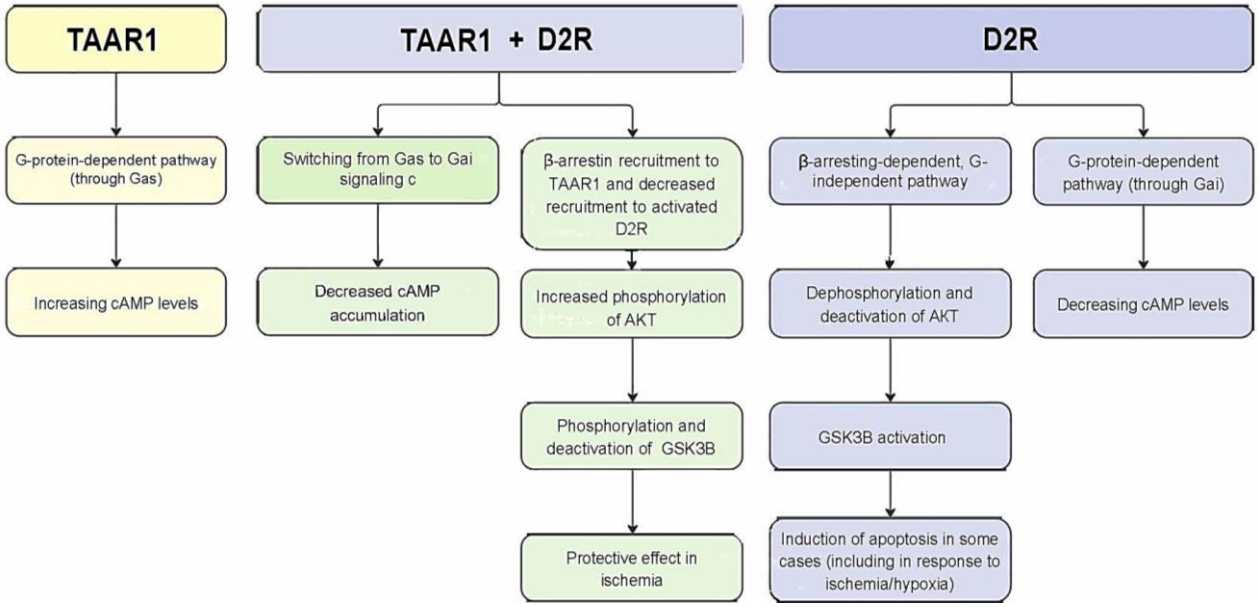


Figure 3. Signaling cascades of homoreceptors TAAR1 and D2R and their heterodimer
Note: TAAR1 - trace amine-associated receptor 1, D2R – dopamine receptor D2, TAAR1-D2R – heterodimer, GSK3β - glycogen synthase kinase-3 beta, $G_{\alpha s}$ и $G_{\alpha i}$ – G_{α} subunits.

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[DOI: 10.22088/IJMCM.BUMS.14.4.980]

Modulation of glutamatergic transmission

There is evidence to suggest that TAAR1 is involved in modulating not only dopaminergic but also glutamatergic synaptic transmission (34).

A study by Espinoza S et al. showed that TAAR1 plays an important role in the modulation of NMDA receptor-mediated glutamate transmission in the prefrontal cortex. The absence of TAAR1 results in decreased NMDA glutamate receptor (NMDAR) activity, indicating that TAAR1 is able to modulate processes and behaviors associated with the prefrontal cortex. An increase in AMPA receptor (AMPAR) activity accompanied the decrease in NMDAR activity. It is known that NMDAR function can negatively affect AMPAR current. In particular, the GluN2B subunit has shown to inhibit surface expression of the AMPAR. Thus, the increased AMPAR current could potentially be explained by a decrease in the GluN2B subunit, which subtly regulates AMPAR availability on the postsynaptic side of the membrane without significant changes in total AMPAR protein.

In addition, decreased NMDAR function may contribute to increased glutamate release from synaptic vesicles and therefore AMPAR current. In TAAR1-KO mice, expression of the GluN1 and GluN2B subunits of the NMDAR was reduced with a concomitant decrease in the phosphorylation site on the GluN1 subunit (35). TAAR1 agonists can suppress hyperactivity in pharmacologic or genetic models of NMDA glutamate receptor deficiency in mice and improve cognitive abilities in rats treated with the NMDAR antagonist phencyclidine (36). The TAAR1 agonist RO5256390 promoted NMDAR incorporation into the cortical cell membrane (34).

The TAAR1 agonist Ulotaront reduced spontaneous glutamatergic synaptic transmission and neuronal activation in brain slices of the striatum and hippocampus, respectively, and concomitantly potentiated electrically evoked excitatory synaptic transmission in both brain regions, suggesting an ability to modulate glutamatergic signaling in a state-dependent manner (i.e., selectively potentiate the evoked synaptic response while simultaneously reducing spontaneous activity). Similar effects in the striatum were also observed with another TAAR1 agonist, RO5166017. In addition, Ulotaront regulates the excitation-inhibition balance in the striatum by specifically modulating glutamatergic, but not GABAergic, spontaneous synaptic events (33).

In a study in a mouse model of Parkinson's disease, the selective TAAR1 agonist RO5166017 affected presynaptic (glutamate release) and postsynaptic (AMPA receptor phosphorylation) glutamatergic neurotransmission in the striatum (37).

Putative mechanisms of influence on glutamatergic transmission

The exact molecular mechanism of TAAR1-related effects on glutamatergic transmission and NMDAR and AMPAR status is unknown. Several possibilities should be considered. First, changes in cortical glutamatergic transmission may be secondary to changes in cortical dopaminergic transmission because TAAR1 exerts a potent modulatory effect on the mesolimbic dopaminergic system, probably through heterodimerization of the D2-TAAR1 dopamine receptor.

The influence of other monoaminergic systems also cannot be excluded (35). There is evidence that TAAR1 is able to modulate the function of the glutamate transporter EAAT2, resulting in changes in glutamate clearance and suggesting a direct link between TAAR1 and glutamate transmission. Because random fluctuations in the synaptic vesicle fusion processes are sensitive to intracellular calcium levels, an alternative mechanistic scenario for the action of TAAR1 agonists is that they regulate neurotransmitter release via TAAR1-induced control of intracellular calcium (37). The TAAR1 agonist RO5256390 promoted the integration of NMDAR into the cortical cell membrane. Finally, NMDAR and AMPAR are phosphorylated by PKAs. Further studies are needed to investigate all these potential mechanisms(35).

Overactivation of NMDAR and the resulting Ca^{2+} toxicity are thought to play a crucial role in ischemic brain damage. Oxygen-glucose deprivation-induced cortical neuronal damage is reversed mainly by NMDA channel blocker (38). Blocking calcium-permeable AMPAR reduces cell death in the hippocampus after ischemia/reperfusion, and modulation of AMPAR improves neurobehavioral deficits and reduces infarct rates through anti-inflammatory, neuroprotective and antiapoptotic effects (39).

Proteins phosphorylated by PKA

Some proteins, that have been shown to be associated with both TAAR1 receptor activation and the phosphorylation action of PKA, were considered

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above. These are kinases of the MARK/ERK pathway and glutamate receptors AMPA, NMDA.

However, PKA is involved in the regulation of the activity of many other proteins as well. The role of TAAR1 in the expression of these intermediates has not been proven. The fact that some of them are expressed in neurons indicates a possible role in the development of neurodegenerative diseases and allows us to consider them as potential targets for neuroprotection (Table 1).

Table 1. Proteins phosphorylated by protein kinase A

Group	Title	Processes in the brain associated with protein	Relation to neuroprotection in ischemia or neurodegenerative diseases
Membrane ion channels and associated receptors	PLM (FXYD1)	- neuronal excitability; -formation of neuronal dendritic trees and spines in the brain (40).	Extracellular K^+ homeostasis is a potential mediator of neuronal damage, as increased K^+ levels increase excitatory activity (41).
	NHE1	- activation of NADPH oxidase and cytokine release in neurons, proinflammatory microglia and reactive astrocytes.	Pharmacologic blockade of NHE1 activity reduces inflammatory microglia responses and enhances oligodendrogenesis and white matter repair in a mouse model of MCAO (42).
	RyR2	- control of neuronal function, - maintenance of synaptic plasticity.	Increased oxidative tone of hippocampal neurons during aging or AD leads to excessive activation of RyR-mediated Ca^{2+} release, and this contributes to the development and exacerbation of pathological conditions. RyR inhibition may protect neuronal function in AD (43)
	SOC (Orai1)	- regulation of reactive astrogliosis, - control of the synthesis and release of a wide range of pro-inflammatory mediators.	Loss of Orai1 in astrocytes suppresses the production of pro-inflammatory cytokines, attenuates inflammation-mediated Ca^{2+} signaling, attenuates neuroinflammation in the hippocampus and blocks the development of depression-like behavior following peripheral inflammation (44).
	PMCA	- cytosolic Ca^{2+} clearance during both resting and neuronal activity (45).	Down-regulation of PMCA may play an important role in impaired neuronal function in the aging brain and its multiple susceptibility to diseases such as AD, PD and stroke (46).
	VDCC	- neuronal excitability and gene transcription in postsynaptic dendrites and soma, - transmitter release in the presynapse (47).	Continuous activation of VDCC during hypoxia causes excessive Ca^{2+} influx, which can trigger cell damage mechanisms: excitotoxicity, mitochondrial dysfunction, ATP depletion, neuroinflammation and DNA damage (48).
Transcription factors	SOX9	- maintaining neural stem cell populations in both embryonic and adult CNS, - gliogenesis (49).	SOX9 upregulation promotes ischemic brain damage by upregulating the FOXO3/CITED2/IKKα axis in a model of MCAO (50).
	NFkB	- differentiation, axon formation and survival, - integration of young neurons into neuronal networks (51).	Regulates the expression of pro-inflammatory genes in response to ischemic damage in microglia cells.
	NFAT	- neurotrophic signaling to regulate axon growth, - integration of neuronal growth with guidance signals that help form synapses and build neuronal circuits.	Preconditioning of PC-12 cells with a Ca^{2+} antagonist in an oxygen-glucose deprivation model suppresses activation of the Ca^{2+}/CaN/NFAT pathway, which increases cell viability and reduces apoptosis and inflammation (52).

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	GLI3	- formation of the brain structure, - growth of the cerebral cortex, - establishment of neurogenic niches in adult individuals	Proteolytic cleavage of GLI (glioma-associated oncogene homolog) into GLI3 (repressor) results in the dysregulation of Smo-Shh, which contributes to the pathogenesis of various neurodegenerative diseases, including AD, PD and HD. Smo-Shh activators help to prevent various neurodegenerative and neuropsychiatric disorders (53).
Signal transductors	PDE4	- control of intracellular cAMP concentrations inside the CNS by hydrolyzing cAMP in neurons	With the increased levels of cAMP, the activation of second messenger-related signaling pathways could decrease inflammation and promote neuroprotection (54).
	DARPP-32	- dopaminergic signaling pathway, - the integration of dopamine and glutamate signaling (55).	The phosphorylation of DARPP-32 inhibits protein phosphatase-1, preventing phosphorylation of intercellular proteins, which reduces the level of neuronal damage during ischemia (56).
Apoptosis regulator	Bad	- neuronal apoptosis, -neuroinflammation, - Aβ clearance in AD (57).	Phosphorylation of Bad prevents apoptosis on the background of cerebral ischemia (58).

Note: PDE3A – phosphodiesterase 3A; NFAT - nuclear factor of activated T cells; Bad - BCL2-associated agonist of cell death; PLM (FXYD1) – phospholemman; RyR2 – ryanodine receptor 2; PKMA - plasma membrane Ca^{2+} ATPase; VDCC – voltage-gated calcium channels; PAPR-α - peroxisome proliferator-activated receptor alpha; NFkB - nuclear factor kappa-B; AD - Alzheimer's disease; PD - Parkinson's disease; HD - Huntington's disease; NHE1 - sodium–hydrogen antiporter; cAMP - cyclic adenosine monophosphate; cGMP - cyclic guanosine monophosphate; GWAS – genome-wide association study; Bcl-2, Bcl-xL, Bax, Bak –- regulators of apoptosis; NOX2 - NADPH oxidase 2; FOXO3 – forkhead box O3, tumor suppressor; CITED2 – regulator of transcription factors; IKKα – inhibitor of nuclear factor kappa B kinase complex; GLI3 – zinc finger protein; Shh - sonic hedgehog signaling molecule; Smo – smoothened, frizzled class receptor; DARPP-32 – neuronal phosphoprotein.

Rho/ROCK signaling pathway

As already mentioned, as a G_{a13}-related receptor, TAAR1 leads to activation of RhoA. Binding to GDP makes Rho inactive, while binding to GTP activates it. Rho that is activated by nucleoside triphosphate in turn activates the next effector, Rho kinase (ROCK), a member of the serine/threonine protein kinase family. Two kinase isoforms, ROCK1 and ROCK2, play a significant role in a wide range of cellular processes. They show different expression patterns: the ROCK1 isoform is mainly specific to tissues outside the nervous system, while ROCK 2 is expressed in the brain and skeletal muscle. Activated ROCK phosphorylates a number of downstream effectors, notably phosphorylating phosphatase and inactivating AKT. ROCK is also involved in apoptosis through breakdown of caspase-3 or granzyme B. The Rho/ROCK pathway regulates many essential cellular functions such as gene transcription, intercellular adhesion, cell cycle progression, dendrite branching, spine morphogenesis, growth cone development, axon guidance, neuroinflammation and neuronal survival and death (59). Excessive Rho/ROCK activity contributes to the pathophysiology of a wide range of diseases, such as subarachnoid hemorrhage, retinal lesions, epilepsy, Parkinson's disease, Alzheimer's disease, ischemic stroke and others. Many researchers consider the potential of this signaling pathway as a therapeutic target, as inhibition of the Rho/ROCK pathway may be effective in the treatment of these diseases.

Active RhoA triggers signaling pathways that lead to the internalization of DAT and EAAT3, neuronal transporters of dopamine and glutamate. The internalization process involves their transfer from the plasma membrane to endosomal compartment membranes (Figure 4). This decreases the entry of neurotransmitters into the nerve cell and increases their concentration in the extracellular environment. Perhaps TAAR1/G_{a13}-mediated internalization of DAT has a protective function in regulating the action of endogenous amines, including dopamine.

High concentrations of dopamine in the cytoplasm are neurotoxic due to the formation of reactive oxygen species (ROS) and quinones, which can cause neuronal damage. Under normal conditions, dopamine, which is transported inside the cell via DAT, is rapidly transferred to synaptic vesicles or metabolized by enzymes. However, if the cytoplasmic dopamine concentration rises to such an extent that the

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mechanisms described above fail to maintain it within safe limits, other pathways may be required to regulate it. Dopamine itself may act as a TAAR1 agonist, causing internalization of its transporter. In HEK293 cells with TAAR1 knockout, AMPH-dependent activation of RhoA is absent, and internalization of DAT and EAAT3 is undetectable (18). Ischemic stroke is accompanied by the upregulation of the Rho/ROCK pathway in neurons and astrocytes. In rodent models of middle cerebral artery occlusion (MCAO), an increase in ROCK activity in the ischemia zone has been described.

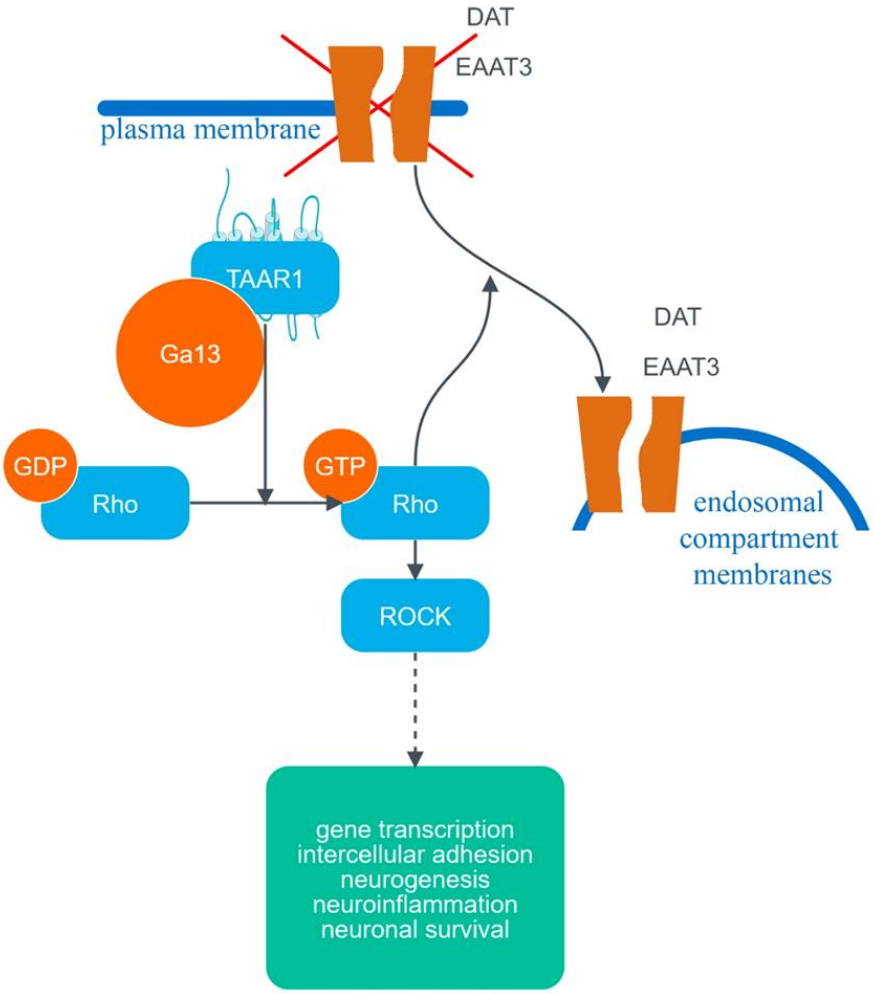


Figure 4. The effect of TAAR1 on the activation of the Rho/ROCK pathway and the internalization of dopamine and glutamate neuronal transporters. Note: DAT – dopamine neuronal transporter, EAAT3 - glutamate neuronal transporters

Although inflammatory responses after acute ischemia help to isolate the injured area, excessive inflammation may exacerbate ischemic damage. ROCK activation after stroke contributes to brain deterioration in the acute phase by stimulating neuroinflammation, increasing secretion of proinflammatory cytokines by microglia, mediating overexpression of adhesion molecules and promoting microvascular damage.

Administration of a ROCK inhibitor increased cerebral blood flow, reduced infarct zone size, prevented ischemia-induced neuronal apoptosis by maintaining AKT signaling pathway activity and improved neurological outcomes. ROCK inhibitor activates astrocytes to produce granulocyte colony-stimulating factor (G-CSF), resulting in induction of neurogenesis and neuroprotection under conditions of oxygen-glucose deprivation.

Thus, the Rho/ROCK pathway can block neurogenesis, resulting in impaired neuronal recovery, and ROCK inhibitors promote angiogenesis and neurogenesis after cerebral ischemia. Inhibition of ROCK significantly reduces focal adhesion and stress fiber formation induced by Thy-1 (CD90) in astrocytes,

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indicating the importance of the Rho/ROCK pathway in processes involved in neuroglial communication in the brain (60).

Discussion

TAAR1 is a classical representative of the G-protein coupled receptor family. It has a rather wide range of full and partial agonists, including trace amines, psychoactive substances, neurotransmitters, etc. TAAR1 stimulation triggers one of the possible signaling pathways dependent or independent on the G-protein. The G-protein independent pathway is mediated by βArr2.

The G-protein-dependent signaling pathway is represented by interaction with the subunits of G_{as} and G_{a13}, and the main pathway for implementing the effects of TAAR1 is the pathway mediated by interaction with the G_{as}. In this case, through the activation of adenylate cyclase, the production of cAMP is launched, which in turn activates protein kinase A (PKA). By phosphorylating various proteins, PKA implements neuroprotective mechanisms. In particular, by activating the MAPK/ERK pathway it leads to a decrease in apoptosis and by activating the CREB factor it triggers the synthesis of transcription factors, which leads to the production of the neuroprotective protein BDNF, contributes to cell survival. In addition, by phosphorylating dopamine and glutamate receptors NMDA and AMPA, PKA reduces the access of these substances into cells, decreasing the degree of their damage. PKA is also able to modulate the activity of a whole group of different proteins founded in the CNS, whose relationship to TAAR1 signaling still remains unclear.

The pathway associated with the G_{a13} subunit is aimed at activating another kinase, PhoA, which causes the internalization of dopamine and glutamate neuronal transporters (DAT and EAAT3), significantly reducing the access of these neurotransmitters, as well as calcium ions, into the cell. On the other hand, RhoA activates Rho kinase (ROCK), which promotes a decrease in neurogenesis and an increase in the production of proinflammatory cytokines.

Studies showed that a single receptor cannot bind to both subunits, but it is unclear what determines the "specialization" of a receptor and how this relates to its location in the cell. Interestingly, both pathways (G_{as} and G_{a13}) can occur in the cell simultaneously, since the first of them is realized throughout the cytoplasm and the second - mainly near the EPR. However, both pathways cannot be colocalized, since PKA inhibits PhoA, turning off the alternative pathway.

In addition to independent action, TAAR1 is capable of implementing a G-protein-independent pathway in the form of a heterodimer with the dopamine receptor D2. Usually, D2R has a high affinity for the β-arr, but in the form of the TAAR1-D2R, it partially loses this property, delegating it to TAAR1. This interaction causes activation of protein kinase B (Akt), which inhibits GSK3β, which leads to a decrease in neuroinflammation and apoptosis. In addition, TAAR1-D2R is able to switch signaling from the G_{as} subunit to G_{ai}, which leads to a decrease in cAMP accumulation and deactivation of PKA. It is important to note that if TAAR1 is an obligate intracellular receptor, it can be carried to the membrane surface as part of the TAAR1-D2R heterodimer. In other words, all the effects of TAAR1 are realized through the action of one of three kinases, the result of which is neuroprotection by reducing apoptosis, neuroinflammation and the access of dopamine and glutamate into the cell.

The ability to affect the dopaminergic and glutamatergic systems has generated considerable interest in TAAR1 agonists as potential drugs for the treatment of schizophrenia. Although the etiology and underlying pathology of schizophrenia remain unclear, a large body of evidence suggests that alterations in several neurotransmitter systems, primarily dopaminergic and glutamatergic systems, are involved in the pathophysiologic processes (34). Ulotaront (SEP-363856), which is currently in phase III clinical development, was the first TAAR1 agonist to demonstrate efficacy in a randomized, double-blind, placebo-controlled phase II clinical trial in patients with acute exacerbation of schizophrenia (61). For two biogenic amines – dopamine and the trace amine thyramine – TAAR1 has a protective effect, preventing their accumulation inside the cell, promoting their deactivation and reducing their activity. It is likely that it is also true for glutamate. These facts allow us to consider TAAR1 agonists as potential drug agents for the treatment of neurodegenerative diseases and psychiatric disorders. On the other hand, the influence of TAAR1 signaling on factors responsible for neurogenesis, apoptosis, neuronal survival and maturation, synaptic plasticity, intracellular calcium

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concentration, etc., makes it possible to talk about their neuroprotective properties in ischemic brain injury.

Acknowledgments

The study was carried out within the framework of the state assignment of the Ministry of Health of the Russian Federation No.123081000021-2(2023-2025).

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