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TAARs Potential Role in Adult Neurogenesis: Narrative Review

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Abstract—Trace amine-associated receptors (TAARs) represent a relatively recently identified family of G-protein coupled receptors that have attracted considerable attention for their potential physiological role in the mammalian brain. TAAR1 is the most extensively studied member of the TAAR family and a promising target for brain diseases therapy. Early research focused on other TAARs (TAAR2–TAAR9) suggested their primary involvement in olfaction. However, more recent studies have revealed their expression in diverse brain regions, including the limbic system and midbrain, implicating them in the regulation of behavior. A growing body of evidence suggests the involvement of several TAAR subtypes in adult neurogenesis, particularly adult hippocampal neurogenesis (AHN), a process critical for memory formation and learning. AHN occurs in the subgranular zone of the dentate gyrus within the hippocampus and generates new excitatory granule cells. The regulatory influence of TAAR1, TAAR2, and TAAR5 subtypes on AHN has been emphasized in several studies. This overview aims to encompass current research findings regarding the role of TAARs in the process of adult neurogenesis.

Keywords: adult neurogenesis, trace amine-associated receptors, hippocampus, subgranular zone, neuropsychiatric disorders

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INTRODUCTION: TRACE AMINES AND TRACE AMINE-ASSOCIATED RECEPTORS

Trace amines (TA) such as β-phenylethylamine, tyramine, p-octopamine, p-synephrine, and tryptamine are endogenous molecules, resembling classical biogenic amines. In mammalian tissues, TAs are distributed heterogeneously at nanomolar ("trace") concentrations (0.1–100 ng/g), due to absence of the vesicular storage (Burchett and Hicks, 2006). Biosynthesis and metabolism pathways of TAs are the same as for classic monoamines. TAs are synthesized from amino acid precursors by aromatic L-amino acid decarboxylase or via monoamines degradation by catechol-O-methyltransferase (Berry, 2004; Gainetdinov et al., 2018; Halff et al., 2023). TAs are primarily broken down by the monoamine oxidase (MAO) enzyme, with the majority being non-selectively metabolized by both MAO-A and MAO-B (Murtazina et al., 2021).

TAs were primarily understood as indirect sympathomimetic agents, inducing vasoconstriction and subsequent blood pressure elevation in vascular systems by direct interaction with adrenergic receptors (Broadley, 2010). Later, TAs' involvement in monoamine neurotransmission and presence in monoaminergic regions of the mammalian brain have drawn scientific attention (Jones, 1981; Burchett and Hicks, 2006). However, data on TAs role in the central nervous system were inconclusive and contradictory.

Discovering a new family of G-protein coupled receptors—trace amine-associated receptors (TAARs)—was a significant breakthrough. In 2001, two independent research groups demonstrated the receptors have binding sites for TAs, which led to their initial designation as trace amine receptors (TARs) (Borowsky et al., 2001; Bunzow et al., 2001). Further studies revealed that only TAAR1 (formerly TAR1) and TAAR4 (formerly TAR2) respond specifically to TAs (Lindemann and Hoener, 2005; Liberles and Buck, 2006). This new evidence prompted a revision of the nomenclature, resulting in the updated term "trace amine-associated receptors, TAARs"(Lindemann and Hoener, 2005).

In humans, TAAR genes are located on chromosome 6 at band q23.2, with six functionally active genes—

TAAR1, *TAAR2*, *TAAR5*, *TAAR6*, *TAAR8*, and *TAAR9*, and three pseudogenes—*TAAR3*, *TAAR4*, and *TAAR7* (Gloriam et al., 2005).

TAAR1 is the most extensively studied member of the TAAR family and a promising target for psychopharmacology due to the close association of TAAR1 with monoaminergic systems. Studies have shown that TAAR1 modulates classical monoamine neurotransmitter systems, such as dopamine and serotonin (5-hydroxytryptamine, 5-HT). Specifically, TAAR1could alter dopamine D2 receptor responsiveness to ligands by forming heterodimers with D2R on neuronal membranes (Espinoza et al., 2011). Furthermore, TAAR1 influences dopamine reuptake by interacting with the dopamine transporter, DAT, causing it to reverse its function and release dopamine from cells (Xie and Miller, 2009). Regarding the serotonergic system, when activated, TAAR1 affects presynaptic 5-HT uptake and promotes 5-HT efflux via the serotonin transporter, SERT (Xie and Miller, 2008).

Remaining TAARs (TAAR2–TAAR9) were believed to express in the olfactory epithelium and to mediate olfactory signaling. However, it turned out that they are equally represented in the central nervous system alongside TAAR1 and are associated with monoamine neurotransmission. These TAARs (TAAR2–TAAR9) expression was found in the limbic regions and monoamine nuclei of the rodent brain (Vaganova et al., 2022; Katolikova et al., 2022). Moreover, model animal studies have shown that lack of TAAR2 and TAAR5 is associated with higher dopamine neurons number in the substantia nigra and increased dopamine levels in the striatum compared to wild type. Also, TAAR2 and TAAR5 knockout (KO) mice are characterized by impaired levels of anxiety and depressive-like behavior. Together these data could explain the possible influence of TAARs on emotion formation and allow us to consider TAARs as a new target for neuropsychiatric diseases.

During the course of active research on TAARs, their contribution to the process of adult neurogenesis became known. This data is an extremely valuable discovery in view of the already proven connection of TAARs with psychiatric disorders. A number of brain disorders pathogenesis is associated with adult neurogenesis level decrease. For instance, an examination of postmortem hippocampal tissue from schizophrenia patients revealed a significant reduction in the number of proliferating cells (Allen et al., 2016). The connection between adult neurogenesis and depression is supported by studies showing reduced hippocampal volume in affected patients, as well as neurogenic responses to antidepressant treatments (Shemiakova et al., 2024). Changes in the level of adult neurogenesis also accompany neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. However, the role of adult neurogenesis in these diseases remains unclear. A critical question persists: is impaired neurogenesis a cause or a consequence of these pathologies?

Thus, investigating the role of TAARs in adult neurogenesis holds significant potential for advancing disease treatment strategies. In this review, we aim to summarize current knowledge regarding the involvement of TAARs in the process of new neuron formation.

TAARs EXPRESSION: A POTENTIAL ADULT NEUROGENESIS LINK

Recent years have seen a surge of experimental research exploring the role of TAARs in adult neurogenesis. These studies employ diverse approaches, including genetic animal KO models and transcriptomic analyses of human and murine brain tissues (Table 1). Since adult neurogenesis is restricted to two brain regions, the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampus dentate gyrus (DG) (Altman, 1962; Kaplan and Hinds, 1977), it is interesting to explore the expression pattern of TAARs in these regions.

Public transcriptomic data analyses have revealed that TAARs are expressed in the hippocampus at relatively low levels. Notably, the expression profiles differ between species: in humans, *TAAR6* (Vaganova et al., 2021; Katolikova et al., 2022) shows the highest expression, whereas in mice, *Taar1*, *Taar2*, *Taar3*, *Taar4*, and *Taar5* are more prominently expressed, moreover *Taar1*, *Taar2*, and *Taar5* were expressed specifically in DG of hippocampus (Katolikova et al., 2022).

Analysis of mRNA expression in humans and rodents also revealed TAARs presence in the hippocampus. Specifically, in humans, *TAAR1* and *TAAR6* transcripts were found in trace amounts in the hippocampus (Borowsky et al., 2001; Duan et al., 2004). In mice hippocampus, *Taar1* expression was confirmed (Borowsky et al., 2001), while *Taar8b* mRNA was detected at near-threshold levels (Mühlhaus et al., 2014). Several TAARs expression in the brain neurogenic niches has also been

Table 1. Progress in the study of TAARs in terms of adult neurogenesis[a]

Gene	Localization of expression	Detection method	Neurogenesis in knockout animals	Neurogenesis markers used	Referenses
TAAR1	Hippocampus	In situ hybridization, RT-PCR	–	–	Borowsky et al., 2001; Duan et al., 2004
Taar1	Hippocampus, DG	Public transcriptomic data	Decreased neurogenesis in SGZ in TAAR1-cKO mice	DCX, SOX2, Ki-67	Katolikova et al., 2022
TAAR2	–	–	–	–	
Taar2	Hippocampus, DG	Public transcriptomic data	Increased neurogenesis in SVZ and SGZ in TAAR2-KO mice	DCX, PCNA	Katolikova et al., 2022, Efimova et al., 2022
Taar3	Hippocampus	Public transcriptomic data	–	–	Katolikova et al., 2022
Taar4	Hippocampus	Public transcriptomic data	–	–	Katolikova et al., 2022
TAAR5	Hippocampus	Public transcriptomic data	–	–	Vaganova et al., 2021; Katolikova et al., 2022
Taar5	Hippocampus, DG, CA1 area, SVZ	Public transcriptomic data, LacZ-staining	Increased neurogenesis in SVZ and SGZ in TAAR5-KO mice	DCX, PCNA	Efimova et al., 2020; Katolikova et al., 2022
TAAR6	Hippocampus	Public transcriptomic data, RT-PCR	–	–	Borowsky et al., 2001; Duan et al., 2004; Vaganova et al., 2021; Katolikova et al., 2022
Taar6	–	–	–	–	
TAAR7	–	–	–	–	
Taar7(abdef)	–	–	–	–	
TAAR8	–	–	–	–	
Taar8(ab*c)	Hippocampus*	RT-PCR	–	–	Mühlhaus et al., 2014
TAAR9	–	–	–	–	
Taar9	–	–	–	–	

[a] The expression patterns are shown specifically for brain regions associated with adult neurogenesis, including the hippocampus (particularly the dentate gyrus (DG) and subgranular zone (SGZ)), and subventricular zone (SVZ) of the lateral ventricles. (*)—only *Taar8b* expression was found in hippocampus.

shown in KO animals. By using LacZ staining protocol TAAR5 expression was found both in SVZ and SGZ (Espinoza et al., 2020), while TAAR2 expression—in hippocampus (Efimova et al., 2022).

Together these findings provide a foundational basis for investigating the role of TAARs in adult neurogenesis and hippocampal functions.

TAARs AND NEUROGENESIS: EVIDENCE FROM KO MODELS

Current knowledge about TAARs contribution to the new neuron formation process is limited to a few studies, probably due to the complexity and high cost of the methods used (Fig. 1). The association of TAARs with adult neurogenesis was first demonstrated in TAAR5-KO mice (Espinoza et al., 2020). TAAR5-KO mice are characterized by an increased number of neural precursors and proliferating cells in SVZ and SGZ (Espinoza et al., 2020). Later, it was shown that TAAR2 absence in TAAR2-KO mice also leads to increased adult neurogenesis in the neurogenic niches (Efimova et al., 2022). TAAR8-KO mice exhibit enhanced adult neurogenesis, with recent studies demonstrating significantly increased neuroblast-like cells density in SVZ (Shemiakova et al., 2025). In the studies, standard

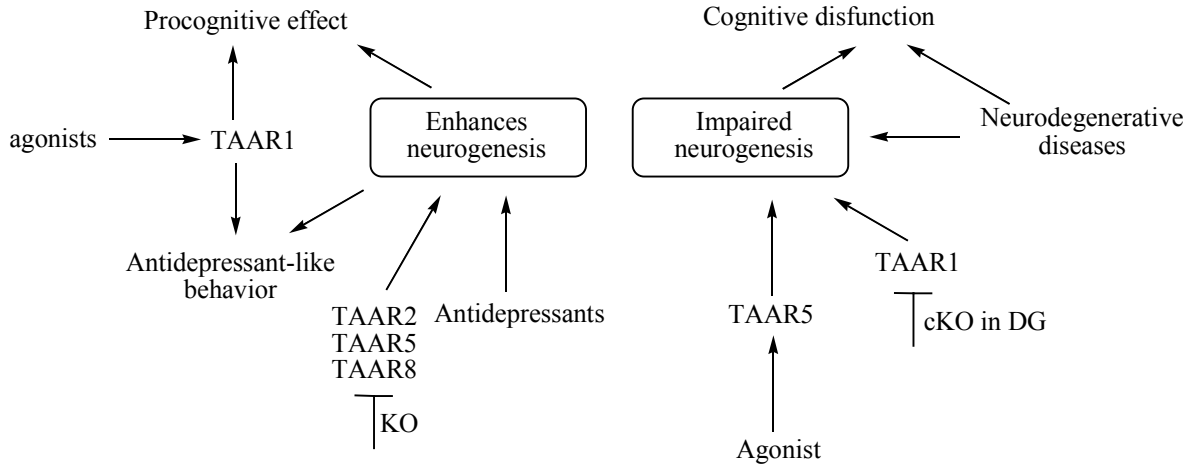

Fig. 1. TAARs and adult neurogenesis interconnection. The diagram provides a schematic representation of the established relationships between TAARs and their role in regulating adult neurogenesis. Current evidence demonstrates that agonist-induced activation of TAAR1 elicits procognitive effects, likely mediated through enhanced adult neurogenesis. This neurogenic enhancement is further associated with the manifestation of antidepressant-like behavioral phenotypes. Conversely, selective knockout of TAAR1 in the dentate gyrus (DG) results in significantly reduced adult neurogenesis, highlighting the receptor's critical role in maintaining neurogenic activity. Complementary studies employing knockout (KO) models of TAAR2, TAAR5, and TAAR8 have revealed enhanced adult neurogenesis relative to wild-type controls. Notably, these findings align with observations that antidepressants concurrently promote neurogenesis and procognitive effects. Impaired neurogenesis correlates with cognitive deficits and has been implicated in the pathogenesis of neurodegenerative disorders.

markers of neurogenesis were used. Doublecortin (DCX) expressing neurons were identified as neuroblast-like, and PCNA-positive as proliferating cells. Together, these markers offer complementary insights into the dynamics of adult neurogenesis. Beyond canonical neurogenic zones, PCNA-positive cells were also detected inside the lateral ventricle walls in both KO lines, with DCX-positive cells observed in this region in TAAR2-KO (Efimova et al., 2022).

Importantly, both TAAR2-KO and TAAR5-KO mice exhibit a notable population of migrating DCX-positive cells within the white matter above the hippocampus. This migration pattern does not align with the canonical rostral migratory stream from the SVZ, suggesting alternative migratory routes and underscoring the need for further research to elucidate the destination and functional significance of these cells (Espinoza et al., 2020).

Finally, TAAR1 impact in adult neurogenesis was demonstrated in conditional KO (cKO) model in mice (Zhang et al., 2024). cKO technique is employed to selectively inactivate genes in specific tissues or developmental stages (Lobe and Nagy, 1998). Selective TAAR1-KO in DG of the hippocampus resulted in reduced densities of immature neuronal precursors (DCX-positive neuroblasts and SOX2-positive neural stem/progenitor cells), with no effect on actively proliferating cells (Ki-67-positive cycling progenitors). Moreover, in a chronic social defeat stress model, TAAR1 partial agonist RO5263397 administration mitigated stress-induced reductions in neurogenesis, increasing both DCX-positive and Ki-67-positive cell populations (Zhang et al., 2024). These findings support a facilitatory role for TAAR1 activation in adult neurogenesis.

FROM NEUROGENESIS TO BEHAVIOR: TAARs AS REGULATORS OF COGNITIVE AND EMOTIONAL PROCESSES

Indirect evidence for altered neurogenesis can be observed through its behavioral correlates. For example, impaired hippocampal neurogenesis has been linked to cognitive deficits in multiple brain disorders (e.g., depression, Alzheimer's disease). Conversely, therapeutic restoration of neurogenesis often correlates with improved learning and memory performance (Shemiakova et al., 2024).

TAARs contribution to the process of forming new neurons is confirmed by animal studies. Activation of

TAAR1 leads to an improvement in cognition, while TAAR1-KO animals demonstrate the opposite behavior. TAAR1 full (RO5256390) and partial (RO5263397, RO5203648) synthetic agonists improve cognitive performance, including attention and memory, in primates and rodents (Revel et al., 2012, 2013; Wu et al., 2021). Administration of 3-iodothyronamine—thyroid hormone derivatives and TAAR1 endogenous agonist, produced prolearning and antiamnestic effects in mice (Rutigliano et al., 2018). On the other hand, TAAR1-KO mice exhibit impaired working memory performance, increased anxiety-like behaviors, and reduced self-grooming compared to wild-type controls) (Wolinsky et al., 2006; Zhukov et al., 2020, 2022).

The procognitive effects of TAAR1 agonists have also been observed in pathological conditions. Ulotaront (SEP-363856) is one of the most prospective TAAR1 agonists in schizophrenia treatment (Correll et al., 2021). Unlike currently available antipsychotics that primarily address positive symptoms of schizophrenia (such as hallucinations and delusions), Ulotaront effectively targets across all symptom domains—including negative symptoms (e.g., social withdrawal, anhedonia) and cognitive (e.g., working memory deficits) ones. This broader efficacy profile could significantly improve patients' quality of life. While preclinical and early-phase studies indicated Ulotaront therapeutic potential, phase 3 clinical trials revealed no statistically significant superiority over placebo (Sumitomo Pharma Co and Otsuka Pharmaceutical Co, 2023; https://news.us.sumitomo-pharma.com/2023-07-31-Sumitomo-Pharma-and-Otsuka-Announce-Topline-Results-from-Phase-3-DIAMOND-1-and-DIAMOND-2-Clinical-Studies-Evaluating-Ulotaront-in-Schizophrenia). Despite its lack of clinical efficacy, TAAR1 remains an attractive therapeutic target, with novel compounds currently under development (Lu et al., 2025).

At present, TAAR1 agonists have been most studied in the aspect of schizophrenia. Emerging evidence increasingly implicates TAAR1 in the pathogenesis of neurodegenerative diseases, where neurogenesis plays a critical role. Several contradictory studies have shown the role of TAAR1 in Parkinson's disease. TAAR1-KO mice demonstrated a smaller loss of dopamine neurons in the Parkinson's disease model by intrastriatal administration of 6-OHDA. In contrast, activation of TAAR1 by an agonist led to a decrease in dopamine levels and worsening of motor symptoms (Alvarsson et al., 2015). A new pilot study has shown the effectiveness of Ulotaront in people with psychosis in Parkinson's disease, without worsening the manifestations of motor and cognitive impairment (Isaacson et al., 2023). Similarly, learning and memory impairment were improved in a mouse model of Alzheimer's disease by targeting TAAR1 with an agonist RO5256390 (Leo et al., 2022).

Mental and neurodegenerative diseases are often accompanied by a decline in cognitive function. And in some cases, such as Parkinson's disease and Alzheimer's disease, a decrease in learning ability may manifest itself before the clinical stage and irreversibility of symptoms. Thus, cognitive dysfunction can be considered as an important symptom and prognostic sign of some conditions (Goldman et al., 2015).

The dorsal hippocampus plays a key role in learning—a process critically dependent on adult neurogenesis (Fanselow and Dong, 2010). Notably, the above-described neurogenesis reduction in TAAR1-cKO mice was localized specifically to the dorsal hippocampus. Together, the neurogenic deficit and behavioral abnormalities in TAAR1-cKO mice provide compelling evidence for TAAR1's critical role in maintaining AHN.

While the role of TAAR1 in cognition is relatively well-characterized, the contributions of TAAR2 and TAAR5 remain less understood. TAAR5-KO mice have been shown to exhibit increased hippocampal theta rhythm power density (Kalinina et al., 2021), which may be related to improved spatial memory and attention (Buzsáki, 2002). Moreover, administration of the putative non selective TAAR5 agonist, α-NETA, resulted in significant changes in the gamma rhythm of brain activity and could lead to signs of cognitive deficit (Belov et al., 2020). Overall, these data support the findings of increased neurogenesis in TAAR5-KO mice dorsal hippocampus, but further studies are needed.

It is important to add that TAAR2-KO and TAAR5-KO are characterized by reduced levels of anxiety and depressive-like behavior. This behavior may indirectly indicate increased adult neurogenesis in the ventral hippocampus, since it contributes to the formation of emotions (Fanselow and Dong, 2010; Kheirbek and Hen, 2011). However, to date, no studies have investigated neurogenesis in the ventral hippocampus of TAAR-KO animal models. The observed increase in neurogenesis coupled with reduced anxiety- and depressive-like behaviors suggests that TAAR2 and TAAR5 antagonists may represent promising antidepressant candidates. This

is particularly compelling given the well-established association between depression and reduced hippocampal neurogenesis, as well as the neurogenic effects of antidepressants.

Interest in other TAARs as potential therapeutic targets in psychiatry is relatively recent, and thus, they have studied less extensively. Furthermore, the current lack of selective ligands limits the ability to conduct experiments analogous to those performed with TAAR1.TAAR2 and TAAR5 have been studied to a much lesser extent, but there are serious prerequisites for their connection with both neurogenesis and neuropsychiatric diseases.

CONCLUSION

The study of trace amine-associated receptors (TAARs) represents one of the most prospective areas in modern neuropsychiatry. Of particular interest is their involvement in the pathogenesis of schizophrenia, depression, and neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. This therapeutic potential stems from TAARs' ability to modulate key neurotransmitter systems—dopamine, serotonin, and glutamate. While TAAR1 has been the most extensively studied and has already yielded promising pharmacological candidates, other family members, particularly TAAR2 and TAAR5, are emerging as equally important players despite their initial classification as olfactory receptors.

A key focus of this review has been the role of TAARs in regulating adult neurogenesis, especially in the hippocampus. Our analysis reveals a fascinating dichotomy: genetic deletion of TAAR2 or TAAR5 leads to enhanced neurogenesis, while TAAR1 selective knockout in dentate gyrus produces the opposite effect. These neurogenic changes correlate with behavioral phenotypes—improved cognitive performance in TAAR5-KO animals versus cognitive deficits in TAAR1-cKO models. Notably, most studies have examined the dorsal hippocampus, which is primarily associated with cognitive functions. However, the observed antidepressant and anxiolytic effects in TAAR2-KO and TAAR5-KO mice suggest that neurogenic changes in the emotion-related ventral hippocampus may be equally important, though this remains to be fully investigated.

The therapeutic implications of these findings are substantial. TAAR1 agonists, such as Ulotaront, show clinical potential not only for schizophrenia but possibly for neurodegenerative disorders as well. Equally exciting is the prospect of developing TAAR2/TAAR5 antagonists as novel antidepressants, given their ability to promote neurogenesis and reduce anxiety-like behaviors. However, significant challenges remain, particularly the lack of selective ligands for TAAR2 and TAAR5, which currently limits our ability to fully explore their therapeutic potential. Future research should prioritize the development of such tools, along with more detailed investigations of region-specific neurogenesis and translational studies to bridge the gap between preclinical findings and clinical applications.

ABBREVIATIONS AND NOTATION

AHN—adult hippocampal neurogenesis;

5-HT—5-hydroxytryptamine;

DCX—doublecortin;

DG—dentate gyrus;

KO and cKO—knockout and conditional KO, respectively;

MAO –monoamine oxidase;

SGZ—subgranular zone;

SVZ—subventricular zone;

TAs—trace amines;

TAARs—trace amine-associated receptors;

TARs—trace amine receptors.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies involving patients or animals as test objects.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION

Conceptualization: T.S.S. Writing: T.S.S. and E.N.P. All authors have read and agreed to the published version of the manuscript.

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