

# Potential contributions of trace amines in Alzheimer's disease and therapeutic prospects

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**Trace amines and their biochemistry:** Trace amines represent endogenous monoamines present in very low concentration (usually nM) in the brain in comparison to classical monoamine neurotransmitters. These trace amines can regulate the amount of the classical monoamine neurotransmitters in the synaptic cleft. Trace amines that have crucial roles in neuromodulation and neurotransmission include *p*-tyramine,  $\beta$ -phenylethylamine, tryptamine, 3-methoxytyramine and their derivatives including octopamine, synephrine, *N*-methyltyramine, *N*-methyltryptamine and *N*-methylphenethylamine. The decarboxylation of aromatic L-amino acids by aromatic amino acid decarboxylase (AADC) (EC 4.1.1.28) is the primary source of these trace amines in cell (Gainetdinov et al., 2018). The distribution of AADC throughout the body varies between tissues. The decarboxylation of tyrosine, phenylalanine and tryptophan leads to formation of tyramine,  $\beta$ -phenylethylamine and tryptamine, respectively (**Figure 1A and B**). Although initially thought to have no pathological and physiological relevance, trace amines proved to be more important with the discovery of trace amine associated receptors (TAARs). These trace amines have been reported to play a crucial role in regulating dopamine and serotonin levels in the synaptic cleft by signaling through TAARs. TAARs are Type A G-protein coupled receptors, which become selectively activated by *p*-tyramine and  $\beta$ -phenylethylamine but not by the classical monoamine neurotransmitters. In the meantime, other trace amines including tryptamine and octopamine also interact with TAARs as agonists (Berry, 2016).

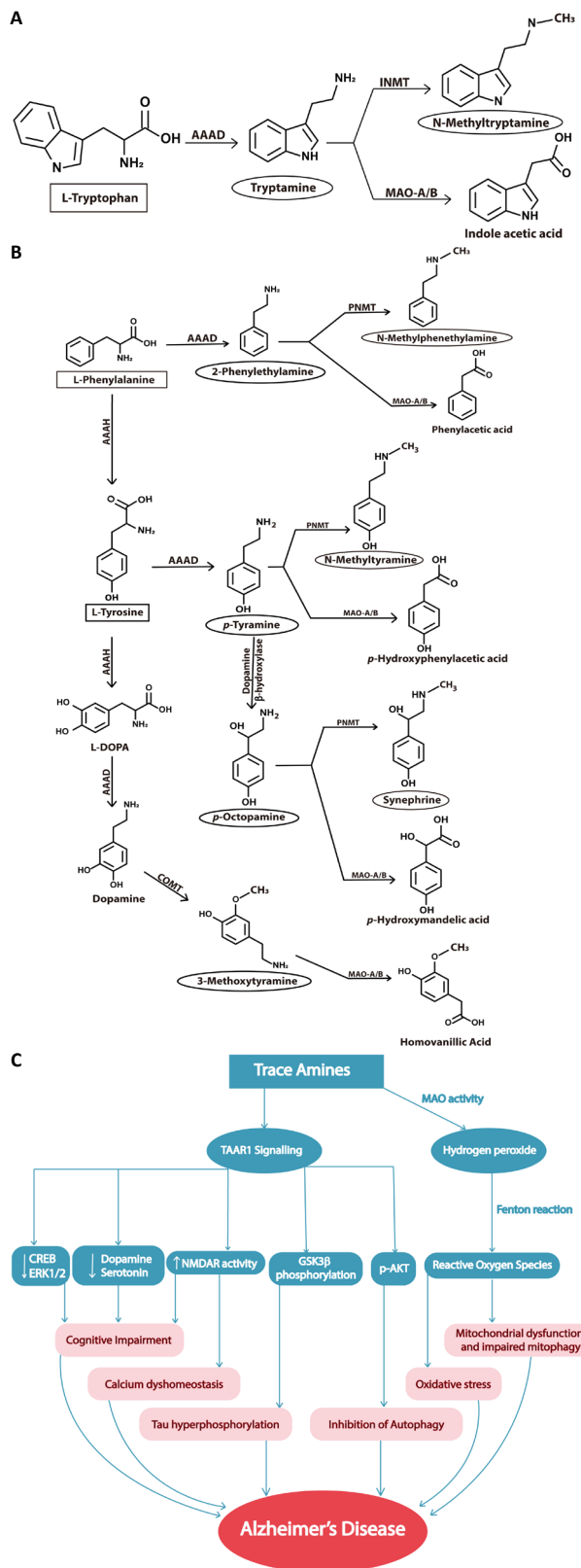
**Trace amine associated receptor (TAAR) signaling and trace amine metabolism:** Nearly 28 TAAR receptor subtypes (TAAR1-28) have been described, among which TAAR (1–9) have been found to be present in terrestrial vertebrates and only 6 of them in humans. Depending upon the location in the body, the predominant type of TAAR specific to a tissue is different. TAAR1 is the most predominant receptor type present in the human brain and is proposed to be crucial for brain functioning (Berry, 2016). Trace amines can diffuse through lipid

bilayers, entering cells and interacting with TAAR1 inside cells. Apart from trace amines, classical monoamines such as dopamine can also bind the TAAR1 receptor. The binding of trace amines to TAAR1 inside cells assists its heterodimerization with dopamine receptor 2 (D2R), which causes translocation of the TAAR1-D2R complex to the membrane. The binding of trace amines with TAAR1 and the TAAR1-D2R interaction causes reduction in cyclic adenosine monophosphate (cAMP). This decrease in cAMP leads to reduced phosphorylation of cAMP response element binding protein and extracellular signal regulated kinase (ERK1/2), negatively regulating downstream signaling. The translocation of TAAR1-D2R complex to the membrane in dopaminergic and serotonergic neurons reduces the dopamine and serotonin firing rate from respective neurons (Berry et al., 2017). Such regulation of release of dopamine neurotransmitters from dopaminergic and serotonin from serotonergic neurons is tightly regulated for proper synapsis and cell-cell communication. However, abnormalities in the regulation of neurotransmitter release/firing may have serious consequences to neuronal functioning. Furthermore, trace amines have also been reported to reduce activity of  $\beta$ -arrestin 2, which increases protein kinase B (Akt) and glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) phosphorylation (Harmer et al., 2015). The phosphorylated Akt may inhibit autophagy through mTOR activation and phosphorylation of GSK3 $\beta$  may cause its activation of protein kinase activity leading to phosphorylation of tau protein downstream (Dhakal et al., 2019). Additionally, TAAR1 signaling has been found to modulate the glutamate transmission through N-methyl-D-aspartic receptors (NMDAR). Benefits of using TAAR1 as a therapeutic target have already been demonstrated in models of schizophrenia by a recent study using TAAR1 modifiers. The animals treated with TAAR1 agonists showed antipsychotic, antidepressant and improved cognition (Berry et al., 2017).

The difficulty in studying trace amines and their associated neurological disorders is due to their very low concentration and rapid turnover (half-life < 30 seconds). Their blood to brain clearance and enzymatic degradation play a vital role in balancing their

brain concentrations at a given time. Trace amines are degraded by enzymatic oxidative deamination due to monoamine oxidases (MAO), notably MAOA and MAOB. All the trace amines are degraded by both the enzymes except  $\beta$ -phenylethylamine, which is only the substrate for MAOB (Pryor et al., 2016). Additionally, the degradation of these trace amines by these MAO enzymes has been found to produce hydrogen peroxide (Bortolato et al., 2008). In normal cells, these reactive oxygen species (ROS) generated by trace amine metabolism are neutralized by the help of reduced glutathione converting the toxic species into non-toxic ones. In contrast, any abnormalities in recovery of the cell from such oxidative stress may cause cellular damage. The efficient recovery from oxidative stress gradually decreases with ageing.

**Trace amines and their role in Alzheimer's disease (AD):** Diseases like schizophrenia, bipolar disorder, depression, attention deficit and hyperactivity disorder, Parkinson's disease, Huntington's disease, migraine, obsessive-compulsive and related disorders have been found to be associated with trace amines. Despite a huge interest in trace amine related studies, there was no evidence supporting its association with AD until recently. AD is an age-related multifactorial progressive neurodegenerative disorder that is a leading cause of death in elderly populations due to dementia. The pathological hallmarks of AD include loss of proteostasis, oxidative stress, alteration in distribution of biometals, genomic instability, mitochondrial dysfunction, disrupted neuronal synapsis, amyloid plaque deposits in brain, tau neurofibrillary tangles and cognitive deficits (Dhakal et al., 2019). The disease progression ultimately leads to death of the affected person. The absence of direct evidence to connect defective trace amine metabolism with AD may have decreased focus for further research exploring its importance in AD pathology. Meanwhile, indirect evidence supports the involvement of trace amines' in AD pathology (**Figure 1C**). Specifically, lower levels of dopamine and serotonin, disrupted calcium homeostasis and increased monoamine oxidase activity are some important events in AD pathology that provide insight on defective trace amine metabolism (Mousseau and Baker, 2012). In fact, the reduction of dopamine and serotonin has a detrimental effect on cognition during AD progression. Furthermore, NMDAR mediated glutamate excitotoxicity and GSK3 $\beta$  mediated hyperphosphorylation of Tau protein are also major hallmarks of AD (Dhakal et al., 2019). Although there is no evidence supporting involvement of TAAR1 in AD pathology,



**Figure 1 | Biosynthesis of important trace amines and their intracellular fate and possible role of trace amine metabolism.**

(A) Synthesis of tryptamine and its derivative from L-tryptophan. (B) Synthesis of other trace amines and their derivatives. Metabolites in rectangles and ellipses are precursor aromatic amino acids and trace amines, respectively. (C) Possible role of trace amine metabolism and TAAR signaling in Alzheimer's disease pathology. AAAD: Aromatic amino acid decarboxylase; AAAH: aromatic amino acid hydroxylase; COMT: catechol-O-methyltransferase; GSK3β: glycogen synthase kinase 3 beta; INMT: indolethylamine N-methyltransferase; MAO: monoamine oxidase; NMDAR: N-methyl-D-aspartate receptor; p-AKT: phosphorylated protein kinase B; PNMT: phenylethanolamine N-methyltransferase; TAAR: trace amine associated receptor.

theoretically the modulation of the NMDAR receptor and activation of GSK3β due to TAAR1 signaling may have a role in AD pathology. Hence, targeting the TAAR1 receptor could be a novel multifactorial approach for treatment of AD.

A metabolic by-product of trace amine degradation by MAO is hydrogen peroxide, which can deplete intracellular reduced glutathione in the presence of Aβ<sub>42</sub>. The depletion of intracellular glutathione in mitochondria may lead to mitochondrial DNA damage and enhance mitochondrial dysfunction. However, the clearance of damaged mitochondria through mitophagy and the biogenesis of new mitochondria help restore normal cellular function. Additionally, AD is characterized by increased accumulation of biometals including iron, zinc and copper. Increased iron and copper levels in neuronal cells of AD patients may further exacerbate the oxidative damage by enhancing the Fenton reaction producing more hydroxyl radicals from the hydrogen peroxides (Dhakal et al., 2019). Furthermore, during degradation of trace amines MAO may get hyperactivated, which may lead to impairment in lysosomal regeneration and autophagic clearance through inactivation of transcription factor EB (Santin et al., 2016). This may in turn lead to accumulation of misfolded proteins and protein aggregation and could cause loss of protein homeostasis and disturbances in lipid metabolism by affecting lipolysis. These evidences of disrupted cellular homeostasis align with the findings from AD patients suggesting involvement of trace amines in AD progression.

A dearth of studies investigating trace amines' connection with AD could be due to lack of study models that can sufficiently predict on trace amine functions and their intracellular fate. Yeast models are very useful in such instances where other cellular models may have limited importance. The studies investigating the oxidative damage, mitochondrial function and its regeneration or repair can be easily monitored using yeast models due to their ability to grow without functional mitochondria. Furthermore, more than 60% of yeast genes are conserved in humans evidenced by presence of human homologs or at least one conserved domain. Although yeast does not contain all disease-associated human proteins, it still contains numerous proteins that can interact with human proteins (Khurana and Lindquist, 2010).

Although, higher levels of trace amines, p-tyramine, 2-phenylethylamine and tryptamine, have been shown to increase ROS in previous studies (Churro et al., 2010; Sorato et al., 2014; Phillips and Macreadie,

2018), no investigation was performed to identify the direct relation of trace amines with AD pathology until recent studies (Accorroni et al., 2020, Dhakal and Macreadie, 2020). Accorroni and colleagues demonstrated the improvement in long term potentiation in the presence of TAAR1 agonist in mouse models of AD. The evidence of improvement in learning and memory of mouse models shows promising results, while the molecular mechanism on how the agonists function in the model remains elusive. Moreover, the second study showed *p*-tyramine and amyloid beta 42 (Aβ<sub>42</sub>) were synergistically toxic to *Saccharomyces cerevisiae*. *p*-Tyramine enhanced dose-dependent oxidative stress and caused mitochondrial dysfunction in *S. cerevisiae* cells expressing Aβ<sub>42</sub>, while control yeast showed no effect. In the study, the induction of a high number of petites denoted impairment in mitochondrial clearance and regeneration. These findings not only implied a synergistic increase of ROS in cells, but also synergistic impairment of mitophagy or mitochondrial biogenesis. The findings of the study suggest *p*-tyramine exacerbates the Aβ<sub>42</sub> toxicity in yeast implying its possible involvement in AD pathology. Although *S. cerevisiae* does not contain a protein that represents the TAAR receptor, it provides a unique platform with numerous similarities to human neurons. In the meantime, the yeast system possesses numerous conserved fundamental processes and mechanisms including microautophagy, macroautophagy, ubiquitin proteasome system, unfolded protein response, stress response, apoptosis, cell cycle, type II secretion system, energy metabolism and conserved genetics. Easy manipulation of the genome and availability of analytical platforms to study yeast has provided extra power for greater understanding of AD pathology (Khurana and Lindquist, 2010). The yeast model has provided simple platform to unravel the intracellular fate of *p*-tyramine in the presence of Aβ<sub>42</sub> in eukaryotic cell model.

### Future implications of using trace amine and TAAR signaling as a therapeutic target in AD:

The presence of evidences of reduced dopamine and serotonin, hyperactivation of MAO, impaired mitochondrial turnover and regeneration, increased oxidative stress, loss of proteostasis, lipid metabolism imbalances and impairment of synapsis during AD progression could also be due to dysregulation of trace amines in the brain microenvironment (Dhakal et al., 2019; Dhakal and Macreadie, 2020). Recent findings of synergistic toxicity of *p*-tyramine in Aβ<sub>42</sub> producing yeast cells may indicate its involvement in AD pathology. Both the trace amine metabolism and TAAR

signaling are important for synapsis and proper functioning of neurons. The use of TAAR1 modifiers could be a potential therapeutic strategy for treatment of AD pathology, at least for improvement of cognition, redox balance and mitochondrial functioning. The antagonists of TAAR1 could be important to improve cognition by enhancing dopamine and serotonin levels in brain microenvironment of AD patients. Furthermore, TAAR1 signaling inhibition has potential to reduce hyperactivated NMDAR thus reducing glutamate excitotoxicity highly implicated in AD brain. The possible reduction of NMDAR activity by TAAR1 antagonists in AD could also balance the calcium and sodium influx in neuronal cells, which may help cells restore calcium homeostasis and reduce generation of ROS due to calcium overloading of mitochondria. In addition, restoration of calcium inside cell could also restore protein folding machinery, lysosomal functions and improve cellular proteostasis. Meanwhile, other TAAR1 modifiers such as TAAR1 agonists not metabolized by MAO may have a beneficial role, which may enhance synaptic NMDAR functions, restoring calcium signaling and other downstream synaptic signaling. However, activation of extra-synaptic signaling via TAAR1 agonists may exacerbate the AD pathology. Hence, further investigations to understand the impact of trace amine metabolism and TAAR1 signaling is imperative before it is considered as a novel strategy to treat AD.

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