Cellular and Molecular Neurobiology (2020) 40:189–190
https://doi.org/10.1007/s10571-020-00800-x

COMMENTRY

Trace Amines and Trace Amine-Associated Receptors: A New Frontier in Cell Signaling

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Received: 13 January 2020 / Accepted: 21 January 2020 / Published online: 31 January 2020

Abstract

Trace amines, including β-phenylethylamine, *p*-octopamine, *p*-tyramine, and tryptamine, are produced in high levels in invertebrates where they play major roles in homeostasis regulation in a manner similar to that of adrenergic systems in mammals (Rutigliano et al. in Front Pharmacol 8:987, 2017; Gainetdinov et al. in Pharmacol Rev 70(3):549–620, 2018; Nagaya et al. in Neurosci Lett 329(3):324–328, 2002). In mammals, however, their levels are very low, initially prompting these molecules to be termed "trace" or "minor" amines in mammals with only a secondary role in the regulation of more abundant biogenic amines including catecholamines and serotonin (Gainetdinov et al. in Pharmacol Rev 70(3):549–620, 2018). The more recent discovery of trace amine-associated receptors (TAARs) revealed major, previously unsuspected roles of the trace amines and has led to increasing interest within the scientific community. For example, TAARs have been proposed to modulate signaling through dopamine (Schwartz et al. in Expert Opin Ther Targets 22(6):513–526, 2018). Furthermore, these receptors are implicated in both numerous physiological functions including regulation of sleep, olfaction, metabolism, and immunity as well in disease (e.g., substance abuse, neuropsychiatric disorders) (Gainetdinov et al. in Pharmacol Rev 70(3):549–620, 2018; Rutigliano et al. in Front Pharmacol 8:987, 2017). Consequently, trace amine and TAAR research is rapidly growing and is of great translational relevance. In this Special Issue, leaders in trace amine and TAAR research offer both reviews and original research papers that cover a wide range of topics from involvement of TAAR signaling in metabolic regulation and neurophysiology to implications of this signaling in neuropsychiatric diseases including substance abuse and schizophrenia. While a diverse range of topics is covered by these works, the common theme running through all of them is the increasing awareness that trace amine and TAAR signaling represent novel signaling mechanisms in the brain and periphery. These topics are both highly timely and of considerable importance not only for those working in the field but also for the neuroscience community at large.

In this issue, Rutigliano and Zucchi (2019) review the growing evidence of the associations between genetic variants in the TAAR superfamily in both neuropsychiatric and metabolic diseases. Of these disorders, trace amine signaling has been particularly implicated in the mechanisms of psychostimulant action, especially given the ability of amphetamines to signal via TAAR-mediated pathways (Lindemann et al. 2008; Revel et al. 2012; Jing and Li 2015; Underhill et al. 2019). Consequently, Liu et al. (2020) comprehensively review involvement of trace amine-associated receptor 1 (TAAR1), one of the most characterized TAARs, in psychostimulant addiction and its treatment. Indeed, TAAR1 agonists may serve as useful tools both for modulating these pathways in addiction as well as for discovery of new brain signaling pathways. Thus, Xu and Li (2019) review agonists of both olfactory and non-olfactory TAARs, including their structural and functional relevance, to the study of monoaminergic systems in health and disease. Dorotenko et al. (2019) specifically examine TAAR1-selective partial agonist RO5263397 in modulating executive cognitive function using a rat model. They demonstrate that RO5263397 has effects on attention, cognitive flexibility, and impulsivity—critical cognitive domains affected across

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the spectrum of neuropsychiatric disorders that require new targets for pharmacologic therapies.

Zhukov et al. (2019) provides a new perspective on TAAR1 signaling outside of the brain, particularly as a function of aging. Using a TAAR1 knockout mouse model, the authors show that loss of TAAR1 expression, while quite important for a variety of neurologic functions, does not play a comparable role either in hematologic function nor affects the regulation of thyroid hormones across different stages of aging. In addition to the hematologic system, TAAR1 signaling has also been strongly implicated in the gastrointestinal system, suggesting important links between the brain and gut. Accordingly, Bugda Gwilt et al. (2019) review the emerging roles of trace amines and TAAR1 along the brain-gut-microbiome axis as well as the implications of this work for better understanding the links between comorbid gastrointestinal and neuropsychiatric illnesses. Importantly, this work raises the possibility that manipulating trace amine along this brain-gut-microbiome axis signaling may be a new therapeutic target for neuropsychiatric illnesses.

While the majority of research on trace amine receptor signaling has focused on TAAR1, Belov et al. (2019) examine trace amine-associated receptor 5 (TAAR5) in central nervous system neuromodulation. The authors demonstrate in a rodent model that TAAR5 stimulation can modulate striatal dopamine neurotransmission as well as spatial synchronization of gamma oscillations under physiological conditions. These findings suggest that TAAR5 signaling is involved in the altered gamma rhythms associated with brain activity changes in experimental models of schizophrenia.

In conclusion, our special issue showcases the increasing interest in trace amine and TAAR signaling both within the central nervous system as well as in the periphery and points the way to exciting future directions with both basic scientific and clinical therapeutic applications.

Acknowledgements The authors would like to thank Drs. Raul Gainetdinov and Marius Hoener for helpful discussions.

Author Contributions The manuscript was written and edited by ZF and JMS.

Funding This work was supported by the Department of Defense (PR141292) (Z.F.).

Compliance with Ethical Standards

Conflicts of interest The authors report no conflicts of interest.

Research involving Human Participants and/or Animals No human participants or animals were involved in this work.

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