In two very recent papers using primary cells, the detection of amines, especially 2-PEA, by Taar4 [29], TAAR1 and TAAR2 [30], was reported to occur at concentrations five to six orders of magnitude lower than the amine concentrations used previously for cell cultures. Zhang et al. used perforated patch-clamp current recordings from the dendritic knobs of olfactory sensory neurons from isolated mouse main olfactory epithelium (Figure 1A) [29]. By this method they were able to characterize eg. Taar4-expressing olfactory sensory neurons to be broadly tuned and highly sensitive towards certain amines. For instance, the most potent amine 2-PEA induced currents in Taar4-olfactory sensory neurons at concentrations ranging from 1x10^{-11} M to 3x10^{-7} M. In the work presented by Babusyte et al., the same amine 2-PEA induced immune cell functions at concentrations ranging from 1x10^{-11} M to 1x10^{-7} M [30]. When applied to neutrophils, T-cells or B-cells, 2-PEA potently induced immune cell functions, such as chemotactic migration, cytokine or immunoglobulin production, respectively (Figure 1B) [30]. Notably, TAAR1 and TAAR2 were the receptors that mediated the 2-PEA-induced cellular responses in leukocytes. Both groups used gene-targeted approaches to

**Tracing Amines to their Receptors: A Synopsis in Light of Recent Literature**

*Agne Babusyte and Dietmar Krautwurst*

**Abstract**

Trace amine-associated receptors (TAAR) have been an elusive species of G protein-coupled receptors (GPCR), so far, mainly because of their suboptimal expression in heterologous cell systems. Little connection could be established between the name-giving low physiological concentrations of their putative amine agonists, and their tissue-specific biological function. At the same time, there is growing evidence that suggests ectopic expression of certain TAAR, beyond their supposed typical tissue expression as olfactory receptors in the olfactory epithelium, at least in mice. Two recent publications now shed light on the potent activation by specific amines of certain TAAR in different primary cells: in olfactory sensory neurons (OSN) of the main olfactory epithelium (MOE) of mice, and, unexpectedly, in human peripheral blood leukocytes.

Biogenic amines are bioactive compounds. They are derived from enzymatic decarboxylation of e.g. certain amino acids, and are metabolized by monoamine oxidases. Certain amines can be found in the plasma and in the central nervous system at low pico-to nanomolar concentrations [1-6], and thus have been termed ‘trace amines’ [7,8]. Receptors, that specifically recognise trace amines, initially have been found in the brain [7,9,10]. These ‘trace amine-associated receptors’ are members of rhodopsin-like Family A of GPCR. Recently, they have been identified in neurons of olfactory epithelia of mouse and zebrafish, where they may detect volatile amines as odorants or pheromones [11-14]. Gene expression for 4 out of the six intact human TAAR genes was reported in human nasal mucosa at trace levels [15].

The impact of certain biogenic amines, such as β-phenylethylamine (2-PEA) and tyramine, on blood pressure, cardiac function, brain monoaminergic systems, and olfaction-guided behaviour has been demonstrated, mainly in studies with rodents [2,10,13,14,16-18]. Gene-targeted receptor knock-out mice revealed Taar1 as modulator of dopaminergic neurotransmission [19,20]. This animal model encouraged many laboratories to engage in a further characterization of e.g. human TAAR1 and its agonists in heterologous cell systems, such as HEK293, COS-7, CHO, and HGA16 cells, mainly using cAMP assays [7,9,21-27]. However, in these cell cultures expressing TAAR1, EC50 values (the concentration that yields 50% of maximum effect) for its gold standard agonist 2-PEA ranged from 0.1 µM to 1.9 µM, which is one to two orders of magnitude higher than the concentration of 2-PEA in plasma of healthy individuals [5,28].

*Corresponding author: Dietmar Krautwurst, German Research Center for Food Chemistry – Leibniz Institute, Physiology, Freising, Germany, Tel: 08161-712634; Fax: 08161-712670; E-mail: dietmar.krautwurst@izt.tum.de

Received: May 03, 2013 Accepted: June 27, 2013 Published: July 01, 2013
demonstrate a receptor-dependent activation of the primary cells investigated.

Whether a tissue expression of TAAR genes in general is considered ‘typical’ or ‘ectopic’ may, however, be merely a point of view, and depends on the data set available. For instance, expression in the olfactory epithelium was shown for 14 of the 15 intact mouse Taar genes [14], as well as for 4 of the 6 intact human TAAR genes [15]. Thus, and at least supported by experiments with Taar knock-out mice [31], TAAR are considered to typically function as olfactory receptors. However, mouse Taar expression was also reported in the gastrointestinal tract, spleen B-cells and NK-cells, spleen, and testis [32-34]. Human TAAR expression was reported for the brain and a variety of non-olfactory peripheral tissues (Figure 2) [7,34-39]. In different types of blood leukocytes, for instance, Babusyte et al. recently show now expression of 5 out of the 6 intact human TAAR [30]. Of these, TAAR1 and TAAR2 appear to be most abundantly expressed receptors in leukocytes. In contrast to mouse olfactory sensory neurons, TAAR1 and TAAR2 appear to dimerize in human leukocytes, where they play a major role in mediating amine-induced immune cell functions. Notably, mouse Taar1 and Taar2 were also detected in B-cells and NK-cells, but Taar1/TAAR1 is absent from the main olfactory epithelium (Figure 2).

Taken together, the works published by Zhang et al. [29] and Babusyte et al. [30] are important demonstrations of TAAR agonist-mediated activities at physiological relevant amine concentrations, suggesting that the major advantage of primary cells over cell cultures may be their sensitivity for agonists. The reason may be an optimal functional receptor expression, and the employment of the original receptor signal transduction cascade. On the other hand, hard to obtain primary cells may be limited to investigation of rather small families of receptors, especially when considering the effort to establish large numbers of e.g. gene-targeted animals. Moreover, complexity due to co-expression of receptors may be a limiting factor for any receptor deorphanization endeavor using primary cells. What are the amine concentrations that induce cellular functions in vivo remains as an open question for the time being. These two recent publications, nevertheless, encourage an optimistic view on the soon identification of the specific agonists for TAAR, and other orphan olfactory receptors.

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Author Affiliation

1German Research Center for Food Chemistry – Leibniz Institute, Physiology, Freising, Germany

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