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The New Wave of Blocking Taste

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ABBREVIATIONS GPCRs, G protein-coupled receptors; P1, Adenosine receptors; P2, adenine nucleotide receptors

KEYWORDS bitter taste; purinergic taste signaling; taste inhibition; taste masking; taste receptors; taste suppression

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Taste is divided into 5 categories: sweet, bitter, sour, salty, and umami. The sweet taste usually detects carbohydrates such as sugars, the bitter taste is linked to a variety of compounds that have different properties and structures and many of them are toxic. The therapeutic compounds can be listed under this group. The sour taste is related to weak acids such as citric or acetic acids and other organic acids. The salty taste resembles the taste of sodium chloride, and the umami taste or (the savory taste) is linked to amino acids such as glutamate and aspartate which are available in meat, fish, cheese, and many vegetables.[1]

Taste sensation is evaluated by taste buds which are specific organs designed to distinguish taste, they are located within the tongue epithelium; it contains specialized cells which act as sensory receptors for different tastes. These cells are divided into types I, II and III. Type I cells are about half of the total number of cells in the taste buds, they have narrow and irregular shape nuclei, they contain enzymes and transporters that remove neurotransmitters and work on redistribution of the potassium ions associated with ion transport channels. Type II cells have a larger diameter than type I, have spherical nuclei, and act as a receptor for sweet (sugars), umami (amino acids) and bitter tastes. Type II cells are about one third of the total number of cells in the taste buds. These taste cells express taste receptors which are categorized as G protein-coupled receptors (GPCRs) which are named taste receptor type 1 or 2 (T1R1, T1R2, T1R3, T2Rs). T1R2 and T1R3 are receptors which respond to sweet and umami tastes. T2Rs belong to the GPCRs family and are receptors for bitter taste. Type III cells represent 2% to 20% of total cells in the taste buds. They respond to sour taste (weak acids, i.e., citric acid). Salty taste is detected by undefined taste buds.[2–7]

Purinergic signaling includes purine and pyrimidine receptors which were identified and cloned in the 1990s. There were 2 types identified: Adenosine receptors (P1) and adenine nucleotide receptors (P2). The adenosine receptors (P1) were classified into 4 subtypes (A_1, A_{2A}, A_{2B}, A_3). The P2 receptors were classified into 8 subtypes of G-coupled protein receptors ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$), and seven subtypes of cation ion channel receptors ($P2X_1$-$P2X_7$). P1 and P2 purinergic receptors are distributed in brain, kidney, heart, lung, and gut. They are implicated in epilepsy, vascular diseases, immune responses, gout and tumors. P2X2 and P2X3 are expressed in taste cells on the tongue. They are considered heteromultimer receptors and ATP major transmitters in the taste cells. In a study published in 2015, knockout mice of P2X2 and P2X3 lacked response to all taste stimuli. This was a direct implication to their involvement in taste stimulation (see figure 1).[8–15]

AF-353 (see Figure 2) is a novel P2X3 and P2X2/3 antagonist. Studies in rats reveled an oral bioavailability of 32.9% elimination half-life of 1.63 hours and 98.2%

Figure 1. Classification of purinergic receptors.

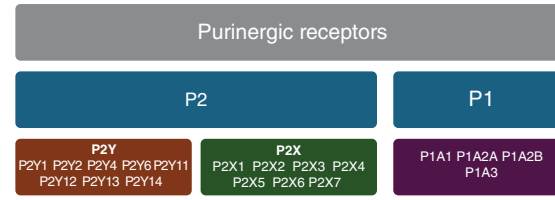
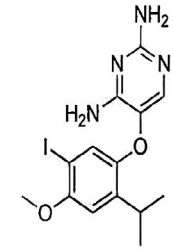


Figure 2. Chemical structure of AF-353.



5-(5-iodo-4-methoxy-2-propan-2-ylphenoxy)pyrimidine-2-4-diamine

plasma protein binding. The inhibitory potency estimate pIC50 for inhibiting human and rat P2X3 was 8.0 and human P2X2/3 was 7.3.[16,17]

Flammer et al[18] utilized AF-353 to evaluate its ability to inhibit all types of taste stimulants in mice and humans. For this purpose, the authors used 3 different concentrations of AF-353 (125, 250, and 500 μM) to block the taste of bitterness stimulant represented individually in quinine hydrochloride, 0.169 mM, sucrose octaacetate, 0.0632 mM, urea, 750 mM, praziquantel, 0.487 mM, and tenofovir alafenamide, 0.844 mM; sweetness taste stimulant represented in sodium saccharin, 2.1 mM, and sucrose, 450 mM; sourness taste stimulant represented in citric acid, 4.8 mM, and monopotassium glutamate, 600 mM); saltiness taste stimulant represented in sodium chloride, 150 mM, and astringency taste stimulant represented in citric acid in humans. The long-term objective as stated by Flammer et al[18] was "to develop a bitter blocker that suppresses bitterness as completely and rapidly as possible for a duration that would allow drug ingestion, but no longer than this." The experimental design was initiated by subjects rinsing their mouth with filtered water 4 times to remove any residues in their mouths. Thereafter, each subject placed 10 mL of individual taste stimulant solution in his/her mouth for 5 seconds then immediately expectorant. After that they recorded the intensity of each taste stimulant (sweet, sour, salty, bitter, and astringent) on a scale of 1 to 33. After 5 minutes from the stimulant study (time 0), subjects tried 10 mL of AF-353 solution or 10 mL vehicle as a control and swished for 30 seconds. They also repeated this for another 30 seconds. After 5 minutes, they tried the previous taste stimulant again and repeated the stimulant at 10, 15, 30, 60, and 90 minutes after the initial AF-353 treatment. Separately for the bitterness experimental design, they asked the human subjects to rinse with variable concentrations of AF-353 (125, 250, and 500 μm) for two 15 seconds, two 30 seconds rinses and two 60 seconds rinses over 60, 90, and 120 minutes to evaluate the degree of taste blocking. Results indicated that 15- and 30-second rinses of 125, 250, and 500 μm of AF-353 suppresses the taste of 0.169 mM of quinine hydrochloride QHCl and up to 50% recovery takes up to 90 minutes. The bitterness recovery was much slower for 30 seconds rinse with 500 μm of AF-353. Overall, they noticed a block of bitter, sweet, sour, salty, and astringency tastes and the recovery took about 90 to 120 minutes for full recovery. Flammer et al[18] provided a novel approach to block the taste of bitter drugs.

There are several challenges to the experimental design of Flammer et al.[18] Typically, when you block the taste of any drug, you provide the drug and taste suppressant in the same vehicle as it is not feasible to ask the patient to take the taste suppressant 5 minutes before taking the medication, plus if you use a taste suppressant that has the affinity to interact with specific receptors that can influence a pharmacological and physiological response in the body, you will have to make sure there is very limited absorption from the taste buds and the gastrointestinal tract which opens the door to multiple questions about the affinity of the taste suppressant and the actual drug with bitter taste toward the taste receptors. Which entity has stronger affinity to the taste receptors and for how long this affinity can last. The amount of the taste suppressant used and its bioavailability? In the Flammer et al[18] study, AF-353 has an efficacy that has lasted up to 90 and 120 minutes which is a very long time. It will not be acceptable to patients not being able to taste food nor drinks for up to 2 hours after taking the medication.

A good taste suppressant is the one that blocks the taste during taking the medication but does not last more than few minutes from the time of consuming the medication. This issue can be resolved by designing novel taste suppressants that have limited absorption from the oral cavity and gastrointestinal tract, strong or medium affinity toward binding to the taste receptors relatively to the drug itself and has quick removal from taste buds by saliva. Currently, taste masking is limited to either adding natural or artificial sweeting agents to overwhelm the taste receptors or by encapsulating the drug within a biodegradable polymer to prevent contact with the taste buds. The Flammer et al[18] study opens a new door toward the discovery of novel molecules for the purpose of taste masking by competitive inhibition of taste signaling.

Article Information

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