Cannabinoid-Related Olfactory Neuroscience in Mice and Humans

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Cannabinoids have been used for centuries for their psychoactive effects. The major active ingredient of Cannabis sativa, delta⁹-tetrahydrocannabinol (THC), gains increasing clinical interest and has been approved in North American and European countries for treatment of several conditions including spastic neuropathic pain in multiple sclerosis and AIDS-associated anorexia. THC is marketed either in combination with cannabidiol, which among other effects may enhance endogenous anandamide signaling indirectly by altering the activity of the fatty acid amide hydrolase (Bisogno et al. 2001; Massi et al. 2008), as Sativex or can be obtained solely in its synthetic form as dronabinol, for example, marketed as Marinol (for a review of the endocannabinoid system, e.g., Piomelli 2003). The clinical introduction of cannabinoid-based therapies has been progressing with justifiable caution, which owes to their addiction potential but also to the incomplete understanding of the mechanisms of cannabinoid signaling and the clinical effects. Timely with respect to this clinical interest a major step toward our understanding of the role of cannabis in hunger and the sensory perception of foods has been provided recently (Soria-Gómez et al. 2014).

In comprehensive experimental assessments using knock-out mouse models and optogenetic techniques cannabinoid signaling was shown to promote food intake by increasing odor detection (Soria-Gómez et al. 2014). Importantly, the discovered mechanism involved an expression of CB₁ receptors at axon terminals of cortical glutamatergic neurons that project to the olfactory bulb (OB) and at intrinsic cells in the OB. In full line with the translational paradigm of biomedical research, the authors conclude their report with a perspective to the human relevance of the discovered mechanisms and make references to patients with advanced cancer or eating disorders.

However, 2 lines of evidence hint at some difficulties in translating these results from the mouse model to humans. Firstly, CNR₁, that is, the gene coding for CB₂ receptors, was not found to be expressed in the human OB in 2 recent independent reports. Specifically, by submitting tissue from a postmortem sampled OB to peptide fractionation followed by liquid chromatography and tandem mass spectrometry, CNR₁ was not among 1427 genes identified to be expressed at protein level in the human OB [supplementary files 1 and 2 of Fernández-Irigoyen et al. (2012)]. Similarly, in 5 human OBs harvested intraoperatively or postmortem, and Affymetrix GeneChip analysis (Human Gene 1.0 ST Array, Affymetrix) CNR₁ was again absent from the 669 genes found to be expressed in human OBs [table 1 and the supplementary table in Lötsch et al. (2013)]. Moreover, differences in gene expression in olfactory tissues between humans and mice probably also apply to the first neuron in the pathway of processing olfactory input as CNR₁ seems also to be absent from the human olfactory epithelium [supplementary table S7 in Keydar et al. (2013)].

The reproducible absence of CNR₁ from human OB tissues is contrasted by the consistent findings of its expression in OBs harvested from mice. A search of the NCBI Geoprofiles database at http://www.ncbi.nlm.nih.gov/geo-profiles (22 September, 2014) for “cnr1 and OB” produced 73 hits. All evidence in that database was from the organism Mus musculus. However, the expression of CNR₁ in the OB is not limited to mice. Evidence of CNR₁ expression in the OB is also available from other species such as Rattus norvegicus (Pettit et al. 1998) or Xenopus laevis (Cesa et al. 2001). Such species differences in the olfactory system are conceivable when considering the differences in olfactory performance. In particular rodents are macrosomatic, that is, possess a good sense of smell, at least partly in contrast to humans who are often thought to be microsmatic. It fits that mice express 1035 different olfactory receptors, which is the third most among chordates after rats (1207 receptors) and opossums (1188 receptors; Niimura 2009), whereas humans express only roughly a third (387 receptors) of olfactory receptors as mice (Niimura 2009). An additional indicator of striking differences in organization of the human olfactory system is the large number of glomeruli in the OB (>5000) compared with the mouse with about 1800 glomeruli (Maresh et al. 2008).
A second line of evidence points at differences between mice and humans at the behavioral level of chemosensory function. While a cannabis intake is generally thought to increase appetite, which is consistent with the marketing of the CB1 receptor antagonist rimonabant as an anorectic anti-obesity drug, the evidence for olfactory effects of THC is mainly limited to anecdotal reports (Green et al. 2003). By contrast, in controlled assessments THC failed to enhance olfactory or gustatory sensations. Specifically, THC at an oral dose of 20mg impaired, rather than improved, the performance of healthy subjects in a standard clinical olfactory test. Its administration was followed by an increase in olfactory thresholds and an impairment of the discrimination of different odorants (Walter et al. 2014). This implies an effect of THC on human olfaction that is even opposite to evidence obtained in animals where for example in X. laevis, the endocannabinoid 2-arachidonoyl-glycerol produced, depending on the hunger state of the animal, lowered odorant detection thresholds via cannabinoid CB1 receptor activation (Breunig et al. 2010) whereas under CB1 blockade at olfactory receptor neurons, responses to odorants were diminished (Czesnik et al. 2007).

To the absent enhancement of human olfaction in controlled studies adds the lack of THC effects on gustatory sensations. Specifically, THC at oral doses of 10 and 15mg for men and women, respectively, lacked influence on taste intensity and hedonic responses for sweet, sour, salty, and bitter food stimuli (Mattes et al. 1994). By contrast, a role of the cannabinoid system in mice has been well documented by showing that endocannabinoids, in particular anandamide or 2-arachidonoylglycerol increased gustatory nerve responses to sweeteners without affecting responses to salty, sour, bitter, and umami compounds, and this effects were not seen in CB1 but not CB2 knockout mice and were diminished by pharmacological blockade of CB1 receptors (Yoshida et al. 2010). However, other than with olfaction where negative evidence about an expression of CB1 receptors in important parts of the human olfactory system is available as mentioned above, for gustatory neurons evidence from human tissues, either positive or negative, seems so far lacking.

While research on the importance of the (endocannabi)noid system for olfaction primarily addresses the physiological function of this sense, the role of the receptors for the endogenous cannabinoids as targets for exogenous cannabinoids immediately involves drug effects on olfaction, and this similarly applies to gustation. These observation date back 150 years when Fröhlich reported a significant weakening of his sense of smell after the oral ingestion of 80mg morphine (Fröhlich 1851). Further drug effects on human olfaction (Lötsch et al. 2012) have been frequently reported, however, remarkably rarely from controlled studies while most findings are still anecdotally based on single case observations about drugs causing smell or taste alterations (Henkin 1994).

Taken together, there are several at least unresolved hints at fundamental disagreement between humans and mice, which challenges translation. Importantly, the absence of cannabinoid CB1 receptors in one although important part of the human olfactory, and perhaps gustatory, system does not mean that cannabinoids have no importance in human chemosensation at all; it only indicates that the mechanisms identified to be important in mice do not one to one translate into humans. The accessibility of both, human olfactory function to the depth including direct recordings from olfactory receptor neurons from humans (Lapid et al. 2011) and olfactory-relevant human tissue materials (Fernández-Irigoyen et al. 2012; Lötsch et al. 2013) emphasizes that it is possible to combine the discovery of novel biologic mechanisms in mouse models with concomitant human assessments in integrally translational studies. Indeed, this seems to be in line with an overview of the knowledge about functioning of the olfactory system that highlighted results obtained from studying humans whom the authors consider an underutilized, yet critical, animal model for olfaction (Zelano and Sobel 2005).

References


