The essence of appetite: does olfactory receptor variation play a role?

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ABSTRACT: Olfactory receptors are G-protein-coupled chemoreceptors expressed on millions of olfactory sensory neurons within the nasal cavity. These receptors detect environmental odorants and signal the brain regarding the location of feed, potential mates, and the presence of possible threats (e.g., predators or chemical toxins). Olfactory receptors also are present in organs outside of the nasal cavity where they bind to molecules such as nutrients and metabolites from the animal's internal environment to elicit physiological responses, including changes in gut motility, ventilation rate, and cellular migration. Recent evidence supports an additional role of olfactory receptors in the regulation of appetite in humans and rodents. In particular, genetic variation among individuals in specific odorant receptor genes has been linked to differences in their feeding behaviors, food choices, and the regulation of energy balance. This review provides a general overview of the olfactory receptors of vertebrates and their genetic variability and provides supporting evidence for a physiological role of olfactory receptors in appetite regulation of livestock. Basic research on olfactory receptors of livestock and their ligands should facilitate the development of novel odorant receptor agonists and identification of specific olfactory receptor variants that may be developed to enhance animal production efficiency.

Key words: appetite regulation, feed intake, genetic variant, odorant, olfactory receptor

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The first molecular characterization of the mammalian sense of smell by Buck and Axel (1991) earned the Nobel Prize in Physiology or Medicine in 2004. Since that time, olfactory receptor genes have been described and classified in livestock species including cattle, pigs, and chickens through comparative genomics. In addition, connections between the olfactory system and appetite have been investigated by neuroscientists and human nutritionists to gain a better understanding of human feeding behavior, food choice, and the regulation of energy balance, particularly to treat appetite-related disorders, such as obesity, bulimia nervosa, and anorexia nervosa (Ruijschop et al., 2009; Palouzier-Paulignan et al., 2012; Islam et al., 2015; Rolls, 2015). However, practically no research has been published on the links between the olfactory system and appetite regulation in production animals or how we might take advantage of these connections that have been demonstrated in humans and rodents to improve feed intake and intake-related traits (e.g., rate of gain and carcass composition) in livestock species. Therefore, the purpose of this review is to briefly describe the olfactory receptors of vertebrates and their genetic variability and to provide supporting evidence for a physiological role of olfactory receptors in appetite regulation of livestock. The goal is to promote interest in basic research on olfactory receptors of livestock species and their ligands in order to facilitate the development of novel odorant receptor (**OR**) agonists and genetic selection

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of particular receptor variants that enhance animal production.

STRUCTURE AND FUNCTION OF ORS

Two major regions of the nasal cavity of vertebrates function in odor perception. These are the olfactory epithelium and the vomeronasal organ, the latter of which may or may not be functional depending on the species (Spehr and Munger, 2009). These tissues contain different types of chemoreceptors, including ORs, vomeronasal receptors, and trace amine associate receptors that detect odorants, pheromones, and volatile amines, respectively, and transmit these chemical messages to the olfactory bulb (odorants and volatile amines) and accessory olfactory bulb (pheromones) of the brain (Buck, 2000; Liberles and Buck, 2006; Dalton and Lomvardas, 2015). The ORs, the focus of this review, are expressed on millions of olfactory sensory neurons within the olfactory epithelium, although each olfactory sensory neuron expresses only a single OR protein type on the cilia of its dendrites (Serizawa et al., 2004; Hayden and Teeling, 2014). However, each OR can bind and detect multiple odorant molecules, and conversely, each odorant can bind to multiple ORs with varying binding affinities, creating a distinct pattern of odorant binding and OR activation which enables animals to discriminate very diverse and complex odors (Malnic et al., 1999). These chemical messages are essential for animal survival by assisting animals in locating feed, detecting toxins in the environment, alerting them to the presence of predators, and identifying and selecting potential mates (Spehr and Munger, 2009). It also is becoming clearer that ORs may have an additional role in the regulation of appetite.

Structurally, ORs are classified as G-protein-coupled receptors, which in classical models bind odorants within the nasal mucus and initiate nerve impulses that are carried to the brain (Purves et al., 2001). Specifically, odorant binding to the receptor causes activation of the G-protein, G_{olf}, which then stimulates the conversion of ATP to cAMP via adenylate cyclase activation. The cAMP opens cyclic nucleotide-gated ion channels, allowing Ca^{2+} and Na^{+} ions to enter the cell and opening of Ca^{2+}-gated Cl^{-} channels that permit Cl^{-} movement out of the cell. The movement of ions results in depolarization of the olfactory sensory neuron and creates an action potential that is carried along the axon to the brain. It is now understood that OR expression is not limited to the olfactory epithelium of the nasal cavity. There is also "ectopic" expression in many organs, such as liver (Wu et al., 2015), pancreas (Kang et al., 2015), and lung (An and Liggett, 2018) where ORs can detect the internal environment of the animal and impact a myriad of other physiological processes (reviewed by Kang and Koo, 2012 and Chen et al., 2018). These include chemotaxis of sperm (Flegel et al., 2016) and migration of muscle cells during differentiation (Pavlath, 2010), regulation of blood pressure via changes in circulating concentrations of VFA that bind ORs in the kidney and stimulate renin secretion (Natarajan and Pluznick, 2016), and changes in respiration rate (e.g., through binding of lactate during hypoxia to ORs expressed in the carotid artery to stimulate hyperventilation; Chang et al., 2015) as well as alteration of gut motility. For example, OR-expressing enterochromaffin cells in the gut are activated by compounds like eugenol to release serotonin that affects gut motility (Braun et al., 2007) and increases satiety (Voigt and Fink, 2015). Of interest, unlike the olfactory sensory neurons of the nasal cavity, more than one receptor type may be expressed per cell in these tissues. For instance, Flegel et al. (2016) detected approximately 90 different ORs expressed in human sperm cells which varied in their distribution among the acrosomal cap, head, and flagellar regions. These ORs present in the olfactory epithelium as well as other tissues detect a variety of chemical cues that may ultimately impact endocrine and metabolic centers, affecting feeding behavior or appetite as described in the following section.

EVIDENCE FOR FUNCTIONAL ROLE OF ORS IN APPETITE REGULATION

Experimental evidence indicates that specific odorants can activate ORs in the olfactory epithelium to influence animal appetite. The effects of these odorants appear to be mediated by changes in secretion of orexigenic or anorexigenic neuropeptides as well as activity of the gastric vagal nerves. For example, a 10-min exposure of rats to grapefruit oil or its primary odorant called limonene was shown to inhibit the activity of efferent vagal nerves innervating the stomach (Shen et al., 2005a), which should reduce gastric emptying. Furthermore, in the same study, a 15-min exposure to these compounds three times per week for 6 wk reduced food intake and body weight of rats. On the contrary, the same exposures to lavender oil or its main odorant linalool was shown to stimulate activity of gastric vagal nerves and increase rat food intake and BW

(Shen et al., 2005b; Tanida et al., 2006). In each of these studies, the responses were abolished by local nasal mucosa anesthesia or anosmia induced by $ZnSO_4$ treatment of the nasal cavity, indicating the necessity for olfactory stimulation in the observed responses. Furthermore, it was shown that a 10 min exposure to these compounds not only affects mRNA expression of the appetite stimulator neuropeptide Y in rat olfactory nerve cells (Rolf B1.T) and primary rat olfactory ensheathing cells but inhalation of essences of limonene and linalool also alters circulating concentrations of NPY in human subjects (Chen et al., 2012). That is, consistent with a stronger appetite induced by linalool, both *NPY* mRNA and serum NPY were increased in these studies, and the opposite was observed with limonene.

There is also evidence that some ectopic ORs may play a role in appetite regulation, including mouse *OR51E2*. Fleischer et al. (2015) used transgenic mice that express green fluorescent protein on *OR51E2* to demonstrate that this receptor is expressed on enteroendocrine L cells within the crypts of the colon and that all *OR51E2*-positive cells within the mouse colon coexpress the appetite-regulating gut hormone peptide YY (**PYY**). The authors interpreted this finding as a likely functional connection between *OR51E2* and PYY release. Yet, only about a third of PYY-positive cells co-expressed *OR51E2*, indicating that regulation of PYY secretion likely involves additional mechanisms beyond the potential role of *OR51E2*. Additionally, a small percentage of *OR51E2*-positive cells in this study also co-expressed glucagon-like peptide 1 (**GLP-1**). This is of particular interest in the context of appetite regulation as both PYY and GLP-1 are believed to mediate what is known as the "ileal brake," a feedback mechanism whereby the introduction of nutrients (especially energy-rich foods) to the lower gut results in PYY and GLP-1 release from L cells, slowing of gut emptying, reduced gut motility, and an increased sense of satiety (Spreckley and Murphy, 2015). It was further demonstrated by Fleischer et al. (2015) that propionate is an activator of *OR51E2*, providing evidence that this OR may be a critical link in appetite regulation; whereby, propionate derived from microbial digestion in the colon could activate *OR51E2* and stimulate the release of PYY and GLP-1 from L cells as a satiety signal.

A very similar OR protein, *OR51E1*, was shown to be expressed throughout the gastrointestinal tract of pigs, with the highest concentration in the region connecting the stomach to the duodenum (Priori et al., 2015). Notably, this OR was shown to colocalize on enteroendocrine cells containing PYY and serotonin (Priori et al., 2015), both of which regulate gut motility and appetite (Braun et al., 2007; Spreckley and Murphy, 2015; Voigt and Fink, 2015). One of the ligands of this OR is butyrate (Adipietro et al., 2012), produced by microbes in the intestinal lumen. Indeed, there appears to be evidence for mechanistic links between ORs and appetite regulation not only in rodents and humans, but also in a livestock species.

Lastly, there are notable connections among nutrient-sensing mechanisms and hormones that regulate energy balance and appetite with the olfactory and central nervous systems which have been reviewed extensively by Palouzier-Paulignan et al. (2012) and Julliard et al. (2017). The notion is that activity of the olfactory system is heavily influenced by hormonal, nutritional, and metabolic cues of energy balance that impact animal odor-related behaviors like feed intake and food preference to assist in maintaining their energy homeostasis. Hormonal examples include orexins A and B, which stimulate food intake, and their receptors that are expressed at the transcript and protein levels in both olfactory sensory neurons and surrounding areas of the olfactory mucosa, as well as the hypothalamus (Caillol et al., 2003). Likewise, leptin, which suppresses appetite, and its receptors are expressed on olfactory receptor neurons and in the hypothalamus (Baly et al., 2007). These hormonal signals, along with activation of other nutrient receptors (e.g., members of the solute carrier transporter family; Julliard et al., 2017), can directly impact olfactory sensitivity and odorant detection through changes in the frequency and amplitude of neuronal firing as well as the expression of odorant binding proteins that present odorants to ORs in the olfactory mucosa (Palouzier-Paulignan et al., 2012). Namely, as demonstrated in rodents, fasting increases olfactory sensitivity and time spent exploring food-related odors, and satiety decreases them (Prud'homme et al., 2009), which ultimately could impact feeding behavior and feed intake. Clearly, expression of appetite-regulating peptides and their receptors in addition to nutrient receptors on olfactory neurons and their proximity to the hypothalamus provide opportunities for extensive cross talk between olfaction and appetite regulation begging further exploration in livestock species.

GENETIC STRUCTURE OF ORS

The OR gene family comprises the largest gene family in mammals (Gilad et al., 2005; Fleischer et al., 2009). In humans, the OR family comprises ~30 Mb, or 1% of the genome, where OR genes are distributed across nearly all chromosomes, but often occur in clusters within a chromosome (Glusman et al., 2001). For example, 313 intact OR genes are located on human chromosome 11 alone, whereas nine other chromosomes have only one to five intact OR genes, and chromosomes 8, 20, and the Y chromosome are devoid of any OR genes (Malnic et al., 2004). Numerous OR pseudogenes (~300) also exist (Malnic et al., 2004) in which a mutation has occurred resulting in a nonfunctional OR protein. Genomic studies indicate that the number of OR genes is highly variable across species and may be related to each species' ecology as well as its dependence on smell vs. other senses like vision for locating feed (Vandewege et al., 2016). For instance, bottlenose dolphins, which live in an aquatic environment and depend on echolocation for locating prey, have fewer than 30 OR genes of which only about half are functional, whereas cattle and rodents have between 1,100 and 1,600 functional OR genes (Hayden et al., 2010; Lee et al., 2013). Notably, the African elephant may have the greatest number of functional OR genes at about 2,000 which is believed to provide them with a very keen sense of smell (Hayden et al., 2010; Niimura et al., 2014). In fact, it has been proposed that African elephants have the ability to distinguish between ethnic groups of people based on smell. Specifically, exposure to odors of the Kenyan Maasai tribe who routinely hunt elephants elicit a greater fear response by African elephants than do odors of the Kamba tribe who lead an agricultural lifestyle and do not hunt elephants (Bates et al., 2007).

Extensive genetic variation exists in human OR genes which impacts olfactory function. For example, it is estimated that 66% of OR genes contain insertions/deletions, SNPs, and copy number variations (**CNVs**; Olender et al., 2012). CNVs are large segments of DNA (>1 Kb) that are repeated within the genome, and the number of repeats of this region varies from one individual to another (Freeman et al., 2006). The genetic variations can change the encoded AA, create nonsense codons in encoded ORs, or in the case of CNVs, differences in the expression level of a particular OR. Thus, genetic variation in ORs contributes to differences among individuals in their ability to smell, their sensitivity to different odors, which can differ by several orders of magnitude, as well as odor or food preferences, and feed intake (Keller et al., 2007; Hasin-Brumshtein et al., 2009; Choquette et al., 2012). For instance, SNPs in genes like *OR11H7P* and *OR6A2* are associated with sensitivity to the sweaty smell of isovaleric acid (Menashe et al., 2007) and preference for the herb cilantro (Eriksson et al., 2012), respectively. An SNP in *OR2J3* affects the ability to detect the grassy smell of cis-3-hexen-1-ol (McRae et al., 2012), and an SNP in *OR5A1*, which results in an AA change in one of the extracellular loops of the receptor, affects the preference for the floral scent of beta ionone and food choices (Jaeger et al., 2013). Lastly, SNPs in human *OR7D4* affect the degree of aversion of individuals to the smell of androstenone, one of the compounds responsible for boar taint (Keller et al., 2007). Polymorphisms in this gene are also associated with human susceptibility to hunger and body mass index (Choquette et al., 2012), providing a possible link between OR variation and human appetite regulation.

Lastly, similar to humans, considerable variation has been shown to exist among OR genes of cattle and swine. For instance, 40% of OR genes sampled by Lee et al. (2013) exhibited CNVs across and within cattle breeds. Likewise, 66% of OR genes overlap CNV regions in the pig genome (Paudel et al., 2015). Thus, these CNVs within the OR gene loci provide substantial opportunity for animal-to-animal variation in OR function and impacts on phenotype, such as appetite or feed intake.

ORS VARIATION ASSOCIATED WITH LIVESTOCK PRODUCTION TRAITS

To date, a few genome-wide association studies have reported associations between OR genetic variants and feed intake or intake-related traits of livestock, such as rate of gain, carcass composition, and residual feed intake (**RFI**), defined as the difference between observed and expected feed intake based on production level proposed by Koch et al. (1963). For example, Veerkamp et al. (2012) identified 500 genes that were located near SNPs significantly associated with the traits of BW, DMI, or BCS in European first-parity Holstein dairy cows. These genes were enriched in olfactory, taste, and pheromone receptors, suggesting a functional role for variation in OR genes in regulation of feed intake of dairy cows. Similarly, a genome-wide association study of pigs identified 25 OR genes located near SNPs significantly associated with

RFI (Do et al., 2014), and another study in beef cattle identified *OR9Q2* as a positional candidate gene contributing to RFI in the SimAngus breed (Seabury et al., 2017). Thus, olfactory transduction may be an important biological pathway contributing to variation in feed conversion efficiency measured as RFI. Furthermore, a study of Nellore cattle identified three OR genes (*OR2D3*, *OR2D2*, and *OR6A2*) within the 46 Mb region of BTA 15 associated with DMI, two OR (*OR52J3* and *OR51A7*) in the 50 Mb region of BTA 15 associated with ADG, and *OR9A4* in the 105.9 Mb region of BTA 4 associated with RFI (Olivieri et al., 2016). A second study in Nellore cattle also identified a cluster of OR within the 31 to 32 Mb region of BTA 5 associated with carcass marbling (Magalhães et al., 2016). Of interest, a study of beef steers of various breeds exhibiting divergent residual weight gain also showed differential mRNA expression in ileum of *LOC618173*, an OR similar to *OR52K1* that was identified in a previous genome-wide association study as associated with weight gain in crossbred beef cattle (Lindholm-Perry et al., 2015). However, differences in ileal expression of this transcript could not be confirmed by the authors within a separate beef cattle population differing in ADG and ADFI. Finally, our laboratory recently completed a genome-wide analysis of CNVs and their association with production traits of Holstein dairy cows including DMI and RFI and identified significant CNVs associated with both traits overlapping OR genes (Zhou et al., unpublished data): first, *OR2A2* gene, located on BTA and a second CNV region associated with RFI that includes two other ORs, *OR2T12* and *OR2AK2*. Collectively, these results indicate that multiple ORs are positional candidate genes contributing to differences in feeding and appetite-related traits of livestock and may play an important role in appetite regulation.

MANIPULATING APPETITE VIA ORS

Overall, there appears to be reasonable evidence to support a functional link between ORs and appetite regulation in production animals and the potential to manipulate appetite and feed intake via direct OR activation or selection for particular OR genetic variants. Herein, we propose two approaches by which specific ORs or odorants could be identified and studied for targeted manipulation in livestock species based on prior techniques described for rodents and humans (Figure 1). First, one could isolate and culture-specific OR-expressing cells such as primary colonic

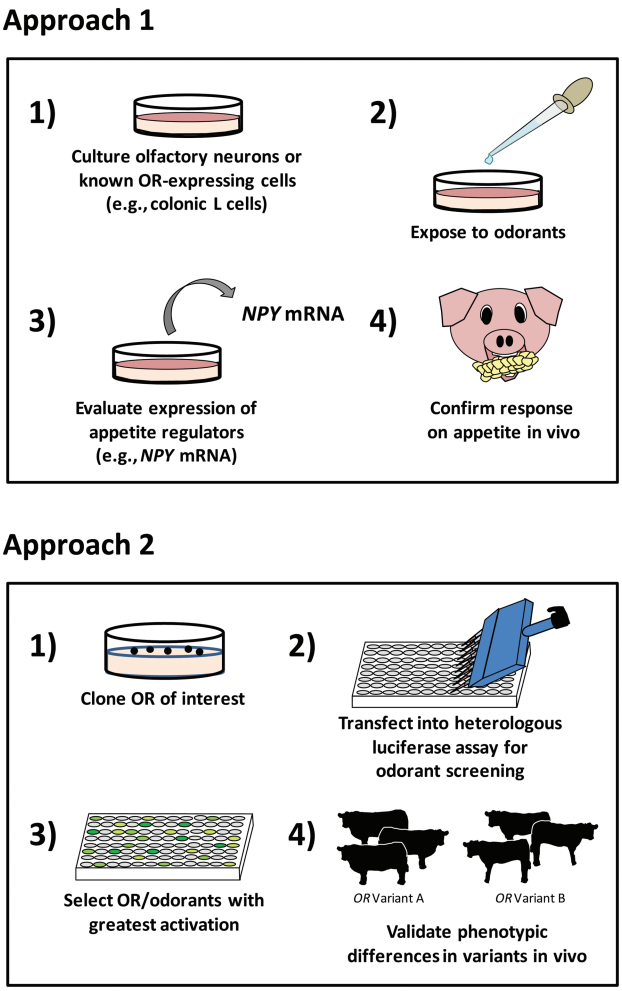

Figure 1. Proposed approaches by which specific ORs or odorants could be identified and studied for targeted manipulation in livestock species based on prior techniques described for rodents and humans.

L cells or olfactory neurons from the species of interest and then quantify their mRNA expression or protein production of known appetite regulators (e.g., NPY or PYY) in response to exposure to various odorants. Then, odorants with the desired effects in vitro could be evaluated in live animals to determine whether they produce the desired effects on appetite and feed intake. As described earlier, this approach was employed by Chen et al. (2012) who exposed Rolf B2.T cells or cultured rat olfactory ensheathing cells to differing concentrations of linalool or limonene for various time periods to assess the cellular responses in *NPY* mRNA expression. The *NPY* mRNA expression concentrations served to indicate the appetite-regulating potential of these compounds and provided a model system to screen additional odorants of interest.

Second, specific ORs from the species of interest (including different genetic variants of a particular receptor) could be cloned, transfected into a heterologous luciferase assay, and used

as a high-throughput screening tool to evaluate receptor reactivity to various odorants (Zhuang and Matsunami, 2008; Mainland et al., 2014). Specifically, different OR clones could be arrayed into a 96-well (or greater) assay plate and exposed to putative appetite-altering odorants of choice to determine the receptors (and variants) with the greatest activation potentials based on luciferase assay. Alternatively, a single OR of interest could be screened against multiple appetite-altering odorants and concentrations to identify the odorant with the greatest stimulating ability. Ultimately, selected OR–odorant combinations could be targeted for further evaluation in live animals to confirm anticipated effects on DMI or feed preference as well as OR variant associations with other appetite-related production traits such as ADG or carcass marbling.

SUMMARY AND CONCLUSIONS

In summary, there appears to be reasonable evidence suggesting a link between olfactory receptors and appetite regulation, and variation in these receptors could contribute to differences in individuals in terms of feed intake, weight gain, and body composition. There are practical applications for developing novel compounds to activate various receptors to manipulate these processes in production animals or to select for particular OR genetic variants within the population to support desired outcomes on livestock production. Basic research focused on olfactory receptors of production animals and their ligands to regulate appetite has yet to be explored and provides an enormous opportunity to enhance appetite-related traits, such as feed intake, weight gain, and carcass composition for greater production efficiency.

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