Biochemistry & Physiology: Open Access

Wekesa, Biochem Physiol 2012, 1:2
DOI: 10.4172/2168-9652.1000e110

Editorial Open Access

Signaling in the Mammalian Vomeronasal Organ

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Pheromones are chemical signals which provide conspecifics information about gender, dominance and reproductive status [1]. They elicit innate and stereotypical reproductive and social behaviors, along with neuroendocrine and physiological changes. The vomeronasal organ, as part of the accessory olfactory system, is the site for pheromone binding to specific receptors, thus initiating a signal transduction pathway leading from the vomeronasal neurons to the hypothalamus-pituitary axis, *via* the medial amygdale [2]. Molecular evidence has led to the isolation of three independent families of vomeronasal receptor genes (VR) known as V1Rs [3], V2Rs [4-6], and V3rs (Pantages and Dulac [7]) that encode putative pheromone receptors. Vomeronasal neurons are classified based on the vomeronasal receptor type and the G-protein to which they are coupled. Vomeronasal receptor neurons with cell bodies in the apical half of the sensory epithelium express the G-protein alpha subunit $G\alpha_{i2}$ and project to the anterior part of the Anterior Open Bite (AOB), whereas neurons in the basal regions of the Vomeronasal organ (VNO) neuroepithelium express the G protein alpha subunit $G\alpha_o$ and project to the posterior regions of the AOB [8-10]. More recent studies have introduced the formyl peptide receptor (FPR) as a possible chemosensory receptor [11]. FPRs are selectively expressed in the neuroepithelium, express either $G\alpha_{i2}$ or $G\alpha_o$, and are highly dispersed throughout the neuroepithelium [12]. Possible roles for the FPRs include the assessment of conspecifics or other species, based on variability in normal bacterial or mitochrondrial proteins [13]. Recently, it has also been shown that the two classes of vomeronasal receptors V1Rs and V2Rs use different strategies to encode chemosensory information [14].

The initial event of pheromonal detection requires the activation of specific receptors by pheromones and the transduction of the stimulus. The expression of three types of pheromone receptors supports the idea that they might be involved in different types of chemosensory information. The presence of three types of G-proteins might also suggest that the transduction processes of different pheromones might also be different. A recent study by Chamero et al. [15] using electrophysiology and calcium imaging techniques has provided evidence that $G\alpha_o$ might be involved in signal transduction of peptide and protein cues by vomeronasal sensory neuron (VSN) that express V2Rs and are $G\alpha_o$ -positive and also express at least one of the formylpetide receptors [12]. They found that the $G\alpha_o$ mutant male mice are less aggressive, and the maternal aggression in females is also severely reduced [13]. Studies have shown that vomeronasal transduction involves release of IP_3 [16-19]. In the garter snake, a chemo attractant isolated from its prey induced the generation of inositol-1,4,5-trisphosphate in the VNO [18]. It has been shown that dialysis of IP_3 into the turtle and rat VNO induces inward currents [17]. The female porcine and mouse VNO can be stimulated by chemosensory cues to cause an increase of IP_3 [16,19]. These results suggest that pheromonal information is mediated *via* the IP_3-dependent pathway in the vomeronasal receptor neurons. Electrophysiological recordings have demonstrated that stimuli applied to the VN epithelium causes an increase in firing rate of individual neurons in the AOB [18,20]. Furthermore, stimuli applied to the surface of VN receptor neurons or IP3 dialyzed into VN receptor neurons cause membrane depolarization, as demonstrated using patch-clamp recordings in snakes [21].

Although, the mechanism(s) involved in Ca^{2+} influx in chemosensory transduction in the VN system remains unknown, transient receptor potential (TRPC2) proteins have been implicated in Ca^{2+} influx, as either Ca^{2+} channels [22] or non-selective cation channels [23-28], and in some cases the function of TRPC2 channels involve interaction with IP3Rsm [23,27,29]. In rat, TRPC2 has been shown to be expressed in VN neurons and is heavily localized to VN sensory microvilli [30]. TRPC2 might represent the primary conductance that is activated by pheromone signals, or could mediate a secondary amplification of the pheromone response. The identification of the TRPC2 has led to a model of the VNO signal transduction that parallels the *Drosophila* phototransduction cascade [30]. According to this model, G-protein activation by vomeronasal G-protein-coupled receptors (GPCRs) triggers a phospholipase C-dependent cascade, which in turn directly activates either TRPC2 or another associated conductance. What is the mechanism of TRPC2 activation? Phospholipase C (PLC) activity results in the cleavage of phosphatidylinositol-4,5-biphosphate, leading to an increase in the intracellular concentrations of the second messengers IP_3 and DAG, both of which have been implicated in TRPC2 activation [31,32]. Patch Clamp recordings of hamster VNO neurons identified the abundant expression of Ca^{2+} activated non-selective cation channel, with properties that are consistent with a direct role in VNO sensory transduction, or with an indirect function in amplifying the primary sensory response [30]. The TRPC2 channel has been shown to induce the flow of calcium ions in response to pheromones, such as 2-heptanone and 2,5-dimethylpyrazine [28]. Studies by Stowers et al. [33] and Leypold et al. [34] showed that the genetic ablation of TRPC2 either eliminates or strongly reduces the sensory response of the VNO to urine or volatile pheromones. In 2004, Lucas et al. [35] proposed that the primary electrical response to pheromones depends on diacylglycerol (DAG) and not on IP_3 or arachidonic acid. It is possible that DAG may activate certain pathways which are currently unclear. These studies demonstrate that IP_3 and TRPC2 play a role in VSN activation, but a thorough characterization of the properties and pharmacology of the IP_3-activated currents remains to be done. Another issue is that some pheromonal responses have been shown to occur in the absence of the TRPC2, suggesting that it might not be the only channel involved in VNO transduction. A recent study by Kelliher et al. [36] showed that the pregnancy block effect can still occur in the absence of the TRPC2 channel. Murine MHC class I peptide ligands are the first identified vomeronasal stimuli that can mediate the pregnancy block effect [37,38]. In order to investigate the transduction pathways of

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Received October 19, 2012; **Accepted** October 22, 2012; **Published** October 24, 2012

Citation: Wekesa KS (2012) Signaling in the Mammalian Vomeronasal Organ. Biochem Physiol 1:e110. doi:10.4172/2168-9652.1000e110

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MHC class I peptides, Kelliher et al. [36] used mice with a homozygous deficiency in the TRPC2 cation channel gene. They found that the loss of the TRPC2 channel did not influence the formation of social memories in the context of the Bruce effect, thus indicating that TRPC2 is not part of the transduction cascade of some social cues, by peptide-sensitive vomeronasal sensory neuron's (VSNs) located in the basal zone of the VNO or that it participates in a redundant system. Their results suggest an alternative, TRPC2-independent signal transduction mechanism in the detection of molecular cues required for the Bruce Effect [36]. Phenotypic discrepancies have also been observed between mice exhibiting genetic manipulation or surgical VNO lesions [39-41]. For example, impaired sexual behavior toward females has been reported in male mice after VNO lesions [42] whereas no such deficits were reported in TRPC2$^{-/-}$ mice [33,34,41]. Similarly, in sexually naïve male mice, VNO removal prevents ultrasonic vocalizations in response to female chemo signal [43], whereas robust vocalizations are produced by TRPC2$^{-/-}$ males [33]. These studies suggest that pheromonal transduction is not exclusively mediated by the TRPC2 channels.

There is also controversy regarding the role of IP_3 and diacylglycerol (DAG) in the transduction pathway. The main function of IP3 is to stimulate the release of Ca^{2+} from intracellular stores [44], *via* the IP_3 receptor which functions as an IP3 sensor and a Ca^{2+}-release channel. The regulation of Ca^{2+} signaling in VN receptor bipolar neurons is likely to be important for the control of various Ca^{2+}-dependent processes, such as cell excitability [45], neurotransmitter release [46] and synaptic plasticity [47], as has been reported in other biological systems. Much of the ambiguity and controversy surrounding IP3's role in Ca^{2+}_i dynamics arises from differences in biochemical versus functional studies, evaluating its role as a factor at the membrane in direct gating of TRPC2 [21,35,32,48-51] or conversely, as mediator of internal store release of Ca^{2+}. The latter mode of IP3 activating release of Ca^{2+}_i is coupled to mechanistic description of TRPC2 as a capacitance Ca^{2+} entry (CCE) or store-operated (SOC) channel [52,53]. Further review of current literature also indicates that electrophysiological studies provide the bulk of information garnered so far on membrane (or intracellular) Ca^{2+} and other ionic currents [17,21,32-36,48,49,51,54-59], with few direct studies of Ca^{2+} to validate and add to the electrophysiological data, especially in the context of internal versus external regulation of Ca^{2+} dynamics. Currently, reports of Ca^{2+} imaging, particularly in mammalian systems, provide information on VSNs responses to dilute urine or other complex natural stimuli [49,51,58] and in a very few studies of some of the individual volatile constituents of urine or other natural stimuli [53-55]. In these studies, some questions remain to be addressed thoroughly such as what is the role of IP3 versus DAG in activating TRPC2-mediated Ca^{2+} entry: a corollateral concern is whether TRPC2 is directly gated, or is a CCE channel. Thus, it is evident that Ca^{2+} studies of individual volatile and non-volatile ligands, particularly ones that have been shown to be involved in certain behavioral responses, are needed to completely address current issues in signaling at the membrane surface.

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Citation: Wekesa KS (2012) Signaling in the Mammalian Vomeronasal Organ. Biochem Physiol 1:e110. doi:10.4172/2168-9652.1000e110

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