The Florida State University
Department of Biological Science
214 Biomedical Facility
Program in Neuroscience and Molecular Biophysics
Tallahassee, Florida 32306-4340

Debra Ann Fadool, Ph D.
Associate Professor

Tel: *850 / 644-4775*
Fax: *850 / 645-3281*
E-Mail: *dfadool@bio.fsu.edu*

22 September 2005

Dr. Yves Brun
Systems Biology/Microbiology Faculty Search
Department of Biology
Indiana University, Jordan Hall 142
1001 E. 3rd Street
Bloomington IN 47405-7005

Dear Committee,

Please find my enclosed application that I would like to electronically submit for an Associate Professor level position in your Department of Biology and Biocomplexity Institute.

I have submitted the following files in pdf format:
1. Cover Letter (Jobcover.pdf)
2. Curriculum Vitae (Cvjob.pdf)
3. Document of Long-term Research Plans (JobResearchStatement.pdf) **OR**
4. All three documents in a single pdf file format (DFadoolJob.pdf)

My key published manuscripts (1992-2004) can be found by scrolling to the bottom of the following link:
http://www.neuro.fsu.edu/faculty/fadool/indexfsu.htm

I have three manuscripts that are currently in press for 2005 that I can submit upon request. They are typeset by the editors but still retain editorial copy marks so I didn't want to officially post them to my website until they were corrected for release. Additionally I have one manuscript currently under review.

I have been a faculty member in the Program in Neuroscience and Molecular Biophysics at Florida State University in the Department of Biological Science since August of 1999. Last year I was granted tenure and promotion to Associate Professor. I have several exceptional colleagues in the Chemical Senses, good resources, and enjoy my teaching opportunities as a physiologist and biophysicist. Our administration desires to increase ecology, evolution, and structural anatomists in their long-term expansion of the Department. Through retirement and lack of faculty lines, the areas of genetics (2 faculty) and neuroscience (5 faculty) have dropped below a strong intellectual critical mass in our unit of 43 faculty. Although I heartily regret having to relocate from my colleagues and the city of Tallahassee,

I feel it is academically required to bring my research and the training of my students/fellows to a more competitive level. I desire employment where there is an active and substantial community of cell biologists, neuroscientists, and physiologists. I thrive to hear good symposium speakers, collaborate with laboratories of similar interests, integrate novel technologies into our research objectives, have teaching duties in physiology and related disciplines, and participate in leadership opportunities. As such, I look forward to your review of my credentials for the opportunity that exists in your department. I have not had to assemble such materials for over seven years, so I hope that the cv and research statements are not too lengthy, but they are definitely comprehensive to obtain the information you are seeking.

Most Sincerely,

Debra Ann Fadool
Associate Professor
Program in Neuroscience and Molecular Biophysics

RESEARCH STATEMENT:

It has been written " We do not understand how we think, but we do know that electrical signals passed around by the thinking brain are generated by a single class of protein: the ion channels".[28] I have been fascinated with biophysical mechanisms and interactions of ion channels from the first day of my graduate school interview, when I heard the bursting of a train of action potentials coming from an amplifier of an electrophysiological recording station, and I knew immediately what type of science would continue to intrigue and drive my curiosity. Through my research efforts of the last 10 years, I know that the activity of ion channels is dynamic, responding to intercellular signaling molecules and cytoplasmic factors via protein-protein interactions and covalent modifications[21;25]. My current research in ion channel signaling has been grounded in the field of Chemical Senses, particularly the modulation of ion channels in olfactory transduction pathways contained in the olfactory epithelium, the olfactory bulb, and the vomeronasal organ. I believe that the next challenge, after the previous 2 decades of ion channel structure-function dissection, is to INTEGRATE this information with the aim of understanding how the entire ensemble of channels in a cell, along with their modulatory partners, act together to produce a cellular output. Due to this belief, and despite the origins of my primary funding from the NIDCD, I consistently push the boundaries of Chemical Senses and spill into the larger areas of tyrosine phosphorylation of potassium channels, brain insulin signaling and diabetes, sensory deprivation and nerve regeneration via neurotrophin signaling and reproductive physiology to explore the protein-protein interactions of ion channels on a systems physiology tract. While I have retained electrophysiology as our primary approach and expertise to understand ion channel interactions, I have always been eager to retool, rethink, collaborate, and design studies that incorporate multiple techniques so that my research has good depth, supports parallel lines of evidence, and most importantly is hypothesis driven. I have always favored a multifaceted approach where different disciplines provide fresh perspective on the questions at hand.

Ion Channel Signaling in the Olfactory Bulb

To understand the capacity of electrical signaling in the olfactory bulb (OB), one must ultimately elucidate the mechanisms by which channel proteins respond to biochemical changes at specific modulatory sites[25]. One such modification is via phosphorylation. One-third of all mammalian proteins are thought to contain covalently bound phosphate[19] and the extent of phosphorylation on a particular protein can be regulated by changing the activity of the cognate protein kinase or phosphatase. Phosphorylation of ion channels on tyrosine residues, as a result of intercellular communication, modulates enzyme activity and creates binding sites for the recruitment of downstream signaling proteins.[20] We know from previous work that a voltage-gated potassium channel (Kv1.3) highly expressed in the OB is a molecular target for multiple phosphorylation by four different tyrosine kinases[6;9;11-13]. Tyrosine phosphorylation evokes changes in the biophysical properties of Kv1.3, such as peak current magnitude, inactivation kinetics, and voltage-dependence[10;34]. Through mutagenesis and use of heterologous expression, we are currently defining the specific modulatory sites on Kv1.3 that permit interaction with proteins that are down-stream signaling components of two of the tyrosine kinases (receptor tyrosine kinases; (RTKs)), the insulin receptor kinase and the TrkB neurotrophin receptor kinase, due to our past and current interest in diabetes and channel activity after sensory deprivation[10;13;34]. We have previously demonstrated that the modulation of Kv1.3 through activation of these RTKs through their preferred ligands, insulin and brain-derived neurotrophic factor (BDNF), is both time and sensory-experience dependent[10;13]. We are concurrently probing the question as to whether insulin- or BDNF-induced modulation of Kv1.3 is affected by co-transfection of adaptor proteins known to be highly expressed in the OB, namely nShc, Grb10, and PSD-95. Our experiments will address the basic tenet of

whether the assemblage of multi-protein complexes creates a scaffold around an ion channel to shape the electrical phenotype of a neuron to the same extent as that confirmed by different ion channels and their contributing conductances. This could help shape global questions as to whether there are different degrees of modulation across neurons expressing different adaptor proteins. We are next testing Kv1.3 co-immunoprecipitation with each of the above receptor tyrosine kinases (RTKs) in the presence of the adaptor proteins we have determined to be modulatory. These experiments would demonstrate physical complexes between a voltage-gated ion channel and a kinase linked by an adaptor protein. Such data would alter conventional thought - adaptor proteins are traditionally thought to link signaling cascades, yet ion channels have not been considered to be a component of these types of transduction cascades. Functionally adaptor proteins would be beneficial to position channels in close proximity to the kinase that regulate their electrical activity. Scaffolds currently described are direct interactions between channel and kinase[17] or between kinase and adaptor protein[1], but this would describe a multiple complex between kinase and channel mediated by an adaptor. For example, we have recent data (**Figure 1**) that are leading us to hypothesize that TrkB and Kv1.3 are linked by nShc (at Y490), and when TrkB internalizes, it could physically bring the Kv1.3 channel with it to decrease total current by the neuron. Thus modulation by BDNF could be very complex, involving phosphorylation, receptor internalization, ion channel trafficking, and adaptor protein linkage. This combinatorial modulation is what we are now testing by designing internal and external epitope tagged channel constructs for which we are monitoring surface expression and points of internalization through confocal imaging, patch-clamping, and immunoprecipitation. Since some of the functionally modulatory adaptor-kinase-channel complexes we have found are phosphorylation dependent and others are independent, we are constructing two classes of mutations that will interrupt the recognition motifs in Kv1.3 or the adaptor proteins for SH2/PTB or SH3 containing protein partnerships, respectively.

Selective mutation of key structural requirements for interaction would identify the molecular mechanism for modulation or complexing at discreet protein-protein interactions. What sole reliance on this type of reductionist approach cannot tell us is how modulation of ion channels by insulin or BDNF operates endogenously in the thinking brain. For this reason we have, in parallel, developed an *in vitro* model of Kv1.3-expressing olfactory bulb neurons and make use of transgenic mice with gene-targeted deletions in the channel or the two RTKs. In this mode we can begin to span questions from protein interactions of signaling partners up to whole animal olfactory discrimination. First we are using primary cultured olfactory bulb neurons (mitral) to determine if the patterning of electrical stimulation affects endogenous release of insulin and BDNF using a non-conventional technique introduced by Dr. Katz called *Elisa in Situ*[2]. By using a combination of developmental postnatal stages, feeder layers, and sandwich cultures[3] we will be able to identify endogenous growth factor release in specific cell types of the olfactory bulb and demonstrate activity-dependent processes affecting tyrosine phosphorylation of ion channels. In similar strategies to explore sensory experience-dependent modulation of Kv1.3 we will induce unilateral naris-occlusion in wild-type and transgenic mice at birth. After a period of sensory deprivation of that ipsilateral projection to the olfactory bulb, we will use the brain slice configuration to explore the predicted rapid neuromodulatory effect of insulin and BDNF modulation of Kv1.3 activity linked to sensory experience. Finally we will biochemically measure if there is a correlative change in tyrosine phosphorylation of Kv1.3 channel, IR kinase, or the TrkB receptor kinase following electrical stimulation or sensory deprivation. These experiments would enforce that changes in neural activity often involve covalent modification of a protein.

Lastly we are most excited about the many new transjectories that the "super-smeller mice" are leading us to pursue. The use of these Kv1.3-null mice has forced us to expand the traditional role of a potassium channel (setting the membrane potential) to further investigate its role in olfactory sensitivity, mitral cell firing patterns, olfactory coding, development of glomeruli in the olfactory bulb, balance of the

molecular scaffold regulating the channel protein, weight loss, general metabolism, and the regulation of glucose. I have established a collaboration with an investigator at University of South Florida who will allow us access to his engineered rodent olfactometers[31] so that we can screen up to 200 compounds per hour to determine if these mice could be use for security operations; the detection of land minds, spoiled or contaminated food compounds, or drugs; the localization of injured persons after natural disasters; or be suitable in military operations to uncover perpetrators of car bombs. Government laboratories in both the United States and Britain have high interest in their potential use over that of dogs and I hope to recruit support for this pursuit through an invited presentation this November at the British Ministry of Defense. I have established a collaboration with two investigators at Yale University so that we may explore, through computational modeling, the contribution of a sodium-activated potassium current (called slack/slick channels)[4;5] that is revealed in the Kv1.3-deficient background. I am quite eager to uncover if there is a change in the circuitry of the Kv1.3-null mice given the increased number of glomerular units for synaptic connections to the first order neurons and the smaller size of these units. I have undertaken genetic breeding of the Kv1.3-null mice with mice that have genetic markers for odorant receptor tagged proteins using knockin IresTauLacZ engineered constructs from an investigator at Rockerfeller University[29] so that I might track any altered projections of the olfactory sensory neurons to the more abundant glomeruli (**Figure 2**). There is also good possibility to cross the Kv1.3-null mice with two recent lines of mice that afford a strategy to discern whether the extra glomeruli in the potassium channel-deficient background are all functional, and if so, do they have the same odorant activity maps as those of the wildtype mice given the increased olfactory discrimination and threshold abilities of the null mice. One line of mice contains a knockin of the molecule synaptoPHorin[7], and a colleague of mine at Boston University and I would like to explore using neural synaptic imaging whether loss of Kv1.3 channel activity perturbs coding by disrupting the pattern of activated glomeruli to specific odor qualities or concentrations. Likewise, since Kv1.3 is expressed in both the olfactory bulb and the olfactory cortex, use of Barley-Pectin engineered mice[37] that track activity from the sensory neurons of the epithelium to the final synaptic projections in the cortex could reveal new organizational qualities about the cortex responsible for olfactory sensitivity in the null mice. We are also currently generating a double mutant mouse with YFP-labeled mitral cell dendrites[15] so that we can examine any fine pattern of dendritic connections of the mitral cell neurons by confocal microscopy and by computational three dimensional reconstruction with the assistance of a colleague of mine in mathematics at FSU. Independent of potential circuitry changes, we do not know if the glomerular changes of the olfactory bulb in the Kv1.3-null mice were induced by loss of Kv1.3 channel protein, its activity, the imbalance in the expression of scaffolding kinases and adaptor proteins surrounding the channel, or even changes in whole animal metabolism. Towards this end, we would like to create a "non-conducting Kv1.3 channel" knockout mouse by disrupting the pore domain of the channel but leaving the structural motifs for protein-protein interaction intact. With the assistance of an expert anatomist next door to my laboratory[16], I will also stereotaxically deliver the Kv1.3 scorpion toxin channel blocker, Margatoxin (MgTx) to the olfactory bulb in wildtype mice. Both of these modified mice would be behaviorally phenotyped for olfactory ability, the expression of scaffolding proteins and modulatory kinases would be measured, and a complete biophysical assessment of mitral cell firing patterns would be made to determine if olfactory gain in function was associated with a structural change in the glomeruli or activity dependence of the ion channel. Finally, I am actively attempting to reverse the weight gain and some of the pleiotropic affects of diabetes by determining whether genetic breeding of the Kv1.3-null mice with models of slow metabolism and obesity (IR knock-out, leptin, and melanotrophic receptor 4 knockout mice) could rescue these phenotypes. Through the continuous collaboration of an exercise physiologist[35] on my floor who allows us access to his FSU-engineered metabolic chambers (**Figure 3**) with computer data acquisition of systems physiology body properties, we have begun testing whether loss of Kv1.3 channel can reduce weight, respiratory quotient, body fat, and insulin sensitivity in these models of disease.

Because the nature of these later transgenic mouse projects is a bit risky and lies outside my current funding at the NIDCD, I keep them supported through restraining experiments to critical pilot studies, branching resources by collaboration, and use level judgement as to when to turn the project or drop it completely. It allows me to uncover fresh areas of neurophysiology that might be of high importance to the scientific community, while retaining stable progress in my currently proposed or committed projects.

Chemical Communication Through Pheromones in the Vomeronasal Organ

A smaller proportion of my laboratory is devoted to the functional regulation of chemo-discrimination in the vomeronasal organ (VNO) using reptilian models. We have optimized isolation procedures to harvest single VNO neurons from two different reptile species with reproductive periods that are seasonally staggered, allowing us the capacity to record pheromone responses approximately 9 months per year[14]. We field trap the stinkpot musk turtle (*Sternotherus odoratus*) locally here in Florida, April to October, and the Chilean lizard (*Liolaemus bellii*) in the Farralones Mountains outside Santiago, Chile in January for recordings Jan. to May. While both species make exceptional physiological preparations due to low oxygen and temperature requirements, the use of two species also provides an experimental complement. The musk turtles have a very large and accessible VNO, unlike the rodent whose minute organ is encapsulated inside the vomer bone below the incisors. The number of viable neurons harvested is very high and simultaneously few animals are required for suitable protein biochemistry determinations of the transduction proteins[8;30]. The Chilean lizards, unlike the musk turtles, cooperate in captivity to respond with discreet behavior displays (tongue flicking, posturing, scent marking, robotic orienting, tail waiving territoriality, head bobbing as the animal pulls pheromone through VNO pump/cavity) when presented with reproductive pheromones. We have learned how to extract pheromone secretions (musk, cloacal extracts, skin pheromones, urine, fecal) from both these species (**Figure 4**).

Like the field of olfactory transduction, chemical communication through pheromone molecules has been largely dominated and greatly advanced through the research of molecular biologists, whom have discovered the localization and identity of the transduction machinery presumed operational to encode odor information. A convincing level of functional expression of the G-protein coupled transduction proteins to encode pheromone molecules has evaded researchers. More elusive still has been a straight forward functional dissection of the transduction events by electrophysiology. Thus far, mammalian pheromone transduction studies in the VNO have warranted the use of large scale functional imaging[24], multielectrode array[18], or *in vivo* array recording[26] due to the low proportion of cells in a population responding to a pheromone stimulus. The high responsivity in our two reptilian models [14], where 40-53% of neurons respond to at least 1 of 5 pheromone-containing body secretions compared with 1-3% in mammals (**Figure 5**), now makes single cell electrophysiology a practical avenue. It will now be possible to determine the ionic basis and calcium sensitivity of the chemosignal-activated conductances, to characterize the single channel biophysical properties of these conductances, and to test whether the assembly of the TRPC2/IP3R3 complex we have biochemically discovered through co-immunoprecipitation[8] promotes or inhibits the functional chemical-activated current in these neurons. Recently armed with an international scientific exchange program with a Chemical Ecologist from Chile, I am excited to integrate the wealth of ecological-based reproductive behavior known for *Liolaemus bellii* with that of our devised single cell electrophysiology approaches so that we can probe how versatile cell signaling can be and how ion channel complexes may affect reproductive behavior. Our preliminary data have lead us to hypothesize that the properties of the VNO or the composition of the chemosignals that it detects, are not static, but change as a consequence of internal or external factors such as ontogeny or seasonality. Secondly we have found the identified transduction channel, the transient receptor potential channel 2 (TRPC2), likely does not operate in isolation, but is regulated by protein-protein interactions

with scaffolding receptors and proteins (**Figure 6**). Such regulation may provide flexibility in transducing chemical information from different body sources or that may change seasonally in concordance with the biology of the animal. We are determining whether seasonality or different body sources affect the chemical discrimination of pheromones. Discrimination will be ascertained using an integrative approach with overlapping data acquired from pheromone-evoked behavior displays[22;23], spatial patterns of neuronal activation (using pheromone plus Agmatine (AGB)-activity dependent mapping)[27;36], and single channel recording using electrophysiology. Molecular mutagenesis, gene-targeted deletion, and co-immunoprecipitation will be used to define a functional role for the ion channel complex surrounding the transduction channel. For example, since the TRPC2 sequence demonstrated a common binding site for IP3R and calmodulin as well as the adaptor protein Homer[32;33], we sought and found isoform-specific expression of Homer protein in the VNO. We hypothesize that the adaptor protein Homer dimerizes and utilizes a coiled coil domain to bridge TRPC channel family members and the IP3-R complex together and that the complex may be primed through pheromone-stimulation, seasonality, or general depolarization. We have compiled a strong set of preliminary data to the IBN (Sensory Systems) at the NSF; which incorporates these ideas and is currently under review. In summary, the goal of our second area of research is not unlike that contrived for the olfactory bulb research above, in that it represents a multidisciplinary approach from behavior to electrical signaling, and we hope to understand how chemical communication is regulated at the level of the ion channel to accommodate whole animal life changes during reproductive seasons.

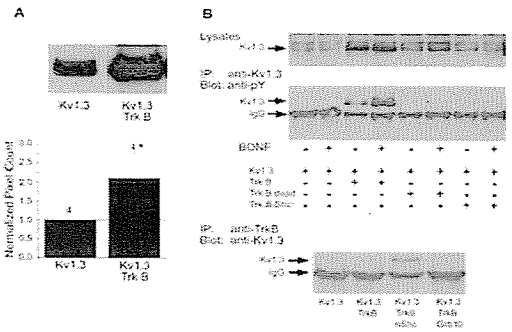

Figure 1: TrkB co-transfection (A) causes upregulation of Kv1.3 channel protein. Phosphorylation of Kv1.3 is lost if either the kinase (TrkB dead) or adaptor protein interactive site (TrkB Shc -) is mutated (B, TOP). Kinase and channel can only form modulatory complex in presence of adaptor protein nShc (B, BOTTOM).

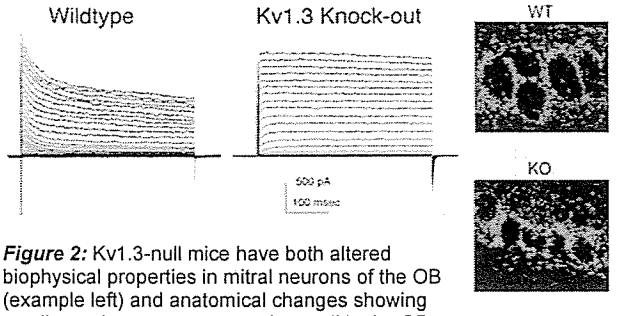

Figure 2: Kv1.3-null mice have both altered biophysical properties in mitral neurons of the OB (example left) and anatomical changes showing smaller and more numerous glomeruli in the OB (right). These properties force one to investigate whether the "super-smeller capacity" (10,000 x that of wt animals) of these null mice is attributed to electrical changes, increased protein interactions, or circuitry changes in the absence of the ion channel protein.

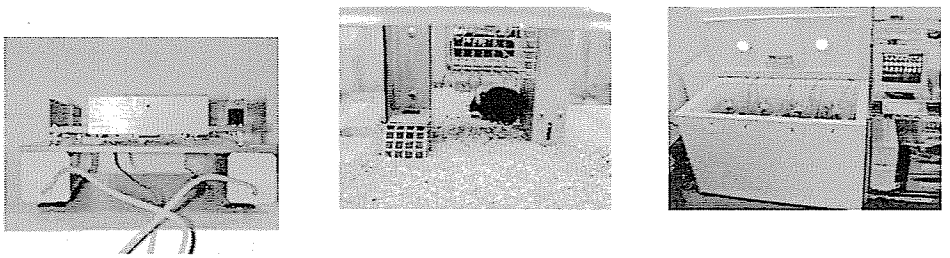

Figure 3: Kv1.3-null mice weigh less and have the same caloric consumption as wt mice. Locomotor activity (left), ingestive behaviors (center), and respiration (right) can be continuously monitored through computer data acquision using FSU engineered equipment designed for systems physiology.

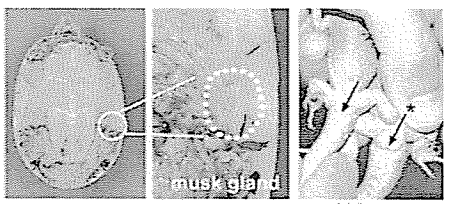

Figure 4: Phermone-secreting glands in reptiles, Left = *S. odoratus* (musk turtle) and Right = *L. Bellii* (Chilean lizard). * = Male, swollen

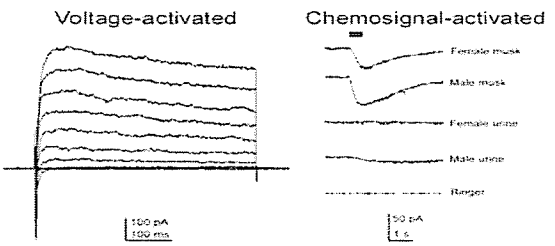

Figure 5: Whole-cell recordings from both *S. odoratus* (musk turtle, shown here) and *L. Bellii* (Chilean lizard) demonstrate that chemosignal-activated (pheromone) conductances can be routinely recorded during the reproductive season of these reptiles and that responsivity is highly tuned. (Left) Family of voltage-activated currents evoked to depolarizing voltage steps. (Right) Single VN neuron is stimulated with 4 pheromone-containing secretions that mediate mating behaviors in the animal.

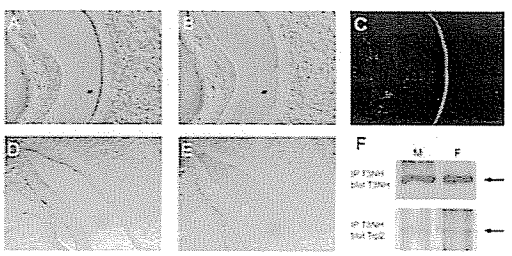

Figure 6: Top = 10 µm cryosection of VNO labeled with αTRPC2 (B-C). Bottom left (E), same αIP3R3. Bottom right (F), Immunoprecipitated (IP) IP3R3 is blotted with αTRPC2 demonstrating a protein-protein partner. (A, D) Dapi stain.

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