Comp Question 2012 – NRSA proposal

For female mammals, reproduction is an energetically expensive function and many aspects of energy balance regulation are altered to meet the energy demands of pregnancy and lactation (Augustine, Ladyman, & Grattan, 2008; Roberts & Coward, 1984). A rich literature, which for the most part stems from work with laboratory female rodents, provides compelling evidence that the changes involve both metabolic as well as behavioral adaptations and engage central as well as peripheral neural and neuroendocrine systems (García et al., 2003; Ladyman, Sapsford, & Grattan, 2011). A lot of attention has been directed to the role of ovarian and pituitary hormones, as well as those of peptides of peripheral and hypothalamic origin in the orchestration of these responses to energy demands; the hormonal profile of female mammals and its impact on central peptidergic systems change in remarkable ways as animals go through pregnancy and lactation.

For this question, assume that the principal investigator (PI) of your research group just returned from a sabbatical doing field work in the rain forest of Brazil. She has brought to the lab a small rodent species that shares many endocrine and behavioral features with laboratory rodents, such as mice and rats. What is remarkable about these animals is that they are strongly monogamous and both males and females take care of the pups until weaning. During the females' pregnancy both sexes cooperate in the building of nests and in the hoarding of food. Preliminary data from your PI's sabbatical work show convincingly that during the pregnancy and lactation of their mates, the males of a breeding pair display many changes in feeding and energy balance that resemble those displayed by pregnant and lactating female laboratory rats. Prominent among these changes in energy balance is a salient hyperphagia and a partitioning of fuels in favor of storage, rather than immediate utilization.

Based on the preliminary behavioral and metabolic data already available about the males of this species (i.e., their hyperphagia and conservative metabolism), your task is to develop a research plan to elucidate the mechanisms responsible for these phenomena in males, with attention to, e.g., hypothalamic neuropeptides (see Brogan, Grove, & Smith, 2000), and to do so by generating and testing hypotheses presented as a research plan typical of NRSA pre-doctoral proposals. Your plan should be informed by the extensive literature about reproduction and energy balance in female rats and the pronounced sex differences present in mammals.

Structure your answer as follows:

1. Prepare a Specific Aims page that identifies the hypotheses to be initially tested. Note that you may have different aims for the different hypotheses or, alternatively your first aim may involve an experiment that could potentially differentiate among competing hypotheses, with the other aims further challenging the hypotheses or hypothesis that survives the initial challenge. Limit this section to 2-3 specific aims. The Specific Aims page is single-spaced; all the other pages of the body of the proposal are double-spaced; the page limit is 12 pages not counting the reference section. Please number your pages.

2. Provide a background section explaining the significance of your research and how your approach is innovative.
3. Provide a detailed description of the experiments that you propose in order to test the hypotheses presented under each specific aim. There is no prescribed or preferred level of analysis for this section. The particular experiments may involve molecular, cellular, system or organismic levels of analysis. What is important is that the experiments proposed serve to differentiate among the alternative hypotheses you present. In this section you should have enough details about the experimental design and proposed treatment of the data to make it possible for reviewers to evaluate the merit of what you want to measure and how you will interpret possible outcomes. For each experiment identify the predicted outcome from each hypothesis, and how the different outcomes may allow you to falsify or support each hypotheses.
4. Include a reference section with full bibliographical information for each paper cited in your proposal. Below is a reading list to get you started but ultimately, it is expected that you will read and discuss more than these five.

Reading list

Augustine, R. A., Ladyman, S. R., & Grattan, D. R. (2008). From feeding one to feeding many: hormone-induced changes in bodyweight homeostasis during pregnancy. *The Journal of Physiology*, *586*(2), 387–397.

Brogan, R. S., Grove, K. L., & Smith, M. S. (2000). Differential regulation of leptin receptor but not orexin in the hypothalamus of the lactating rat. *Journal of Neuroendocrinology*, *12*(11), 1077–1086.

García, M. C., López, M., Gualillo, O., Seoane, L. M., Diéguez, C., & Señarís, R. M. (2003). Hypothalamic levels of NPY, MCH, and prepro-orexin mRNA during pregnancy and lactation in the rat: role of prolactin. *FASEB Journal*, *17*(11), 1392–1400.

Ladyman, S. R., Sapsford, T. J., & Grattan, D. R. (2011). Loss of acute satiety response to cholecystokinin in pregnant rats. *Journal of Neuroendocrinology*, *23*(11), 1091–1098.

Roberts, S. B., & Coward, W. A. (1984). Lactation increases the efficiency of energy utilization in rats. *The Journal of Nutrition*, *114*(12), 2193–2200.

2011

The Problem

Stroke is the third leading cause of death in the US and the leading cause of adult disability. Yet, the treatment options for stroke are extremely limited. Much stroke research has focused on trying to salvage dying neurons or promote neurogenesis. These studies have yielded useful information, but have not produced new treatments[1]. The failure of multiple clinical and pre-clinical trials resulted in the development of a set of guidelines for translational stroke research. These are referred to as the STAIR Guidelines[2] and you should be sure to follow them in your proposed studies.

Your PI has identified a drug that seems to reduce neuronal death in the cortex and striatum after an ischemic stroke, the compound is called Moneymaker. Your NRSA application should focus on testing the therapeutic potential of Moneymaker and identifying the mechanism by which Moneymaker has its effect. Moneymaker could reduce neuronal death by apoptosis, it could also alter the inflammatory response or increase neurogenesis or vascluogenesis / angiogenesis. You are free to choose what type of compound Moneymaker is and what type of receptor it binds to. Potential drug classes are steroids, free radical scavengers, anti-inflammatory agents, statins or growth factors. Information about the type of Moneymaker compound and its receptors should be provided in the background section of your NRSA.

Your Task

Your task is to write an NRSA type proposal which should contain the following elements:

1. A specific aims page - this should include no more than 2 aims and clear testable hypotheses associated with each of these aims (your aims page should be no more than 1 single spaced page)
2. A background with section detailing the significance of your proposed research and why your studies are innovative (2-3 pp)
3. A preliminary data section - you have been provided with a PowerPoint presentation containing some images that you can incorporate into this section as your preliminary data. You should also feel free to generate your own graphs for this section. Consider carefully what data would be necessary to support your hypothesis. Be sure to describe how you collected this data and what it means in relation to your proposed studies. (2-4 pp)
4. A description of the studies you propose to do this should contain the following elements (6-7pp):
    - a description of the animals / cells you intend to use
    - a detailed description of treatments and experimental endpoints (in vivo or in vitro studies and or behavioral outcomes)
    - a discussion of the expected outcomes and why you expect these
    - a discussion of alternative outcomes and approaches
    - a description of the statistical analysis you plan to use
5. You should include references in your proposal, the reference list will not count towards the page limit.

Remember, NRSA grants fund one person's research for 2 years, do not propose more studies than can be done in that time. Your proposal should adhere to the NIH NRSA format (consult NIH webpage if you have questions about the requirement, look for the predoctoral fellowship F31 mechanism). The Aims Page should be provided single spaced, the rest of the text body should be double spaced (10 - 12 pages).

1. Donnan GA. The 2007 Feinberg lecture: a new road map for neuroprotection. *Stroke* 2008; **39**(1)**:** 242.

2. Fisher M, Feuerstein G, Howells DW, Hurn PD, Kent TA, Savitz SI, Lo EH. Update of the stroke therapy academic industry roundtable preclinical recommendations. *Stroke* 2009; **40**(6)**:** 2244-2250.