Poster #84

Effect of PH94B and Steroid Hormones on Nasal Electrogram Responses and Biomarkers of Autonomic Nervous System Activity in Healthy Human Subjects

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INTRODUCTION

- Social anxiety disorder (SAD) is a common and disabling condition with an estimated lifetime prevalence of 12.1% for adults in the United States[1]
- Hyperactivation of the amygdala is involved in the pathophysiology of SAD,[2] and the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is a central regulator of anxiety[3,4]
- PH94B (3β-androsta-4,16-dien-3-ol) is an investigational synthetic neuroactive pherine nasal spray that has demonstrated efficacy in two previous SAD studies[5,6] and is currently under Phase 3 development for the acute treatment of SAD and other anxiety disorders
  - It is proposed that PH94B binds to peripheral chemosensory neurons in the nasal mucosa that activate subsets of olfactory bulb neurons to modulate the olfactory-amygdala neuronal circuits of fear and anxiety[5,7]
  - When stimulated, these neural circuits regulate the release of the inhibitory neurotransmitter GABA in the amygdala, attenuating activity of the sympathetic autonomic nervous system and neural circuits underlying anxiety[7,8]

OBJECTIVE

- In order to differentiate the unique mechanism of action of PH94B from other steroids, we compared the effect of intranasal PH94B administration with intranasal administration of steroidal hormones and control on the electrogram of the nasal chemosensory mucosa (EGNR) and on autonomic nervous system parameters in healthy adult subjects

METHODS

Study Design

- This was a single-blind randomized study performed in 16 healthy adults (8 men and 8 women) age 20 to 60 years. All experimental procedures were conducted after participants signed informed consent
  - Subjects with nasal septum perforation or past/current drug or alcohol use were excluded
- Each subject was invited to participate in two study sessions 2 to 3 days apart, during which test articles and control were administered intranasally
  - Subjects randomly received control (propylene glycol) and study drugs (PH94B, estradiol-β, progesterone, cortisol, and testosterone, 0.4 µg each dissolved in propylene glycol)
  - Study drugs and control were administered intranasally 30 minutes apart as a 1-second aerosolized pulse using a Multifunctional Miniprobe (MM®)

Measurements

- EGNR was assessed using a recording electrode positioned on the surface of the nasal chemosensory mucosa of the medial and dorsal nasal septum
- Noninvasive recording electrodes were placed on the skin surface to monitor the following autonomic reflex activity:
  - Respiratory rate was recorded with a strain gauge placed around the lower thorax
  - Heart rate was measured from the electrocardiogram (standard bipolar I)
  - Electrodermal activity was recorded as skin conductance from the palmar surface of the third and fourth finger
- Autonomic parameters were recorded in 5-minute epochs before and 15-minute epochs after intranasal drug administration
- Recordings were amplified, digitized, and continuously computer monitored and stored for further offline processing and analysis
- The amplitude and frequency of the digitized signals were measured using ACQKnowledge software (Biopac Systems)
- At the conclusion of recording for each drug, subjects provided feedback on their experience and were asked about any change in their state of well-being

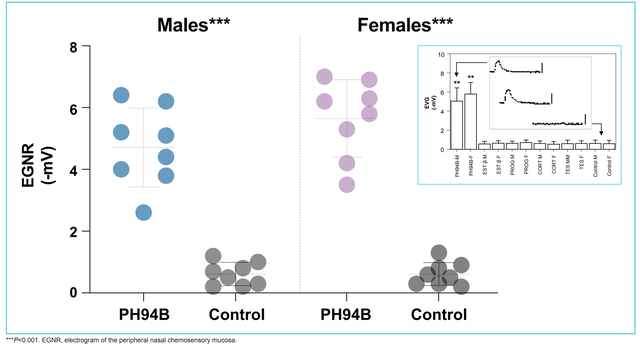
Statistical Analyses

- The mean and standard deviations were calculated, and paired comparisons between treatments were conducted using the Student's t-test

RESULTS

- Intranasal administration of 0.4 µg PH94B resulted in a statistically significant increase in mean EGNR amplitude compared with control (5.0 vs 0.6 mV for men, 5.7 vs 0.6 mV for women; $P<0.001$ for each; **Figure 1**)
  - Administration of 0.4 µg of each steroidal hormone tested yielded EGNR values similar to those observed with control in both males and females (**Figure 1, Inset**)

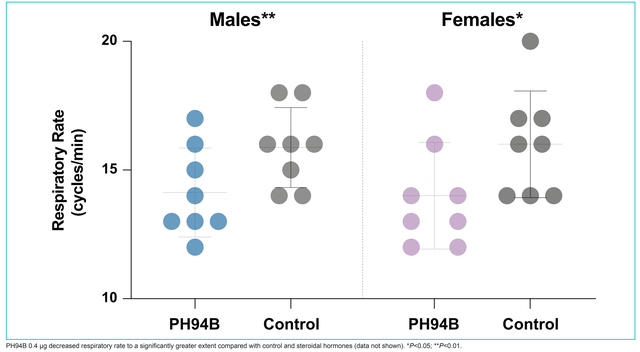
Figure 1. EGNR Amplitude



***$P<0.001$. EGNR, electrogram of the peripheral nasal chemosensory mucosa.

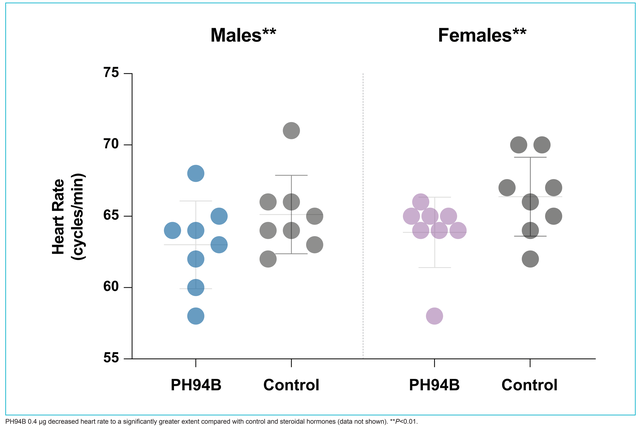
- Intranasal administration of 0.4 µg PH94B significantly decreased respiratory rate (**Figure 2**), heart rate (**Figure 3**), and electrodermal activity (**Figure 4**) compared with control in both men and women
  - Mean respiratory rate, heart rate, and electrodermal activity changes after steroidal hormone administration (data not shown) were similar to those observed with control administration in both males and females

Figure 2. Respiratory Rate



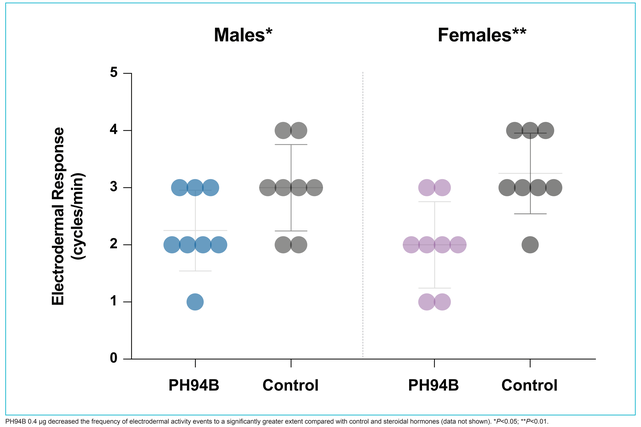
PH94B 0.4 µg decreased respiratory rate to a significantly greater extent compared with control and steroidal hormones (data not shown). *$P<0.05$; **$P<0.01$.

Figure 3. Heart Rate



PH94B 0.4 µg decreased heart rate to a significantly greater extent compared with control and steroidal hormones (data not shown). **$P<0.01$.

Figure 4. Electrodermal Response



PH94B 0.4 µg decreased the frequency of electrodermal activity events to a significantly greater extent compared with control and steroidal hormones (data not shown). *$P<0.05$; **$P<0.01$.

- During interview inquiries, 13 of the 16 subjects (81%) reported they felt more relaxed and less tense 20 minutes after PH94B administration, but not after administration of placebo or steroidal hormones
- No adverse events were reported by subjects

LIMITATIONS

- The findings reported are limited by the small sample size of participants

DISCUSSION

- Intranasal administration of 0.4 µg PH94B significantly increased EGNR amplitude and significantly lowered sympathetic autonomic reflex activity
  - Physiologic range reductions were observed in respiratory and heart rates, and the frequency of electrodermal activity events was also reduced following intranasal PH94B administration
  - Intranasal administration of steroidal hormones produced effects that did not differ significantly from those of intranasal control
  - The increased amplitude of the EGNR observed after PH94B administration was consistent with receptor activation as reported previously[7]
- Changes in autonomic activity following PH94B administration were consistent with a sympatholytic effect leading to calmness and relaxation
- These changes occurred rapidly, and most subjects reported feeling more relaxed and less tense within 20 minutes of administration of PH94B, but not after administration of steroidal hormones or control

CONCLUSIONS

- Intranasal administration of PH94B to healthy subjects, but not control or steroidal hormones administration, activated peripheral chemosensory cells in the nasal mucosa as evidenced by the increase in EGNR amplitude, and rapidly reduced sympathetic nervous system tone within physiologic range
- When questioned, subjects reported feeling more relaxed and less tense after receiving PH94B
- These data support ongoing studies of PH94B for the acute relief of anxiety

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Disclosures

Louis Monti, Rita Hanover, Ester Salmán, Ross A. Baker, Jaakko Lappalainen, and Mark A. Smith: Employees and owners of stock or stock options in VistaGen Therapeutics, Inc.

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