The Neurochemical and Anatomical Profile of Resilience

Presenter: Gabriel Vargas[1,2]

Mary C. Vance,[3]

1. School of Systems of Biology, George Mason University, Fairfax, VA, USA
2. School of Medicine, Uniformed Services University of the Health Science, Bethesda, MD, USA
3. Health, Safety and Work-Life Service Center, United States Coast Guard, Alameda, CA

INTRODUCTION

Resilience is the ability to successfully adapt to stress and adversity. Resilient individuals are able to return to normal after being exposed to a traumatic or chronic stressor, thereby minimizing psychopathologies like PTSD, depression, and other psychiatric disorders due to trauma[1]. This is especially important in populations that are subject to work-related trauma, such as military service members and first responders.

High plasma and CNS levels of Neuropeptide Y (NPY) have previously been identified as a biomarker of resilience.[2, 3] Previous works demonstrate NPY is released during stress with norepinephrine to attenuate the sympathetic nervous system[3,4]. The aim of this scoping literature review is to assess the use of Neuropeptide Y as a biomarker as well as to identify other potential neurochemical or neuroanatomical markers associated with resilience. The results from this review will provide further insight into understanding the neurobiology of resiliency and will provide the basis for assessing changes in resiliency over time. It may also identify areas where further research is needed.

METHODS

PubMed searches were performed using the search ""((Neurochemical OR neurobiological OR anatomical) AND (stress AND resilience)" for a total of 47 results. The article, "Adapting to Stress: Understanding the Neurobiology of Resilience," was used as the primary literature source. Then, nine other studies were included in the final scoping review.

RESULTS

In our review of the literature, we found 5 anatomical markers and 13 neurochemical markers that are implicated in resilient animal or human models.

The neurochemical markers dopamine, norepinephrine, serotonin, cortisol, dehydroepiandrosterone (DHEA), allopregnanolone (ALLO), adrenocorticotropic releasing hormone (ACTH), corticotropic releasing hormone (CRH), brain-derived neurotropic factor (BDNF), galanin, Glutamate, GABA, and endocannabinoids were all found to have correlation to resilience[1,3]. Additionally, a possible stress-resistance neurochemical profile was identified to consist of high levels of NPY, galanin, DHEA, ALLO, and low levels of CRH[4].

We also found anatomical markers that may have predictive power to assess resilience. The first involved an in vivo single-photo emission computerized tomography (SPECT) imaging study that showed increased striatal dopamine transporter (DAT) density in patients with PTSD when compared to traumatized controls without PTSD[5]. Other anatomical markers included increased gray matter and blood flow to areas involving emotional regulation, notably the amygdala, but also the middle temporal gyrus, right ACC, and subcallosal gyrus[6-9]

Regarding dynamic physiological markers that reflect resilience, we identified ACTH as a neurochemical marker that was downregulated long-term during experimental studies after exposure to stress status-post a mindfulness meditation intervention[10].

CONCLUSION

Based on this review, further research is needed to determine if biomarkers change with resilience. One way to study this would be to track a longitudinal cohort that is voluntarily exposed to trauma. We identified a special population exposed to voluntary trauma and training during a two-to-three-year course. The Special Forces, colloquially known as the "Green Berets," are an ideal cohort for the study because they are: organized in a cohort, well tracked, conduct a specific training regimen, exposed to controlled physical and mental trauma multiple times, and have a measurable outcome (pass vs fail). Many will then go on to be exposed to trauma while participating in combat missions around the world.

We hypothesize taking measurements of biomarkers of the cohort during multiple points of the course may reveal a dynamic set of physiologic markers that reflect resilience changes secondary to training. If there is a significant correlation, it will further support a "resilient neurochemical profile" and the possibility that certain interventions can significantly increase resilience.

BIOMARKERS BRIEF DATA SHEET

Sympathetic System Hormones

Norepinephrine (NE)

Stimulus: Many, including stress
Effect: Sympathetic activation
Deleterious effects: "Increased regulation of brain NE systems is observed in patients with PTSD"
Effect Location: CNS and serum
Tested via Plasma: UNK

Neuropeptide Y (NPY)

Stimulus: Many, including stress
Effect: Attenuates sympathetic response
Origin: Widely distributed in CNS
Effect Location: Diffuse in CNS
Tested via Plasma: Yes
Correlation Type: Higher NPY is correlated with decreased PTSD risk.
***Studies conducted in SERE School with promising results**

Hypothalamic-pituitary-adrenal Axis

CRH

Stimulus: Stress / Low Cortisol
Purpose: Stimulates ACTH to control the HPA Axis
Origin Location: Hypothalamus
Systemic: No
Tested via Plasma: Plasma and CSF
Correlation Type: Depends on CRR1 (anxiogenic) and CRHR2 (anxiogenic or anxiolytic) receptor concentration
Feasibility: Low

ACTH

Stimulus: CRH
Purpose: Activates Cholesterol Desmolase for steroid production.
Origin Location: Anterior Pituitary
Effect Location: Zona Glomerulosa
Tested via Plasma: Yes

Cortisol

Stimulus: ACTH
Purpose: Physiologic stress adaptation
Precursor(s): Many, cholesterol-based
Origin Location: Zona Fasciculata
Tested via Plasma: Yes
Correlation Type: Lower cortisol is correlated to increased risk of Depression and elevated levels with PTSD

DHEA & DHEA-S

Stimulus: ACTH
Purpose: Block effects of Glucocorticoids
Precursor(s): Cholesterol
Pregnenolone
17-hydroxypregnenolone
Origin Location: Zona Reticularis
Tested via Plasma: Yes
Correlation Type: People with higher DHEA or higher DHEA-to-cortisol ratio faired better under acute stress in SERE and Combat Diver Qualification Course (CDQC)
***Studies conducted in SERE and CDQC with promising results.**

PURPOSE STATEMENT

1. Determine if physiologic biomarkers can be used to develop a stress-resistant profile.
2. Contingent on 1, determine if the biomarkers in the stress-resistant profile change to a more resilient profile after an intervention. If so, the intervention would be known as stress inoculation.
3. Quantify the stress-inoculation effect of training interventions objectively using hormone profile.

Other Biomarkers

Allopregnanolone (ALLO)

Stimulus: Stress
Effects: Regulatory effects of HPA
MOA: $GABA_A$ receptor complex
Testing fluid: Serum / CNS fluid
Correlation Type: Decreased ALLO levels were noted in MDD, anxiety disorders, impulsive aggression, and schizophrenia.

Brain-derived Neurotropic Factor (BDNF)

Physiologic Effect: BDNF supports neuronal proliferation
Location: Amygdala, Hippocampus, PFC, basal forebrain
Tested via Plasma: No
Significance: Implicated in mood and anxiety disorders
Correlation: Central administration of BDNF has antidepressant-like effects

SPECIAL FORCES QUALIFICATION COURSE (SFQC)

Special Forces Assessment & Selection (SFAS)

Duration: 21 days
Est. Pass Rate: 9% - 20%
Longest Sleep Deprivation: 32 hr
Ave. Weight Lost: 10 lbs
Video of SFAS

Small Unit Tactics (SUT)

Duration: 42 days
Est. Pass Rate: 81% - 89% pass
Longest Sleep Deprivation: 72 hours
Ave. Weight Lost: 12 lbs
*Anecdotally the hardest part of the entire course.

Survival Evasion Resistance & Escape Level C (SERE - C)

Duration: 28 days
Est. Pass Rate: 98%
Longest Sleep Deprivation: 72 hours
Average Sleep: 4 hours
Ave. Weight Lost: 15 lbs
Note: *Course includes physical & mental abuse, sleep deprivation, and food deprivation.
Video of SERE

Robin Sage

Duration: 28 days
Est. Pass Rate: 85%
Longest Sleep Deprivation: 48 hours
Ave Sleep per night: 2 hours
Ave Weight Lost: 6 lbs
Robin Sage

Initial Tests | Pre-phase Tests | Post-phase Tests | Pre-phase Tests | Post-phase Tests | Pre-phase Tests | Phase Pass | Overall Attrition | Final Tests

Test serum before and after every iteration for multiple biomarkers & conduct resiliency questionnaire.
-Compare the biomarkers between three cohorts- Pass, Fail, or Voluntary Withdrawal (Quit).