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RESEARCH HIGHLIGHT

A holistic gene-network approach linking stressor heterogeneity to resilience and susceptibility

Toni-Lee Sterley[1]✉ and Jaideep Bains[1]

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Stress is something everyone is familiar with. Whether it's a traumatic event, work deadlines, illness, or a pandemic, everyone experiences "stress". How one copes with stress depends on many factors, including past experiences, the context of the stressor, and genetic make-up. Yet, while the stressor and coping strategies employed vary from person to person, stress often has similar outcomes. Many individuals experience heightened anxiety that is often accompanied by an urge to withdraw from others. If left untreated, stress can lead to depression. How is it that such variation in stressors and individuals can manifest in similar behavioural phenotypes? And what is different in those individuals who remain resilient to stress-induced behavioural changes?

In their recent paper published in this issue, Caradonna et al [1]. begin to tackle these questions by searching for genomic correlates of stress-induced behavioural phenotypes across disparate preclinical models of stress, each varying in hormonal, genetic and environmental factors (Fig. 1). On behavioural phenotyping, they found that mice treated with corticosterone (CORT, the rodent equivalent of the human stress hormone, cortisol) had increased anxiety- and depression-like behaviours, regardless of whether they were wild type or were heterozygous for the gene encoding brain-derived neurotrophic factor Val66Met (BDNF het-Met, Fig. 1). From the social defeat cohort, two populations emerged defined by social interaction scores –resilient (with higher social interaction scores) and susceptible. Not surprisingly, mice that had been housed in an enriched environment prior to social defeat (Fig. 1) showed greater resilience (21%) than those from standard housing (9%). Furthermore, environmental enrichment increased social interaction in both resilient and susceptible populations, suggesting that it buffers against the emergence of a socially avoidant phenotype. Overall, the behavioural phenotyping showed increased anxiety-like, depression-like, and socially avoidant behaviours in some experimental groups—behaviours that typically arise after stress, and which we will refer to collectively as "affective behaviours" as Caradonna et al. have in their study [1].

For all changes in behaviour there must exist an altered neurobiology, and for changes in neurobiology that are persistent, there must be changes in the expressions of genes coding for proteins involved in neurobiological mechanisms. To identify the neural genomic correlates of behavioural phenotypes, Caradonna et al. focused their investigation to the ventral hippocampus, a brain region that is sensitive to the impact of stress and highly implicated in affective behaviours. They applied whole-genome RNA-sequencing (RNA-seq) to identify differentially expressed genes followed by a stratified RRHO test. They found significant overlap in genes downregulated in CORT-treated mice and susceptible mice from standard housing [1], suggesting that CORT and social defeat employed similar genetic alterations to increase affective behaviours. Another intriguing result was significant overlap in genes upregulated in vehicle-treated mice and in susceptible mice from an enriched environment [1]. Enrichment shifted the overlap away from CORT-treated mice, suggesting that it protected against the genomic changes associated with stress susceptibility. While this shift was not sufficient to prevent a susceptible phenotype (as defined by social interaction scores), it is concordant with behavioural results showing reduced social avoidance in susceptible mice from an enriched environment [1].

Caradonna et al. also performed weighted gene co-expression network analyses on RNA-seq data to determine whether converging groups of genes showed significance for co-expression. Two modules, labelled cyan and yellow, emerged as relevant. The cyan module included upregulated genes of CORT-treated mice and susceptible mice from standard housing, a pattern identical to the RRHO analysis. Mice from these groups also displayed increased affective behaviours, i.e., behavioural susceptibility. The yellow module included differentially expressed genes that were upregulated in vehicle-treated BDNF het-Met mice and susceptible mice from an enriched environment, a pattern similar to RRHO findings. These groups showed reduced affective behaviours, consistent with behavioural resilience (Fig. 1).

The network-based analyses allowed Caradonna et al. to identify several "hub genes"—highly connected genes that drive the function of the entire network. In the cyan module, for example, one hub gene was Wdr7—a gene that has been implicated in depression and alcohol comorbidity in humans [2]. In the yellow module, one hub gene was Tnnt1—a gene that is expressed in mice after being injected with the antidepressant ketamine [3]. In general, the cyan and yellow modules included hub genes associated with stress susceptibility or resilience, respectively [1].

One limitation of the study is that it includes only males. Caradonna et al. explain that in their hands, female mice do not show increased affective behaviours following oral CORT-treatment. This agrees with what others in the stress field have noted (now that the use of females is becoming more prevalent)—that inducing a depressive-like phenotype using CORT treatment is more difficult in female rodents than males (reviewed here [4]).

[1]Department of Physiology & Pharmacology, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada. ✉email: tonilee.sterley@ucalgary.ca

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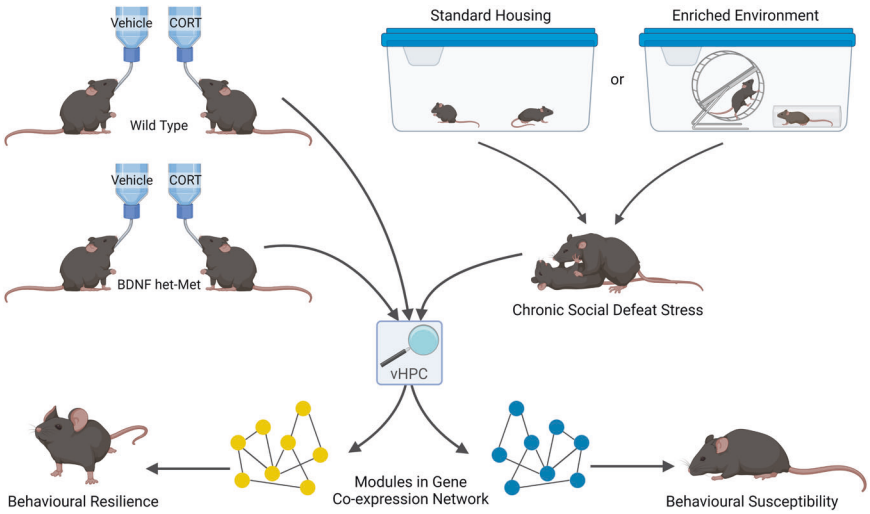

Fig. 1 Converging gene networks regulate behavioural phenotypes of susceptibility or resilience following different preclinical models of stress. In one model, mice received corticosterone (CORT, the rodent equivalent of the human stress hormone, cortisol) in their drinking water for several weeks, mimicking the persistent elevation of stress hormone that occurs during chronic stress. Of these mice, some were heterozygous for the gene encoding brain-derived neurotrophic factor Val66Met (BDNF het-Met); this variant, in which the intracellular trafficking and activity-dependent release of BDNF is disrupted, has been proposed as a model for genetic vulnerability to stress. In a second cohort, mice were housed in standard housing or an enriched environment for several weeks before undergoing chronic social defeat stress, a model of social stress where mice are repeatedly attacked by an aggressor. Network-based co-expression analyses identified gene modules that differed in topological overlap. Two of these modules, arbitrarily labelled yellow and cyan, included differentially expressed genes across all experimental groups. The yellow module included genes that were differentially expressed in mice that also showed behavioural resilience to stress, while the cyan module included genes differentially expressed in mice that showed behavioural susceptibility. Created with BioRender.com.

Additional studies must be conducted with females to explore behavioural changes, or lack thereof, following varying stress paradigms, and the related genomic shifts. A second limitation is the sparse use of behavioural assays; Caradonna et al. used one test for anxiety-like and one for depression-like behaviours in the CORT-treated cohort, and a social interaction test in the social defeat cohort [1]. Subjecting mice from varying stress paradigms to the same battery of behavioural tests would provide a full picture of how the varying stress protocols impact affective behaviours.

Overall, this report by Caradonna et al. holds tremendous value, and fits well with other findings in the field. Others have found similar stress-induced differentially expressed genes using different stress models in different brain regions [1] (Supplementary Table 4)—this shows that the hub genes identified by Caradonna et al. have validity beyond the stress paradigms they used and beyond the ventral hippocampus. Future studies could use these findings to probe the importance of single hub genes in behavioural phenotypes. The real value of this work, however, is that it provides a holistic network of the genetic changes associated with stress-related disorders, moving away from a "one-gene-one disease" paradigm. The data provided here may facilitate an eventual move towards the development of therapeutic interventions that target whole connectivity networks rather than single genes [1].

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Toni-Lee Sterley.