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PSYCHIATRIC DISORDERS

The stresses of womanhood

Post-traumatic stress disorder (PTSD) is a maladaptive psychiatric response to disturbing experiences that affects many individuals over the course of a lifetime, but the biological processes underlying the disorder are poorly understood. Now, Ressler *et al.* have identified a sex-specific association of pituitary adenylate cyclase-activating polypeptide (PACAP) and its receptor (PAC1) with PTSD, which could be useful in improving the diagnosis and treatment of the disorder.

PACAP is a hormone that serves many biological functions, including regulation of the cellular stress response. To investigate the possible role of PACAP signalling in psychological stress, Ressler *et al.* studied a cohort of more than 1,200 highly traumatized subjects with and without PTSD.

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They began by measuring levels of PACAP38 (a PACAP isoform containing 38 amino acid residues) in blood samples from 64 subjects. They found that in females, but not in males, PACAP38 levels correlated with the diagnosis and psychological symptoms of PTSD. Moreover, women — but not men — with high circulating levels of PACAP38 displayed an enhanced startle response in a fear-conditioning paradigm, providing physiological evidence for a link between PACAP signalling and stress responses in females.

Next, the authors searched for a genetic association between PTSD and variants of the genes encoding PACAP (*ADCYAP1*) and PAC1 (*ADCYAP1R1*) in a sample of over 1,200 individuals. Of the 44 single-nucleotide polymorphisms (SNPs) studied, only the *ADCYAP1R1* SNP (designated rs2267735) showed an association with PTSD, and this link was found in females only. Importantly, this SNP occurs within the oestrogen response element of *ADCYAP1R1*. This complements studies showing that oestrogen modulates *ADCYAP1R1* expression and could explain the sex-specific associations identified in the current study. As with PACAP38 levels, the presence of the rs2267735 SNP predicted a heightened startle response in a fear-conditioning paradigm in women.

Epigenetic mechanisms are thought to have a role in regulating the long-term effects of severe trauma. Consistent with this suggestion, Ressler *et al.* showed that methylation of the gene encoding PAC1 was associated with PTSD in a sex-independent manner.

To provide further validation of these findings, the authors used Pavlovian fear conditioning as a model of PTSD in rodents. Quantitative PCR revealed a 1.5-fold increase in *Adcyap1r1* mRNA in the amygdala during consolidation of fear in mice. In addition, female rats implanted with oestrogen pellets exhibited higher levels of *Adcyap1* transcripts in the bed nucleus of the stria terminalis — a region of the extended amygdala that is strongly influenced by sex hormones — than did female rats implanted with control pellets. Thus, oestrogen signalling seems to induce the expression of PACAP.

Together, these studies suggest that oestrogen-regulated PACAP signalling has a role in conferring vulnerability to a maladaptive response to severe trauma. The findings could explain why women are twice as susceptible as men to developing PTSD, and highlight possible biomarkers and therapeutic targets for the disorder.

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ORIGINAL RESEARCH PAPER Ressler, K. J. *et al.* Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. *Nature* **470**, 492–497 (2011)