Study may show how chronic early-life stress raises PTSD vulnerability

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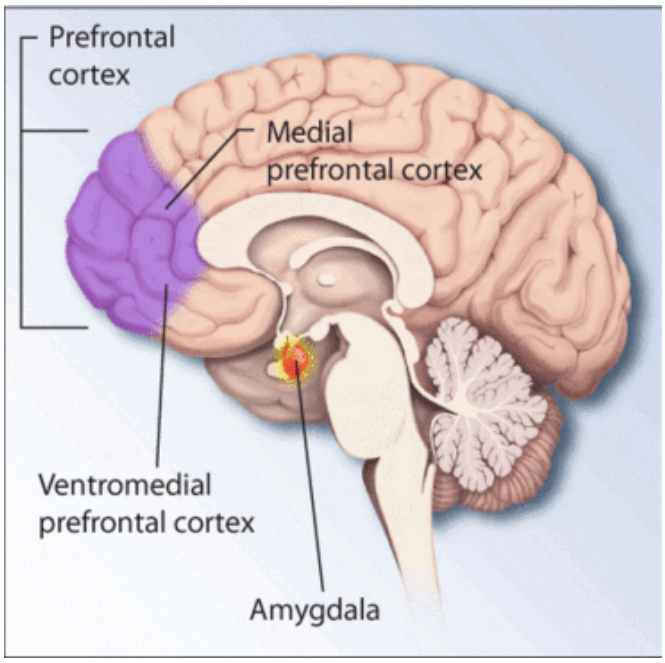

Regions of the brain associated with stress and posttraumatic stress disorder. Credit: National Institutes of Health

A collaboration between investigators at Massachusetts General Hospital and Khyber Medical University in Pakistan may have discovered how chronic stress experienced early in life increases vulnerability to post-traumatic stress disorder (PTSD) later in life. In their report published in *Translational Psychiatry* the researchers describe finding that chronic stress induces a persistent increase in the hormone ghrelin, both in a rat model and in human adolescents. Rats with stress-induced ghrelin elevations were more vulnerable to an excessive fear response long after the stressful experience, a vulnerability that was eliminated by long-term blockade of ghrelin signaling.

"Ghrelin is called the 'hunger hormone,' and while it does play an important role in appetite, it has many other effects," says Ki Goosens, PhD, of the MassGeneral Institute for Neurodegenerative Disease, who led the study. "Several teams have shown that repeated stress exposure increases circulating ghrelin levels in many organisms, but those studies examined ghrelin shortly after the stressor exposure ended. Ours is the first to show that traumatic stress increases ghrelin in humans - specifically in adolescent humans - and the first to look at ghrelin elevation over long time periods after the end of the stressor."

Considerable evidence supports the impact of early-life stress on brain function and on other health outcomes in human adults. Adolescents are known to have increased emotional reactions to their experiences, and stress may enhance that reactivity, increasing vulnerability to several mental health disorders. Since areas of the brain such as the prefrontal cortex that regulate fear-responsive structures including the amygdala continue to develop during adolescence, stress-induced disruption of the developmental process during adolescence could interfere with those regulatory circuits.

To investigate the potential long-term impact of chronic stress on ghrelin levels, the researchers conducted a series of experiments. Chronic stress was induced in a group of adolescent rats by immobilizing them inside their cages daily for two weeks. A control group was handled daily by research team members over the same time period. Not only were ghrelin levels in the stress-exposed rats significantly higher 24 hours after the last stress exposure, as previously reported, they also remained elevated 130 days later, roughly equivalent to 12 years in human lifespan.

To investigate whether long-term stress produced similar persistent ghrelin elevation in humans, the researcher enrolled 88 children from the Khyber Pukhtunkhwa province of Pakistan, an area

affected by more than a decade of terrorist activity. The participants averaged around age 14 at the time of study, and some had either experienced a personal injury or lost a family member in a terrorist attack around four years prior to entering the study. The control group consisted of children who had not experienced those specific types of trauma.

Blood tests revealed that circulating ghrelin levels in the trauma-affected children were around twice those of the control group. Based on interviews with the children and their parents, trauma-affected children also had differences in their sleep, emotional regulation and social isolation, compared with the control group. And while all participants had a body mass index (BMI) within the normal range, the BMIs of trauma-exposed children were significantly lower than those of the control group.

To test the long-term impact of stress-induced ghrelin elevation in the rat model, the research team exposed two other groups of animals to 14 days of either chronic stress induction or daily handling. Two weeks later both groups went through a standard behavioral protocol called fear conditioning, which trained them to expect an unpleasant sensation - a mild but not painful foot shock - when they heard a specific sound. After they learn that association, animals will typically 'freeze' in expectation of the shock when they hear that sound. Compared to the control animals, the chronic-stress-exposed rats showed a stronger fear memory by freezing longer during the sound when it was not paired with a shock.

To test whether blocking ghrelin signaling could reduce the stress-enhanced fear response, the researchers administered a drug that blocks the ghrelin receptor to groups of rats over three different schedules - throughout both the two-week chronic stress induction period and the two weeks prior to fear conditioning, during the stress induction period only or during only the two weeks between stress induction and fear conditioning. While blocking the ghrelin receptor for the full four weeks did eliminate the stress-induced enhanced fear response, blocking ghrelin signaling either only during or only after stress induction did not prevent the enhanced response.

"It appears that blocking the ghrelin receptor throughout the entire period of ghrelin elevation - both during and after stress - prevents fear enhancement when the animals subsequently encounter a traumatic event," says Goosens. "But only blocking the receptor during stress, when ghrelin is initially elevated, or after stress, when it remains elevated, does not prevent the fear-enhanced, PTSD-like response."

She adds, "Previous work from my lab shows that exposing brain cells to high levels of ghrelin reduces their sensitivity to the hormone, which we call 'ghrelin resistance.' We've also shown that ghrelin inhibits fear in unstressed individuals, and we believe that stress-induced ghrelin resistance interferes with that inhibition. Finding a way to reverse ghrelin resistance could have important therapeutic implications. The ability to identify individuals who are more vulnerable to the detrimental effects of stress, as well as the 'tipping point' when they become vulnerable, could enable early intervention with either therapy or medication."

More information: Muhammad I. ul Akbar Yousufzai et al, Ghrelin is a persistent biomarker for chronic stress exposure in adolescent rats and humans, *Translational Psychiatry* (2018). DOI: 10.1038/s41398-018-0135-5

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