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Exposure to stress even before conception causes genetic changes to offspring

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A female's exposure to distress even before she conceives causes changes in the expression of a gene linked to the stress mechanism in the body—in the ovum and later in the brains of the offspring from when they are born, according to a new study on rats conducted by the University of Haifa.

"The systemic similarity in many instances between us and mice raises questions about the transgenerational influences in humans as well, for example, the effects of the Second Lebanon War or the security situation in the South on the children of those who went through those difficult experiences," the researchers said. "If until now we saw evidence only of behavioral effects, now we've found proof of effects at the genetic level."

In previous studies in Prof. Micah Leshem's lab, it was found that exposing rats to stress before they had even conceived (and even at their "teen" stage) influences the behavior of their offspring. This study, conducted in the lab of Dr. Inna Gaisler-Salomon by PhD student Hiba Zaidan, in cooperation with Prof. Leshem, the researchers sought to examine whether there was an influence on genetic expression.

In the study, which was recently published in the journal *Biological Psychiatry*, the researchers focused on the gene known as CRF-1, a gene linked to the body's stress-control system that expresses itself in many places in the brain under stress.

The researchers took female rats that were 45 days old, which is parallel to human adolescence. Some of the rats were exposed to "minor" stress, which included changes in temperature and daily routine for seven days, and compared them to a control group that was not exposed to stress at all. The rats were mated and conceived two weeks later.

In the first part of the study, the researchers examined the ova of the rats that were exposed to stress even before they conceived, and they found that at that stage there was enhanced expression of the CRF-1 gene. For the second part, the researchers examined the brains of newborn rats immediately after birth, before the mother could have any influence on them, and found that even at the neonatal stage, there was enhanced expression of the CRF-1 gene in the brains of the rats born to mothers who had been exposed to stress.

During the third stage, the researchers exposed the offspring – both those whose mothers had been exposed to stress and those whose mothers were not – to stress when they reached adulthood. It emerged that the expression of CRF-1 among the offspring was dependent on three factors: The sex of the offspring, the stress undergone by the mother and the stress to which the offspring were exposed. The female rats whose mothers had been exposed to stress and who themselves underwent a "stressful" behavioral test showed higher levels of CRF-1 than other groups.

"This is the first time that we showed that the genetic response to stress in rats is linked to the experiences their mothers underwent long before they even got pregnant with them," the researchers said. "We are learning more and more about intergenerational genetic transfer and in light of the findings, and in light of the fact that in today's reality many women are exposed to stress even before they get pregnant, it's important to research the degree to which such phenomenon take place in humans."

Provided by University of Haifa