Stress enhances antibody quantity and quality, but impairs immunological memory: Study

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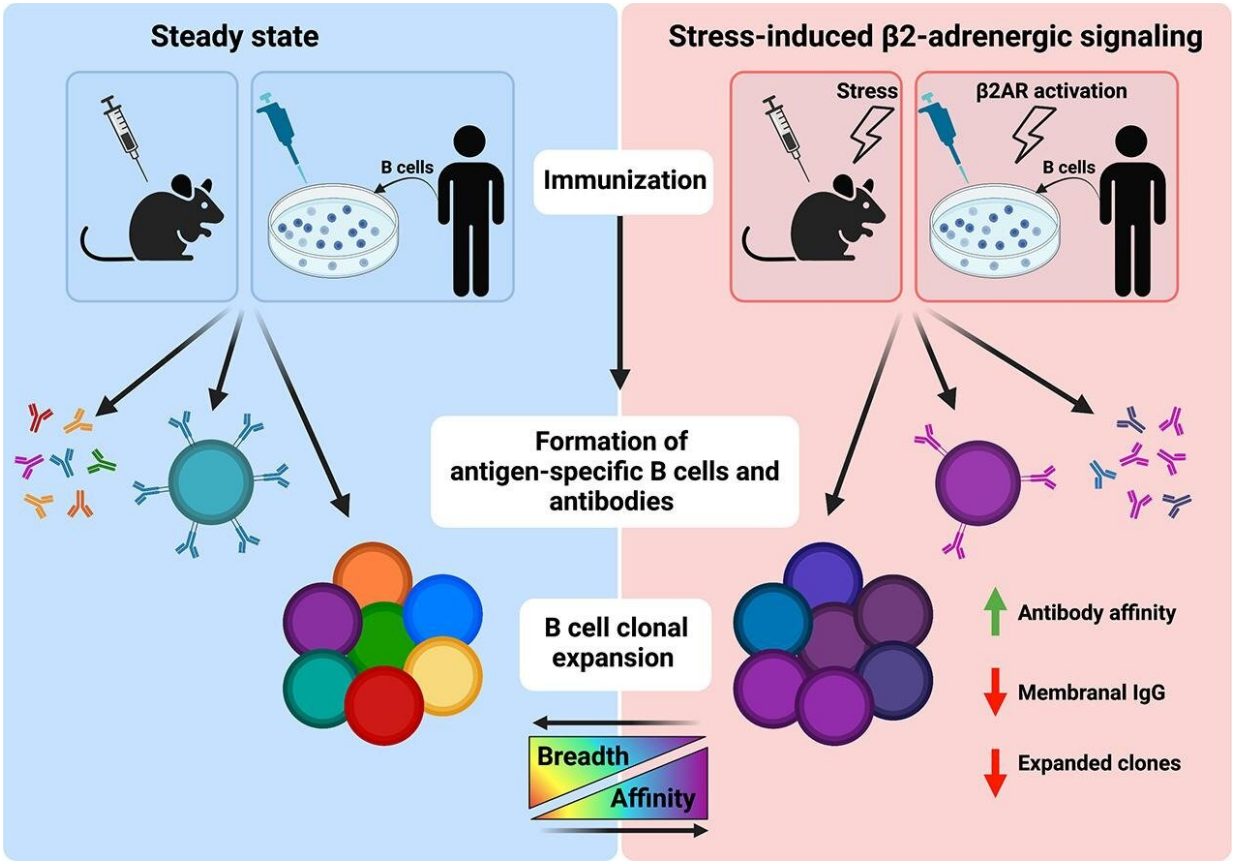

Graphical abstract. Credit: *Brain, Behavior, and Immunity* (2023). DOI: 10.1016/j.bbi.2023.06.020

Researchers at Tel Aviv University demonstrated for the first time that there is a significant link between behavioral stress and the effectiveness of vaccines. They found that acute stress in mice 9-12 days after vaccination increases antibody response to the vaccine by 70% compared to the unstressed control group. This, however, comes at the price of reduced antibody breadth, which results in diminished protection against the pathogen's variants.

The study was carried out in Tel Aviv University and led by Ph.D. student Noam Ben-Shalom from the lab of Dr. Natalia Freund at the Faculty of Medicine and Ph.D. student Elad Sandbank from the Neuro-immunology Lab of Prof. Shamgar Ben-Eliyahu at the School of Psychological Sciences and the Sagol School of Neuroscience. The paper was published in *Brain, Behavior, and Immunity*.

Dr. Freund explains, "In this study we examined, for the first time, the correlation between stress and the body's ability to develop an immune response following vaccination. The prevailing assumption is that the effectiveness of a vaccine is determined mainly by its own quality."

"However, over the years, professional literature has reported influences of other factors as well, such as the age, genetics, and microbiome of the outcomes of vaccination. Our study was the first to investigate the possible effects of acute stress. We found that this mental state has a dramatic impact—not only on the vaccine's effectiveness, but also on how it works."

Acute stress is a mental state caused by immediate threat (either real or imagined), involving the secretion of adrenaline and stimulation. In this study, Dr. Freund and her colleagues vaccinated mice with two different vaccines: the model protein Ovalbumin and a fragment of the SARS-CoV-2 spike protein also used in the COVID-19 vaccine.

Nine days later, just as the adaptive immunity became active and the production of antibodies began, the mice were subjected to a widely used behavioral paradigm simulating acute stress. Two and a half weeks after exposure to stress, namely 30 days after vaccination, the level of antibodies in the blood of vaccinated animals that had experienced stress was 70% higher compared to the control group. This phenomenon was observed in animals vaccinated with either type of vaccine.

At the same time, the researchers discovered that the immune system of the animals that had experienced stress was not cross reactive to variants of the protein used in the vaccine. In other words, following stress the immune system was focused entirely on the original vaccine, showing no response to proteins that were only slightly different—such as variants of concern (VOC) of SARS-CoV-2.

"Initially, we were surprised to find out that the response to the vaccine was much more effective in animals that had experienced stress," says Dr. Freund, "we would have assumed just the opposite—that stressful situations would have a negative impact on the immune system. Nevertheless, with both types of vaccines, we observed a stronger immune response after stress, both in the blood and in B cells (the lymphocytes that produce antibodies) derived from the spleen and lymph nodes of the immunized mice."

"The enhancement of the antibodies' activity following stress was mediated by the cellular receptor that identifies adrenaline—the beta2 adrenergic receptor. When we blocked this receptor, either pharmacologically or by means of genetic engineering, the effects of stress were completely eliminated. On the other hand, to our great surprise, the breadth of the immune response generated by the vaccine was reduced by about 50% following stress."

"In general, the purpose of vaccination is not only protection against a

specific pathogen, but also creating a long-lasting immunological memory for protection against future mutations of that pathogen. In this sense, the vaccines appeared to lose much of their effectiveness after exposure to stress."

According to the researchers, this is in fact a classical 'fight or flight' response, however this time demonstrated at the molecular level. During stress, the immune system produces large quantities of antibodies and stronger antibodies, to address the immediate infection, and this large energetic investment in the here and now comes at the expense of future immunological memory.

Dr. Freund adds, "In the second part of the study we wanted to test whether humans also display the post-stress immune impairment observed in vaccinated mice. For this purpose, we cultured B cells obtained from blood of people who had contracted COVID-19 in the first wave. We then induced stress in these cultures using an adrenaline-like substance that stimulates the beta2 adrenergic receptor, that was identified by us in the first part of the study as a mediator of the response to stress in cells that produce antibodies in mice."

"B cells express a very high level of these receptors, but until now the receptors' role in producing antibodies was not known. In fact, it was unclear why these cells need the ability to respond to adrenaline. We discovered that just like in mice, human cells also exhibit a zero-sum game between the intensity and breadth of the immune response."

"When the adrenaline receptor is activated during stress, the entire immune system is stimulated, generating antibodies that are 100-fold stronger than antibodies produced in cells that had not undergone stress. But here too, the response was narrower: the diversity of antibodies was reduced by 20-100%, depending on the individual from whom the cells were taken."

"RNA sequencing of the cells in which the beta 2 adrenergic receptor was activated, compared to regular cells, indicated that the receptor's activation caused antibody-producing cells to work at maximum capacity (by activating the PI3 kinase protein and phosphorylation of AKT)—at the expense of antibody breadth and diversity."

"From the evolutionary perspective," concludes Dr. Freund, "stress can be caused by different factors."

"We tend to think of mental stress, but physical illness also causes a form of stress. When the body contracts a virus or bacteria it experiences stress, and signals to the immune system that the top priority is getting rid of the pathogen, while investing energy in long-term immunological memory is a second priority. Therefore, stress 9 to 12 days after vaccination, at the time when B cells are generating high affinity antibodies, enhances short-term immunity and damages long-term memory."

More information: Noam Ben-Shalom et al, β2-adrenergic signaling promotes higher-affinity B cells and antibodies, *Brain, Behavior, and Immunity* (2023). DOI: 10.1016/j.bbi.2023.06.020

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