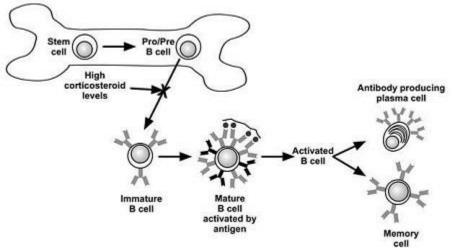
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Stressful times in academics

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Mechanism of how chronic stress, as measured by the secretion of glucocorticoids, causes apoptosis of pre-B cells as they emerge from the bone marrow. This in turn may impair antibody response by decreasing the number of immature B cells, which mature into antibody producing cells.

Image provided by Dr. Bonnie McGregor

It is well known that chronic stress can impair immune function, as measured by antibody response to vaccines. This chronic stress could influence the success of vaccines in preventing sickness and disease. One potential mechanism explaining how chronic stress impairs the immune response to vaccines involves glucocorticoids and B lymphocytes (B cells). The secretion of glucocorticoids, a class of steroid hormones, is a classic endocrine response to stress. Animal and human *in vitro* models demonstrate an increase in these hormones cause apoptosis of pre-B cells as they emerge from the bone marrow. This in turn may impair antibody response by decreasing the number of immature B cells, which mature into antibody producing cells.

Previous work by Drs. Bonnie McGregor, Rachel Ceballos, and colleagues (Public Health Sciences Division), found that low levels of immature B cells (CD19+) *in vivo* were associated with perceived academic stress among graduate students. Academic stress is the cumulative result of multiple factors routinely faced by graduate students during the course of their studies. However, the previous study could draw only limited conclusions due to its cross-sectional nature and lack of biomarker data for stress. To address this gap in knowledge, the authors evaluated the relationship among distress, salivary cortisol and human B cells *in vivo* among first-year graduate students. They presented their results recently in *Stress*.

Study participants included 22 first-year graduate students of the University of Washington, School of Public Health. Thirty non-student control participants were recruited from the community. The investigators performed psychological questionnaires to assess distress, drew blood for lymphocyte analysis, and collected saliva samples for cortisol analysis. This data was collected on all participants before classes began in the fall (T1) and at the end of the first academic year, five days before qualifying exams (T2).

The investigators found similar demographics between the student and comparison samples, except for gender, which was included as a control variable in all-subsequent analyses. Compared to the control participants, students reported greater levels of distress on all measures, except for perceived stress at T1. Hierarchical linear regression was used to assess the longitudinal effect (T1-T2) of student status on measures of distress (perceived stress, negative affect, and depressive symptoms), lymphocyte phenotypes (CD19+CD10+, CD19+DR+, CD3+), cortisol area under the curve (AUC), and cortisol awakening response (CAR). Student status did not predict a significant change over time of immature B cells (CD19+CD10+), mature B cells (CD19+DR+), or T cells (CD3+). However, student status significantly predicted changes in cortisol awakening response (CAR) (Beta = 0.31, p value = 0.049). Specifically, students exhibited greater flattening of the CAR (a 23% increase at T1 to a 2% increase at T2) compared to controls (a 38% increase at T1 to a 27% increase at T2). A normal increase in CAR is between 50-160%. While neither the students nor controls reached this percentage, the students' slight 2% increase at T2 causes some clinical concern. Furthermore, changes in CAR significantly predicted T2 CD19+ B cell percentage after controlling for age, gender, and baseline CD19+ levels (Beta = -0.240, p = 0.024).

What exactly is CAR? In humans, the secretion of cortisol from the adrenal glands follows a diurnal cycle with a profound increase after awakening. This increase after awakening, a phenomenon termed the cortisol awakening response or CAR can represent perceived human stress.

Dr. McGregor first noticed the link between stress and immune response during her time working in a clinical setting, "I found that for two individuals their B cells were half they were supposed to be. One of them had a grant due the next day and the other was going through a divorce. There's also research in mice and dolphins supporting how stress can decrease B cell levels. Here we found that stress-related decreases in CAR may be an early indicator of how glucocorticoids associated with chronic stress impair antibody response to vaccines by decreasing the number of mature B lymphocytes available to become antibody producing cells. The main take home point from this work is that stress can influence immune processes and academics can be a stressful environment."

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<u>McGregor BA, Murphy KM, Albano DL, Ceballos RM</u>. 2015. Stress, Cortisol, and B-Lymphocytes: A Novel Approach to Understanding Academic Stress and Immune Function. *Stress*. doi: 10.3109/10253890.2015.1127913. [Epub ahead of print.]