Brain, Behavior, and Immunity 26 (2012) 747–753

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Vulnerability, distress, and immune response to vaccination in older adults

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ARTICLE INFO

Article history:
Available online 29 October 2011

Keywords:
Influenza vaccination
Inflammation
Aging
Adiposity
Exercise
Stress
Depression
Distress

ABSTRACT

Psychological distress and biobehavioral vulnerability (e.g., arising from being older or sedentary) have independently predicted immune responses to influenza vaccination in older adults. Recent research examining basal inflammatory markers suggests that, rather than having additive effects, distress and vulnerability interact with each other. The present study tested the interactions between distress and age, sex, education, BMI, sleep quality, and physical activity over up to 8 years in older adults ($N = 134$; M age = 74 years) who received annual influenza vaccinations. Measured vaccination responses were changes from baseline in antibody to the three vaccine components, interleukin (IL)-6, and β2-microglobulin. As predicted, the most robust effects were interactions between distress and vulnerability. BMI interacted with stable individual differences in distress to predict antibody response ($t(132) = 3.09$, $p < 0.003$), such that only the combination of low BMI and low distress was associated with a more robust antibody response. Likewise, changes in physical activity over time interacted with changes in distress ($t(156) = 2.96$, $p < 0.004$), such that only the combination of increased physical activity and decreased distress was associated with a more robust antibody response. Finally, there was a smaller tendency for age to interact with stable individual differences in distress ($t(130) = 2.46$, $p < 0.015$), such that distress was more strongly associated with post-vaccination IL-6 at older ages. The synergistic effects of distress and other forms of vulnerability are an important direction for future research and a target for interventions to improve immunological health in older adults.

1. Introduction

Vaccination against influenza in older adults has the potential to provide protection against negative health consequences, including hospitalizations and deaths. However, many older adults do not mount robust antibody responses to the vaccine. When antibody production following vaccination is low, the individual may still be vulnerable to infection and the negative health consequences thereof (Gardner et al., 2001; Hannoun et al., 2004; Webster, 2000). In addition, antibody responses are not the only immune response to vaccination. Vaccination can also induce inflammatory responses. Most side effects of influenza vaccination are related to inflammatory responses, from minor, local responses such as pain to more serious systemic responses such as fever, neuritis, and myelitis. Inflammatory and acute phase responses to vaccination are often transient and last only a matter of days, but there are large individual differences in degree of response, with some people showing increases in inflammatory markers and others, decreases. Furthermore, individual differences – including psychological factors – also affect duration of response, such that increases in inflammatory markers may be evident weeks after vaccination in some people (Bernstein et al., 1998; Carty et al., 2006; Glaser et al., 2003; Segerstrom et al., 2008; Trzonkowski et al., 2004; Tsai et al., 2005). Changes in antibody and inflammatory markers after vaccination are independent of each other (Bernstein et al., 1998; Krakauer and Russo, 2001).

Stress and distress have been associated with both poor antibody responses and higher inflammatory markers in older adults. For example, studies of dementia caregivers have found that caregiving is associated with lower antibody response and, in some cases, higher IL-6 after vaccination (Kiecolt-Glaser et al., 1996; Segerstrom et al., 2008; Vedhara et al., 1999). However, some people may be more immunologically sensitive to the negative effects of stress and distress than others. In studies of healthy middle-aged and older adults, various measures of psychosocial well-being or distress were more strongly related to basal markers of systemic inflammation in women, those who slept poorly, those who did not engage in moderate-intensity physical activity, and those with less education (Friedman et al., 2005; Morozink et al., 2010; Morris et al., 2011; Rethorst et al., 2011; Steptoe et al., 2008). Synergistic effects of distress and demographic and behavioral variables may explain why some studies have not found main effects of stress or distress on antibody responses to vaccine (e.g., Moynihan et al., 2004).

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doi:10.1016/j.bbi.2011.10.009

Other qualities that may increase vulnerability include older age and higher BMI. Even within older age, aging is associated with poorer antibody responses to vaccination and higher basal markers of systemic inflammation (Goodwin et al., 2006; Harris et al., 1999). Higher BMI is associated with higher markers of systemic inflammation, particularly IL-6, due to the presence of active macrophages in adipose tissue, particularly in visceral fat (O'Connor et al., 2009). Therefore, older age and higher BMI may also predispose to higher inflammatory and activation markers after vaccination.

The present study used data from a longitudinal study of psychosocial factors and immunological responses to vaccination in older adults to test the combinations of demographic and behavioral vulnerabilities with psychological distress as predictors of antibody to vaccine components, as well as markers of immune activation and inflammation (β2 microglobulin (β2μ) and interleukin (IL)-6). β2μ is an element of the major histocompatibility complex shed primarily by activated lymphocytes. It is elevated in serum during infection and inflammation, correlates with C reactive protein during influenza infection, and is found in higher levels in serum in healthy older compared with younger adults (Cooper et al., 1984; Zissis et al., 2001). IL-6 is a pleiotropic cytokine involved in the inflammatory cascade and produced by many somatic cells; it is also elevated during inflammation and correlated with C reactive protein (Papanicoloau et al., 1998). We hypothesized that the effects of stress and distress would interact with vulnerability factors to predict undesirable immunological outcomes after vaccination (lower antibody response and higher inflammatory and activation markers). With regard to vulnerabilities, we tested a set of stable demographic vulnerabilities that included age, gender, education, and BMI, and a set of time-varying behavioral vulnerabilities that included physical activity and sleep quality. The specific hypotheses were as follows:

1. Antibody and inflammatory and activation marker changes after vaccination are independent of each other.
2. Vulnerability to undesirable immunological outcomes after vaccination will be associated with older age, female gender, less education, high BMI, poor sleep quality, and low physical activity. Each of these characteristics has predicted undesirable immunological outcomes either alone or in combination with psychosocial factors.
3. The combination of distress and vulnerability will be the best predictor of such outcomes, such that distress is more strongly related to undesirable outcomes among vulnerable individuals.

2. Method

2.1. Participants

Participants were 134 older adults who were recruited through the clinics and the volunteer subject pool of the Sanders-Brown Center on Aging and who had data at baseline (pre-vaccination) and follow-up from at least one annual influenza vaccination during this longitudinal study. The sample was on average 74 years old at enrollment (range = 60–91), slightly more female than male (58% vs. 42%), and well educated, although there was a large range in years of education (M = 16 years, range = 7–22). The sample was predominantly white (96%), with the remainder African–American (4%). All participants were married at enrollment, though no couples were included in order to avoid dependency in the data. There was a small minority (4%) of smokers in the sample.

2.2. Procedure

All procedures were approved by the University of Kentucky Institutional Review Board. Participants were recruited continuously from 2001 to 2007. Those older adults who had expressed interest in participating in research to the Center on Aging were contacted by phone and screened. Inclusion criteria were: age 60 or older, married, and willing to be vaccinated against influenza. Exclusion criteria were: diseases that affect the immune system (e.g., autoimmune disease, cancer); chemotherapy or radiation in the 5 years prior to enrollment; immunomodulatory medications including opiates and steroids; or more than two of the following classes of medications: psychotropics, antihypertensives, hormone replacement, or thyroid supplements. These criteria exclude major influences on immune responses and allow reasonably healthy older adults into the study. More restrictions on medication would result in a sample of older adults that is unrepresentative of the population.

Participants were interviewed semi-annually in their homes. In advance of each interview, they were sent a health behaviors questionnaire that they completed daily on three consecutive days and returned to the interviewer. Participants received a $10 gift card following each interview during a first phase of the study (2001–2006); this amount was increased to $20 during a second phase (2006–2008). Vaccinations were performed annually from 2001 to 2008. Nurses administered the commercially available, seasonal, trivalent influenza vaccine in the participant's home or in the clinic, whichever the participant preferred. Blood draws were taken immediately prior to vaccination and at 2 and 4 weeks following vaccination.

2.3. Measures

2.3.1. Demographics

Subjects reported at their first visit on their date of birth, years of education, and gender.

2.3.2. Medications

A medication list was provided to the interviewer at each visit. Each medication was coded by an RN into medication classes. The medication classes of interest for the present report were beta-blockers (e.g., atenolol, metoprolol, propanolol) and statins (e.g., simvastatin, atorvastatin) and were coded as taken or not taken at each visit. Beta-blockers (taken at 18% of all person-years) were of particular concern with regard to the degree to which they could contribute to extraneous variance in antibody responses via autonomic pathways (see Sanders et al., 2001, for a review), and statins (taken at 38% of all person-years) were of particular concern with regard to the degree to which they could contribute to extraneous variance in inflammatory and activation markers, particularly those related to the acute phase response (see O'Connor et al., 2009, for a review). Therefore, all antibody analyses included beta-blockers as time-varying covariates, and all inflammatory and activation marker analyses included statins as time-varying covariates.

2.3.3. Health variables

Participants provided their height and weight, and BMI was calculated from these reports. Because these data were collected beginning in 2002, a small number of people (N = 13) who completed only one visit before dropping out were missing BMI data. These missing data were replaced with the sex-specific means. (Note that excluding these participants from analysis did not affect the results reported below.) Participants also reported on their smoking history at the first visit.

At each visit, participants reported on their physical activity and sleep quality daily on each of three consecutive days. The mean across the 3 days was used as the visit-level measure. Sleep quality was measured with a single item reading "How well did you sleep last night?" with anchors 0 = "much better than usual" and 100 = "much worse than usual". Physical activity was operationalized the product of the metabolic equivalent of task (MET) and the