



Review

Effects of psychological stress on neutrophil phagocytosis and bactericidal activity in humans – a meta-analysis



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ABSTRACT

Several authors have reviewed the effects of psychological stress on lymphocyte activity. However the effect of psychological stress on neutrophil functions has not been reviewed. The present meta-analysis summarizes evidence of the effects of psychological stress on neutrophil phagocytosis and bactericidal activity collated from a MEDLINE search of the English literature. We searched the database to identify the relevant studies through April 30, 2013. Eleven studies met our inclusion criteria and we divided them into those addressing transient acute stress (3 studies, $n = 74$), academic examinations (4 studies $n = 101$) and chronic stress/life events (4 studies, $n = 193$). We performed a meta-analysis of the data and calculated total standardized mean differences (SMD) to evaluate the effects of chronic stress. Transient acute stressors might both enhance and decrease these neutrophil functions. Academic examinations tended to elevate neutrophil functions. On the other hand, the total SMDs of neutrophil phagocytosis and bactericidal activity altered by chronic stress/life events were -0.589 (95% CI: -0.908 to -0.270 , $p < 0.05$) and -0.547 (95% CI: -0.845 to -0.248 , $p < 0.05$), respectively, indicating suppressive effects on these neutrophil functions. Further systematic review of more pooled studies is warranted to confirm that academic examinations might enhance, whereas chronic stress/life events might suppress these neutrophil functions.

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1. Introduction

Psychological stress might cause immune dysfunction that could lead to several diseases including infectious diseases and cancer. The relationship between immune function and chronic psychological stress has been examined mainly from the viewpoint of lymphocyte function. Schleifer et al. (1983) found significantly suppressed lymphocyte proliferation in individuals during the first two months after the death of a spouse compared with pre-bereavement levels. Gerra et al. (2003) similarly found suppressed lymphocyte proliferation and natural killer cell cytotoxicity at 40 days after bereavement. Some articles have reviewed lymphocyte activity (Segerstrom and Miller, 2004; Graham et al., 2006). In general, acute stress can enhance lymphocyte activity whereas chronic stress suppresses lymphocyte functions. Segerstrom and Miller (2004) found from a systematic analysis that acute time-

limited stress enhances natural killer cell cytotoxicity but suppresses lymphocyte proliferation. They also demonstrated that exposure to chronic stress as well as brief stress such as academic examinations suppressed these lymphocyte functions. However, relatively few reports have described the effect of psychological stress on neutrophils that play an important role in initial protection against infections (Ottonello et al., 1995). Furthermore, in terms of meta-analyses, we could find only one analysis of data from three publications that investigated relationships between academic examinations and neutrophil superoxide production in young patients with asthma at a single facility (Segerstrom and Miller, 2004). Therefore, the effect of duplicate data derived from the same source might need consideration when evaluating results.

The present meta-analysis summarizes evidence of the effects of psychological stress on neutrophil functions in humans. We focused on phagocytosis and bactericidal activity in which superoxide production plays a crucial role (Gough et al., 1997).

2. Methods

2.1. Search strategy

We used the key words, “psychological stress”, “lifestyle”, “life event”, “neutrophil”, “phagocyte” and “granulocyte” to search MEDLINE for

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ANOVA, analysis of variance; CI, confidence interval; FMLP, N-formyl-methionyl-leucyl-phenylalanine; h, hours; LPS, lipopolysaccharides; MA, multivariate regression analysis; m, months; min, minute; NBT, nitro-blue tetrazolium; NS, not significant; PMA, phorbol myristate acetate; r, correlation coefficient; SD, standard deviation; SMD, standardized mean difference; SRBC, sheep red blood cells; TNF- α , tumor necrosis factor- α ; y, years.

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articles about psychological stress and neutrophil functions published in English. We searched the database to identify the relevant studies through April 30, 2013.

2.2. Eligibility

Articles were included in the present analysis if humans actually experienced the defined psychological stress and if neutrophil functions defined as phagocytosis or bactericidal activity including superoxide production were measured.

Articles were excluded if they were not original, such as reviews or case reports, or if physical stressors such as exercise or pain were included. If potentially duplicate data from the same individual were included in two or more publications, only one report was included in the analysis to avoid overlapping data.

2.3. Data extraction

We extracted the following information from each study: first author, year of publication, mean age and number of patients, breakdown of sex, stressor(s) experienced, duration of exposure to stress and profiles of neutrophil phagocytosis and bactericidal activity.

2.4. Statistical analysis

We adopted the Hedges *g* statistic (Borenstein et al., 2009a) for standardized mean differences (SMD) in meta-analyses of studies with continuous measures (comparison of means between stress and control groups). If zero was not included within the 95% confidence interval (CI), then the SMD was considered statistically significant ($p < 0.05$). When paired (matched) data such as comparisons between baseline and after procedures such as evaluations of acute stress were applied in the present systematic review, a correlation coefficient (r) of the two tests was required and the degree of freedom was changed to calculate the SMD (Borenstein et al., 2009a).

After calculating the total (summary) SMD under the fixed and random effects model (Borenstein et al., 2009b), the *Q* value was incorporated to assess heterogeneity. If the *Q* value was statistically significant ($p < 0.05$), then the results of the random effects were emphasized (Petrie et al., 2003).

Publication bias was visually examined using funnel plot asymmetry (data not shown) and the Egger test (Egger et al., 1997), in which the effect size defined as SMD was included in the regression equation:

$$\text{SMD} = a + b \times \text{the number of participants.}$$

Points from a homogeneous set of trials that are not distorted by selection bias will scatter about a line that runs through the origin at standard normal deviation zero ($a = 0$). A regression line that does not run through the origin of an asymmetric funnel plot indicates publication bias. The intercept “*a*” provides a measure of asymmetry, with larger deviation from zero indicating more pronounced asymmetry.

Intercepts with 90% confidence intervals ($p < 0.1$) are recommended to define significant publication bias (Egger et al., 1997).

All data were statistically analyzed using MedCalc Software, Version 9.4.2.0 (Mariakerke, Belgium). *P* values of < 0.05 were considered significant except in the Egger test ($p < 0.1$).

3. Results

3.1. Overview of studies

The MEDLINE searches identified 821 potentially relevant citations. Among these, 17 studies met our inclusion criteria after title and abstract assessment. Seven of these were excluded after reviews of the full text because neutrophil function as defined in the present review

was not actually assessed, experienced stressors were not shown, or participants potentially overlapped despite different study objectives.

The remaining 10 reports were divided into three groups, namely transient acute stress, academic examination stress and chronic stress/life events based on the meta-analysis described by Segerstrom and Miller (2004). At this point, one report describing academic examinations was excluded because baseline data (non-examination period) were not described.

Thus, we assessed transient acute stress based on three studies of humans (74 participants; Ellard et al., 2001; Khanfer et al., 2010, 2012), academic examination stress based on two articles describing four human studies (101 participants; Kihara et al., 1992; Kang et al., 1997) and chronic stress/life events in four human studies (193 study participants; Dekaris et al., 1993; Bartlett et al., 1997; Khanfer et al., 2011; Tsukamoto and Machida, 2012).

3.2. Summary of effects of transient acute stress on neutrophil phagocytosis and bactericidal activity

Table 1 summarizes the effects of 8–15-min psychological stressor tasks on neutrophil phagocytosis and bactericidal activity. Ellard et al. (2001) applied the unstimulated nitro-blue tetrazolium (NBT) test indicating neutrophil superoxide production to young healthy individuals. They found that a 15-min mental stressor task remarkably enhanced NBT reduction activity even under unstimulated conditions. In contrast, Khanfer et al. (2010) found that unstimulated neutrophil superoxide production did not change after a 10-min mental stressor task in young healthy participants, whereas that stimulated by *Escherichia coli* was significantly suppressed (Table 1 and footnotes). Their findings were similar in healthy elderly individuals (Khanfer et al., 2012). They also found that a 10-min mental task significantly elevated neutrophil phagocytosis (Khanfer et al., 2010).

3.3. Summary of effects of academic examinations on neutrophil phagocytosis and bactericidal activity

Table 2 summarizes the effects of academic examination stress on neutrophil phagocytosis and bactericidal activity. Since some of these neutrophil functions were shown only as figures (illustrations) in the literature, they were interpreted into numerical values. Kihara et al. (1992) found elevated neutrophil phagocytosis and superoxide production activity in Japanese students on the day before an academic examination. Even though the stimulators of neutrophil superoxide production differed, the results were similar (see footnotes to Table 1). Kang et al. (1997) identified similar results in young students during an examination period, although the measured time points differed. These phenomena were evident in not only healthy students but also in those with asthma.

3.4. Summary of the effect of chronic psychological stress on neutrophil phagocytosis and bactericidal activity

Table 3 summarizes the effects of chronic psychological stress/life events on neutrophil phagocytosis and bactericidal activity. Although the stressor type and period of stress exposure varied and some findings did not reach statistical significance, each report described that these neutrophil functions tended to be lower in stressed, than in independent control individuals. Dekaris et al. (1993) found significantly reduced neutrophil phagocytic activity in prisoners of war who had been incarcerated for several months and that neutrophil bactericidal activity tended to be decreased compared with controls. Bartlett et al. (1997) reported that children who experienced parental separation or divorce have lower levels of neutrophil bactericidal activity (neutrophil phagocytic activity was similar to that of a control group; but data were not shown). Khanfer et al. (2011) showed significantly reduced neutrophil superoxide production in healthy elderly individuals who had

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