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Increased Natural Killer-Cell Mobilization and Cytotoxicity during Marital Conflict

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Natural killer (NK) cells are reproducibly mobilized into the circulation in response to intense physical exercise or acute psychological stress, and altered expression of adhesion molecules potentially contributes to NK-cell mobilization. Studies of leukocyte mobilization during acute stress have used psychological stressors which facilitate tight experimental control but have limited applicability to everyday life. We therefore used a laboratory model of marital conflict as an experientially meaningful acute stressor to elucidate relationships among conflict, cardiovascular reactivity, and altered leukocyte phenotype and function. Forty-one ethnically diverse, nondistressed, healthy married couples were asked to discuss a specific problem in their marriage for 15 min. Blood pressure and heart rate were measured before, during, and after the discussion, and blood was remotely drawn at the same time points to quantify numbers of specific leukocyte subsets, NK-cell adhesion molecule expression, and NK cytotoxicity. Couples responded to the conflict task with cardiovascular reactivity; increases in the percentages of circulating NK cells and $CD8^+$ T cells and decreases in the percentage of circulating $CD4^+$ T cells; decreases in the percentage of NK cells that express L-selectin; and increases in NK-cell cytotoxicity without a commensurate increase in per-cell cytotoxicity. Rapid downregulation or shedding of L-selectin (CD62L) from NK cells did not contribute to their mobilization during conflict. Instead, $CD62L^-$ NK cells were mobilized while $CD62L^+$ NK cells were selectively retained in the vascular marginating pool and/or in extravascular tissue. From a broader perspective, the data support the hypothesis that altered trafficking of specific leukocyte subsets is an integral component of the fight-or-flight response to an acute stressor.

Key Words: stress; natural killer; leukocytosis; mobilization; adhesion molecule.

INTRODUCTION

Mobilization of natural killer (NK) cells into the circulation is arguably the most reproducible cellular immunological response to acute physical and psychological stressors in humans. For example, numbers of circulating NK cells increase during intense exercise (Maisel, Harris, Rearden, & Michael, 1990; Gabriel, Schwarz, Steffens, & Kinderman, 1992; Murray, Irwin, Rearden, Ziegler, Motulsky, & Maisel,

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1992), parachute jumping (Schedlowski, Jacobs, Alker, Prohl, Stratman, Richter, Hadicke, Wagner, Schmidt, & Tewes, 1994a), distressing mental arithmetic (Naliboff, Benton, Solomon, Morley, Fahey, Bloom, Makinodan, & Gilmore, 1991), and interpersonal interactions (Brosschot, Benschop, Goodart, de Smet, Olff, Heijnen, & Ballieux, 1992). A concomitant increase in NK-cell cytotoxicity also occurs (Murray et al., 1992; Naliboff et al., 1991), although it is unclear whether this is due to an increased in-well percentage of NK cells in cytotoxicity assays or to an increase in per-cell killing. Cellular mobilization is restricted to NK cells, granulocytes, and, to a lesser extent, macrophages and $CD8^+$ lymphocytes, whereas numbers of circulating B cells are generally unchanged, and numbers of $CD4^+$ lymphocytes often decrease in response to acute stressors (Fleshner, Watkins, Lockwood, Bellgrau, Laudenslager, & Maier, 1992; Gabriel et al., 1992; Murray et al., 1992; Naliboff et al., 1991). Mobilization is generally transient, reaching peak levels in less than 30 min, and may be followed by a decrease in numbers of mobilized cells to levels below baseline (Benschop, Rodriguez-Feuerhahn, & Schedlowski, 1996).

Converging lines of evidence implicate the catecholamines epinephrine (E) and norepinephrine (NE) in stress-induced leukocyte mobilization. First, levels of circulating catecholamines increase in concert with mobilization, and injections of β_2 adrenergic receptor antagonists prior to stress prevent mobilization (Benschop, Nieuwenhuis, Tromp, Goodart, Ballieux, & van Doornen, 1994; Schedlowski, Hosch, Oberbeck, Benschop, Jacobs, Raab, & Schmidt, 1996). Second, intravenous injections of E, NE, or the β_2 agonist isoproterenol cause a rapid efflux of granulocytes (Ernström & Sandberg, 1973) and NK cells (Schedlowski et al., 1994a) which is prevented by prior injection of β blockers. Third, the susceptibility of leukocyte subsets to catecholamine-induced mobilization appears to be related to their magnitude of isoproterenol-induced cyclic AMP accumulation (Mills, Berry, Dimsdale, Ziegler, Nelesen, & Kennedy, 1995).

A potential mechanism through which catecholamines could alter NK-cell trafficking and cytotoxicity is via modulation of adhesion molecule expression. Adhesion molecules (AMs) facilitate leukocyte extravasation (directed movement from the circulation into extravascular tissue) and mobilization by mediating interactions with vascular endothelial cells (ECs). Leukocytes extravasate toward a chemotactic factor in a sequential manner, each step of which is mediated by a specific class of AMs: initial stages of loose attachment and rolling are mediated by selectins; firm attachment is mediated by integrins; and transendothelial migration is mediated by AMs belonging to the immunoglobulin superfamily (Springer, 1994; Liao, Huynh, Eiroa, Greene, Polizzi, & Muller, 1995; Newman, 1997). Conversely, leukocyte mobilization during acute stress probably involves rapid shedding of specific AMs from leukocytes which are transiently attached to vascular ECs while rolling along the walls of capillaries. Although NK cells express multiple AMs, including LFA-1, Mac-1, VLA-4, and NCAM (Timonen, Patarroyo, & Gahmberg, 1988; Robertson, Caligiuri, Manley, Levine, & Ritz, 1990; Pinola & Saksela, 1992), the best candidates for mediating NK mobilization are L-selectin (CD62L), which binds glyCAM-1 on ECs to facilitate NK extravasation across lymph node high endothelial venules (HEV) (Lasky, Singer, Dowbenko, Imai, Henzel, Grimley, Fennie, Gillett, Watson, & Rosen, 1992; Bevilacqua, 1993), and H-CAM (hylauronic acid receptor; CD44), which binds extracellular matrix molecules to facilitate NK homing to mucosal lymphoid tissue