

Medizinische Fakultät Charité – Universitätsmedizin Berlin

Campus Benjamin Franklin

aus der Abteilung für Psychosomatik und Psychotherapie

Geschäftsführender Direktor: Prof. Dr. H.-C. Deter

**Auswirkungen von kurzzeitigem psychischem Laborstress auf die
Verteilung von T-Zell-Subpopulationen und Effektormechanismen
des peripher zirkulierenden T-Zell-Pools**

Inaugural-Dissertation
zur Erlangung der medizinischen Doktorwürde
Charité – Universitätsmedizin Berlin
Campus Benjamin Franklin

vorgelegt von
Benjamin Schnee
aus Berlin

Referent: Prof. Dr. med. H.-Chr. Deter

Korreferent: Prof. Dr. C. Scheibenbogen

Gedruckt mit Genehmigung der Charité – Universitätsmedizin Berlin
Campus Benjamin Franklin

Promoviert am: 19.09.2008

Meiner Mutter und meinem Bruder gewidmet

Inhaltsverzeichnis

1	EINLEITUNG.....	9
2	FORSCHUNGSGEGENSTAND.....	11
2.1	Psychoneuroimmunologie.....	11
2.2	Psychophysiologische Stresskonzepte.....	12
2.3	Kommunikation zwischen ZNS und Immunsystem.....	13
2.4	Teil der adaptiven Immunität: T-Lymphozyten.....	15
2.4.1	Vier Subpopulationen von CD4 ⁺ und CD8 ⁺ T-Lymphozyten.....	16
2.4.1.1	T _{naive} und T _{CM}	18
2.4.1.2	T _{EM} und T _{EMRA}	18
2.4.2	Effektormechanismen der T-Lymphozyten.....	19
2.4.2.1	Perforin.....	20
2.4.2.2	Granzyme.....	20
2.5	Auswirkungen von psychischem Stress auf Funktionen des Immunsystems.....	21
3	ZIEL DER ARBEIT.....	25
4	PROBANDEN UND METHODEN.....	27
4.1	Probandenkollektiv.....	27
4.2	Untersuchungsplan.....	29
4.2.1	Untersuchungsablauf.....	29
4.2.2	Psychophysiologischer Belastungstest.....	30
4.2.3	Psychodiagnostik.....	31
4.2.4	Physiologische Parameter.....	32
4.3	Immunologische Parameter.....	33
4.3.1	Differentialblutbild.....	34
4.3.2	Isolierung von mononukleären Zellen aus heparinisiertem Vollblut.....	34
4.3.3	Kryopreservation und Auftauen von Zellen.....	35
4.3.4	Durchflusszytometrie/ FACS.....	35
4.3.5	Färbung der Zellen.....	37
5	ERGEBNISSE.....	39
5.1	Probanden.....	39
5.2	Psychologische Reagibilität.....	40
5.3	Physiologische Reagibilität.....	41

5.4	Immunologische Parameter.....	43
5.4.1	Differentialblutbild.....	43
5.4.2	CD4 ⁺ und CD8 ⁺ T-Lymphozyten, NK-T- und NK-Zellen.....	44
5.4.3	Umverteilung peripherer T-Zell-Subpopulationen unter akutem psychischem Stress: Ergebnisse zu Hypothese 1	47
5.4.4	Expression von Granzym B und Perforin in peripheren CD4 ⁺ /CD8 ⁺ T-Lymphozyten: Ergebnisse zu Hypothese 2	51
5.4.5	Expression der intrazellulären Effektormoleküle Granzym B und Perforin in CCR7-negativen T-Lymphozyten	54
6	DISKUSSION.....	57
6.1	Auswirkungen von akutem psychischem Stress auf die Zusammensetzung und die funktionelle Effektorkapazität des peripher zirkulierenden T-Zell-Pools	57
6.1.1	Psychologische Reagibilität.....	57
6.1.2	Physiologische Reagibilität	58
6.1.3	Immunologische Variablen	58
6.1.3.1	Differentialblutbild.....	59
6.1.3.2	CD4 ⁺ und CD8 ⁺ T-Lymphozyten, NK- und NK-T-Zellen	59
6.1.3.3	Umverteilung peripher zirkulierender T-Zell-Subpopulationen unter akutem psychischem Stress: Zu Hypothese 1	60
6.1.3.4	Auswirkungen akuter mentaler Belastung auf die zytolytische Effektorkapazität des peripheren T-Zellpools: Zu Hypothese 2	62
6.1.3.5	CCR7 – ein potentieller Marker der stressinduzierten Umverteilung.....	63
6.2	Implikationen für die adaptive Immunität	63
6.3	Akuter psychischer Stress und Immunfunktionen: Konzepte im Wandel	66
6.4	Implikationen für Gesundheit und Krankheit	67
6.4.1	Akuter Stress als endogenes Adjuvans bei der primären Immunisierung.....	67
6.4.2	Akuter psychischer Stress und Autoimmunerkrankungen	69
6.4.2.1	Chronisch entzündliche Gelenkerkrankungen	70
6.6	Diskussion zur Versuchsdurchführung	72
7	ZUSAMMENFASSUNG	75
Anhang		
	LITERATURVERZEICHNIS	77
	ABKÜRZUNGSVERZEICHNIS	92

EIGENE PUBLIKATIONEN	93
LEBENS LAUF	94
DANKSAGUNG.....	95
ERKLÄRUNG	96

Literaturverzeichnis**Ader R (1974)**

Letter: Behaviorally conditioned immunosuppression.
Psychosom Med 36: 2: 183-4

Ader R, Cohen N (1975)

Behaviorally conditioned immunosuppression.
Psychosom Med 37: 333-340

Ader R, Felton DL, Cohen N (2001)

Psychoneuroimmunology.
Academic Press, San Diego, U.S.A.

Akbar AN, Terry L, Timms A, Beverley PC, Janossy G (1988)

Loss of CD45R and gain of UCHL1 reactivity is a feature of primed T cells.
J Immunol 140: 7: 2171-8

Akiba H, Kehren J, Ducluzeau MT, et al. (2002)

Skin inflammation during contact hypersensitivity is mediated by early recruitment of CD8⁺ T cytotoxic 1 cells inducing keratinocyte apoptosis.
J Immunol 168: 6: 3079-87

Arlettaz L, Barbey C, Dumont-Girard F et al. (1999)

CD45 isoform phenotypes of human T cells: CD4(+)CD45RA(-)RO(+) memory T cells re-acquire CD45RA without losing CD45RO.
Eur J Immunol 29: 12: 3987-94

Arnon TI, Markel G, Mandelboim O (2006)

Tumor and viral recognition by natural killer cells receptors.
Semin Cancer Biol 16: 5: 348-58.

Atanackovic D, Brunner-Weinzierl MC, Kroger H, Serke S, Deter HC (2002)

Acute psychological stress simultaneously alters hormone levels, recruitment of lymphocyte subsets, and production of reactive oxygen species.
Immunol Invest 31: 2: 73-91

Atanackovic D, Schulze J, Kroger H, Brunner-Weinzierl MC, Deter HC (2003)

Acute psychological stress induces a prolonged suppression of the production of reactive oxygen species by phagocytes.
J Neuroimmunol 142: 1-2: 159-65

Austrup F, Vestweber D, Borges E, et al. (1997)

P- and E-selectin mediate recruitment of T-helper-1 but not T-helper-2 cells into inflamed tissues.
Nature 385: 6611: 81-3

Bachen EA, Manuck SB, Marsland AL, et al. (1992)

Lymphocyte subset and cellular immune responses to a brief experimental stressor.
Psychosom Med 54: 673-679

Banchereau J, Steinman RM (1998)

Dendritic cells and the control of immunity.
Nature 392: 6673: 245-52

Barnaba V, Franco A, Paroli M, et al., (1994)

Selective expansion of cytotoxic T lymphocytes with a CD4+CD56+ surface phenotype and a T helper type 1 profile of cytokine secretion in the liver of patients chronically infected with Hepatitis B virus.
J Immunol 152: 3074-3087

Barry M, Bleackley RC (2002)

Cytotoxic T-Lymphocytes: All Roads Lead To Death.
Nat Rev Immunol 2: 401-409

Benschop RJ, Nieuwenhuis EE, Tromp EA, Godaert GL, Ballieux RE, van Doornen LJ (1994)

Effects of beta-adrenergic blockade on immunologic and cardiovascular changes induced by mental stress.
Circulation 89 (2): 762-9.

Benschop RJ, Rodriguez-Feuerhahn M, Schedlowski M (1996)

Catecholamine-induced leukocytosis: early observations, current research, and future directions.
Brain Behav Immun 10: 77-91

Besedovsky HO, Sorkin E, Felix D, Haas H (1977)

Hypothalamic changes during the immune response.
Eur J Immunol 7: 323-325.

Besedovsky HO, Del Rey A, Sorkin E, Dinarello CA (1986)

Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones.
Science 233: 652-654.

Blalock JE (2005)

The immune system as the sixth sense.
J Intern Med 257 (2): 126-38

Bosch JA, Ring C, de Geus EJ, Veerman EC, Amerongen AV (2002)

Stress and secretory immunity.
Int Rev Neurobiol 2002 (52): 213-53

Bosch JA, Berntson GG, Cacioppo JT, Dhabhar FS, Marucha PT (2003)

Acute stress evokes selective mobilization of T cells that differ in chemokine receptor expression: a potential pathway linking immunologic reactivity to cardiovascular disease.
Brain Behav Immun 17: 4: 251-9

Bosch JA, Berntson GG, Cacioppo JT, Marucha PT (2005)

Differential mobilization of functionally distinct natural killer subsets during acute psychological stress.

Psychosom Med 67: 3: 366-75

Bratke K, Kuepper M, Bade B, Virchow JC Jr, Luttmann W (2005)

Differential expression of human granzymes A, B, and K in natural killer cells and during CD8+ T cell differentiation in peripheral blood.

Eur J Immunol 35: 9: 2608-16

Brosschot JF, Benschop RJ, Godaert GLR, et al. (1992)

Effects of experimental psychological stress on distribution and function of peripheral blood cells.

Psychosom Med 54: 394-406

Burns VE, Drayson M, Ring C, Carroll D (2002)

Perceived stress and psychological well-being are associated with antibody status after meningitis C conjugate vaccination.

Psychosom Med 64(6): 963-70

Butcher EC, Picker LJ (1996)

Lymphocyte homing and homeostasis.

Science 272: 5258: 60-6

Cacioppo JT, Malarkey WB, Kiecolt-Glaser JK, et al. (1995)

Heterogeneity in neuroendocrine and immune responses to brief psychological stressors as a function of autonomic cardiac activation.

Psychosom Med 57:154-164

Calcagni E, Elenkov I (2006)

Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases.

Ann N Y Acad Sci 1069: 62-76

Campbell JJ, Haraldsen G, Pan J, et al. (1999)

The chemokine receptor CCR4 in vascular recognition by cutaneous but not intestinal memory T cells.

Nature 400: 776–80

Campbell JJ, Murphy KE, Kunkel EJ, et al. (2001)

CCR7 expression and memory T cell diversity in humans.

J Immunol 166: 2: 877-84

Carrasco J, Godelaine D, Van Pel A, Boon T, van der Bruggen P (2006)

CD45RA on human CD8 T cells is sensitive to the time elapsed since the last antigenic stimulation.

Blood 108: 9: 2897-905

Champagne P, Ogg GS, King AS et al., 2001

Skewed maturation of memory HIV-specific CD8 T lymphocytes.
Nature 410: 106-111

Charo IF, Ransohoff RM (2006)

The many roles of chemokines and chemokine receptors in inflammation.
N Engl J Med 354: 6: 610-21

Chen G, Shankar P, Lange C, et al (2001)

CD8 T cells specific for human immunodeficiency virus, Epstein-Barr virus, and Cytomegalovirus lack molecules for homing to lymphoid sites of infection.
Blood 98: 156-164

Chrousos GP (1995)

The Hypothalamic–Pituitary–Adrenal Axis and Immune-Mediated Inflammation.
N Engl J Med 332: 20: 1351-1363

Cohen S, Tyrrell DA, Smith AP (1991)

Psychological stress and susceptibility to the common cold.
N Engl J Med 325: 9: 606-12

Darmon AJ, Nicholson DW, Bleackley RC (1995)

Activation of the apoptotic protease CPP32 by cytotoxic T-cell-derived granzyme B.
Nature 377: 446–448

DeRijk RH, Eskandari F, Sternberg EM (2004)

Corticosteroid resistance in a subpopulation of multiple sclerosis patients as measured by ex vivo dexamethasone inhibition of LPS induced IL-6 production.
J Neuroimmunol 151: 1-2: 180-8

Dhabhar FS, Miller AH, McEwen BS, Spencer RL (1995)

Effects of stress on immune cell distribution. Dynamics and hormonal mechanisms.
J Immunol 154: 10: 5511-27.

Dhabhar FS, McEwen BS (1997)

Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: A potential role for leukocyte trafficking.
Brain Behav Immun 11: 286-306

Dhabhar FS, McEwen BS (2001)

Bidirectional effects of stress and glucocorticoid hormones on immune function: Possible explanations for paradoxical observations.
In Ader R, Felten DL & Cohen N (Eds.), *Psychoneuroimmunology (3rd ed.)*. Academic Press, San Diego, CA, USA. pp. 301-338

Dhabhar FS (2002)

Stress-induced augmentation of immune function--the role of stress hormones, leukocyte trafficking, and cytokines.
Brain Behav Immun 16: 6: 785-98.

Dhabhar FS, Viswanathan K (2005)

Short-term stress experienced at time of immunization induces a long-lasting increase in immunologic memory.

Am J Physiol Regul Integr Comp Physiol 289: 3: 738-44

Dopp JM, Miller GE, Myers HF, Fahey JL (2000)

Increased natural killer-cell mobilization and cytotoxicity during marital conflict.

Brain Behav Immun 14: 1: 10-26

Edwards KM, Burns VE, Reynolds T, Carroll D, Drayson M, Ring C (2006a)

Acute stress exposure prior to influenza vaccination enhances antibody response in women.

Brain Behav Immun 20: 2: 159-68

Edwards KM, Burns VE, Allen LM, et al. (2006b)

Eccentric exercise as an adjuvant to influenza vaccination in humans.

Brain Behav Immun [Epub ahead of print]

Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES (2000)

The Sympathetic Nerve—An Integrative Interface between Two Supersystems: The Brain and the Immune System.

Pharmacol Rev 52: 595–638.

Fournier C (2005)

Where Do T Cells Stand in Rheumatoid Arthritis?

Joint Bone Spine 72: 6: 527-532

Gannon GA, Rhind S, Shek PN, Shephard RJ (2002)

Naive and memory T cell subsets are differentially mobilized during physical stress.

Int J Sports Med 23: 3: 223-9

Gattorno M, Prigione I, Morandi F et al. (2005)

Phenotypic and functional characterisation of CCR7⁺ and CCR7⁻ CD4⁺ memory T cells homing to the joints in juvenile idiopathic arthritis.

Arthritis Res Ther 7: 2: 256-67

Geginat J, Lanzavecchia A, Sallusto F (2003)

Proliferation and differentiation potential of human CD8⁺ memory T-cell subsets in response to antigen or homeostatic cytokines.

Blood 101: 11: 4260-6

Gett AV, Sallusto F, Lanzavecchia A, Geginat J. (2003)

T cell fitness determined by signal strength.

Nat Immunol 4: 4: 355-60

Glaser R, Sheridan J, Malarkey WB, MacCallum RC, Kiecolt-Glaser JK (2000)

Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine.

Psychosom Med 62: 6: 804-7

Glaser R, Kiecolt-Glaser JK (2005)

Stress-induced immune dysfunction: implications for health.
Nat Rev Immunol 5: 3: 243-51.

Gorbachev AV, Fairchild RL (2001)

Induction and regulation of T-cell priming for contact hypersensitivity.
Crit Rev Immunol 21: 5: 451-72

Hammond KJ, Pelikan SB, Crowe NY et al., (1999)

NKT cells are phenotypically and functionally diverse.
Eur J Immunol 29: 3768-3781

Harris ED Jr. (1990)

Rheumatoid arthritis. Pathophysiology and implications for therapy.
N Engl J Med 322: 18: 1277-89

Hengel RL, Thaker V, Pavlick MV, et al. (2003)

Cutting edge: L-selectin (CD62L) expression distinguishes small resting memory CD4+ T cells that preferentially respond to recall antigen.
J Immunol 170: 28-32

Herbert TB, Cohen S, Marsland AL (1994)

Cardiovascular reactivity and the course of immune response to an acute psychological stressor.
Psychosom Med 56: 4:337-44

Herrmann M, Scholmerich J, Straub RH (2000)

Stress and rheumatic diseases.
Rheum Dis Clin North Am 26: 4: 737-63

Hislop AD, Gudgeon NH, Callan MF, et al. (2001)

EBV-specific CD8+ T cell memory: relationships between epitope specificity, cell phenotype, and immediate effector function.
J Immunol 167: 2019-2029

Jenkins MK, Khoruts A, Ingulli E, et al. (2001)

In vivo activation of antigen-specific CD4 T cells.
Annu Rev Immunol 19: 23-45

Jezova D (2005)

Control of ACTH secretion by excitatory amino acids: functional significance and clinical implications.
Endocrine 28: 3: 287-94

Johannes B, Fischer F (1990)

Computer-Modelle der Belastung zur Untersuchung der Abhängigkeit der individuellen Stress-Reaktivität vom Belastungstyp.
XXIII. Tagung der STAg KMB INTERKOS-MOS, Koshike, CSFR

Johannes B, Kirsch K, Fischer F (1995)

Voice measurement of oral communication and the experiment „REGULATION“. Extended Abstracts and Participants Forum 7th Microgravity Summer School. Topic: Space and Telemedicine, Schnellenberg Castle 4th – 7th July, 1995. pp 143-146

Johnson EO, Vlachoyiannopoulos PG, Skopouli FN, Tzioufas AG, Moutsopoulos HM (1998)

Hypofunction of the stress axis in Sjogren's syndrome.
J Rheumatol 25: 8: 1508-14

Kagi D, Ledermann B, Burki K, Hengartner H, Zinkernagel RM (1994)

CD8+ T cell-mediated protection against an intracellular bacterium by perforin dependent cytotoxicity.
Eur. J. Immunol 24: 3068–72

Kambayashi T, Assarsson E, Michaelsson J, et al. (2000)

Emergence of CD8+ T cells expressing NK cell receptors in influenza A virus-infected mice. *J Immunol* 165: 9: 4964-9

Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R (1995)

Slowing of wound healing by psychological stress.
Lancet 346: 8984: 1194-6

Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J (1996)

Chronic stress alters the immune response to influenza virus vaccine in older adults.
Proc Natl Acad Sci USA 93: 7: 3043-7

Kilpelainen M, Koskenvuo M, Helenius H, Terho EO (2002)

Stressful life events promote the manifestation of asthma and atopic diseases.
Clin Exp Allergy 32: 256-263

Kimura K, Isowa T, Ohira H, Murashima S. (2005)

Temporal variation of acute stress responses in sympathetic nervous and immune systems. *Biol Psychol* 70: 2:131-9

Kraan MC, Haringman JJ, Weedon H et al., 2004

T cells, fibroblast-like synoviocytes, and granzyme B+ cytotoxic cells are associated with joint damage in patients with recent onset rheumatoid arthritis.
Ann Rheum Dis 63: 5: 483-8

Landmann R (1992)

Beta-adrenergic receptors in human leukocyte subpopulations.
Eur J Clin Invest 22: I: 30-36

Lanzavecchia A, Sallusto F (2000)

Dynamics of T lymphocyte responses: intermediates, effectors and memory cells.
Science 290: 92–97

Lanzavecchia A, Sallusto F (2005)

Understanding the generation and function of memory T cell subsets.
Curr Opin Immunol 17: 3: 326-32

Maes M, Song C, Lin A et al. (1998)

The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety.
Cytokine 10: 4: 313-8

Maier SF, Watkins LR (1998)

Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition.
Psychol Rev 105: 1: 83-107

McEwen BS (1998)

Protective and damaging effects of stress mediators.
N Engl J Med 338: 3:171-9

McEwen BS, Seeman T (1999)

Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load.
Ann N Y Acad Sci 896: 30-47

Meng Y, Harlin H, O'Keefe JP, Gajewski TF (2006)

Induction of cytotoxic granules in human memory CD8+ T cell subsets requires cell cycle progression.
J Immunol 177: 3: 1981-7

Metalnikov S, Chorine V (1926)

Rôle des réflexes conditionnels dans l'immunité.
Ann Inst Pasteur 40: 893-900

Michie CA, McLean A, Alcock C, Beverley PC (1992)

Lifespan of human lymphocyte subsets defined by CD45 isoforms.
Nature 360: 6401: 264-5.

Mohr DC, Hart SL, Julian L, Cox D, Pelletier D (2004)

Association between stressful life events and exacerbation in multiple sclerosis: a meta analysis.
BMJ 328: 7442: 731

Moser B, Loetscher P (2001)

Lymphocyte traffic control by chemokines.
Nat Immunol 2: 2: 123-8

Munck A, Guyre PM (1986)

Glucocorticoid physiology, pharmacology and stress.
Adv Exp Med Biol 196: 81-96

Nagata S, Golstein P (1995)

The Fas death factor.

Science 267: 1449–1456

Nguyen KT, Deak T, Owens SM, et al. (1998)

Exposure to acute stress induces brain interleukin-1beta protein in the rat.

J Neurosci 18: 6: 2239-46

Novotny GEK, Heuer T, Schöttelndreier A, Fleisgarten C (1994)

Plasticity of innervation of the medulla of axillary lymph nodes in the rat after antigenic stimulation.

Anat Rec 238: 213-224

Novotny GEK, Heuer T, Schöttelndreier A, Fleisgarten C (1995)

An ultrastructural quantitative analysis of ten innervation of axillary nodes of the rat after antigenic stimulation.

Anat Rec 243: 208-222

Ohkawa T, Seki S, Dobashi H, et al. (2001)

Systematic characterization of human CD8+ T cells with natural killer cell markers in comparison with natural killer cells and normal CD8+ T cells.

Immunology 103: 281-290

Owen N, Steptoe A (2003)

Natural killer cell and proinflammatory cytokine responses to mental stress: associations with heart rate and heart rate variability.

Biol Psychol 63: 2: 101-15

Pallanti S, Lotti T, Urpe M (2005)

Psychoneuroimmunodermatology of atopic dermatitis: from empiric data to the evolutionary hypothesis.

Dermatol Clin 23: 4: 695-701

Pittet MJ, Speiser DE, Valmori D, Cerottini JC, Romero P (2000)

Cutting edge: cytolytic effector function in human circulating CD8+ T cells closely correlates with CD56 surface expression.

J Immunol 164: 1148-1152

Podack ER, Dennert G (1983)

Assembly of two types of tubules with putative cytolytic function by cloned natural killer cells.

Nature 302: 442–445

Roman E, Miller E, Harmsen A, et al. (2002)

CD4 effector T cell subsets in the response to influenza: heterogeneity, migration, and function.

J Exp Med 196: 957-968

Ronday HK, van der Laan WH, Tak PP et al. (2001)

Human granzyme B mediates cartilage proteoglycan degradation and is expressed at the invasive front of the synovium in rheumatoid arthritis.

Rheumatology 40: 55–61

Russell JH, Ley TJ (2002)

Lymphocyte-mediated cytotoxicity.

Annu Rev Immunol 20: 323-70

Saint-Mezard, P, Chavagnac C, Bosset S, et al. (2003)

Psychological stress exerts an adjuvant effect on skin dendritic cell functions in vivo.

J Immunol 171: 4073-4080

Sallusto F, Lenig D, Forster R, Lipp M, Lanzavecchia A (1999)

Two subsets of memory T lymphocytes with distinct homing potentials and effector functions.

Nature 401: 708-712

Sallusto F, Geginat J, Lanzavecchia A (2004)

Central memory and effector memory T cell subsets: function, generation, and maintenance.

Annu Rev Immunol 22: 745-63

Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR, Oja H (2000)

The role of acute and chronic stress in asthma attacks in children.

Lancet 356: 9234: 982-7

Sanders VM (2006)

Interdisciplinary research: noradrenergic regulation of adaptive immunity.

Brain Behav Immun 20: 1-8

Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W (1987)

Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor.

Science 238: 4826: 522-4

Sapolsky RM, Romero LM, Munck AU (2000)

How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions.

Endocr Rev 21: 1: 55-89

Satoh M, Seki S, Hashimoto W, et al. (1996)

Cytotoxic gamma delta or alpha beta T cells with a natural killer cell marker, CD56, induced from human peripheral blood lymphocytes by a combination of IL-12 and IL2.

J Immunol 157: 3886-3892

Scalzo AA (2002)

Successful control of viruses by NK cells--a balance of opposing forces?

Trends Microbiol 10: 470-474

Schedlowski M, Pröhl F, Alker J, et al. (1993)

Psychophysiological, neuroendocrine and cellular immune reactions under psychological stress.
Neuropsychobiology 28: 87-90

Schedlowski M, Hosch W, Oberbeck R, et al. (1996)

Catecholamines modulate human NK cell circulation and function via spleen-independent beta 2-adrenergic mechanisms.
J Immunol 156: 1: 93-9

Schedlowski M, Tews U (1999)

Psychoneuroimmunology: An Interdisciplinary Introduction.
Kluwer Academic/ Plenum Publishers, New York, U.S.A.

Schulz H, Schulz KH (1997)

Kurzfristige psychische Belastung und Immunfunktionen – eine metaanalytische Übersicht
In KH Schulz, J Kugler, M Schedlowski (Hrsg.) *Psychoneuroimmunologie: Ein interdisziplinäres Forschungsfeld*. Verlag Hans Huber, Bern, Schweiz. pp 21-59

Schwendemann J, Choi C, Schirmacher V, Beckhove1 P (2005)

Differentiation of Activated Human Peripheral Blood CD8 and CD4 Effector Memory T Cells
J Immunol 175: 1433–1439

Schwenkmetzger P, Hodapp V, Spielberger CD (1992)

Das State-Trait-Ärgerausdrucks-Inventar STAXI: Handbuch.
1. Auflage, Hans Huber Verlag, Bern, Schweiz

Seegerstrom SC, Miller GE (2004)

Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry.
Psychol Bull 130: 4: 601-30

Selye H (1982)

History and present status of the stress concept.
In L. Goldberger and S. Breznitz, (eds), *Handbook of Stress: Theoretical and Clinical Aspects*.
Free Press, New York, USA. pp 7-17

Shresta S, Heusel JW, Macivor DM, Wesselschmidt RL, Russell JH, Ley TJ (1995)

Granzyme B plays a critical role in cytotoxic lymphocyte-induced apoptosis.
Immunol Rev 146: 211

Skapenko A, Leipe J, Lipsky PE, Schulze-Koops H (2005)

The role of the T cell in autoimmune inflammation.
Arthritis Research & Therapy 7: II: S4-S14

Slifka MK, Rodriguez F, Whitton JL (1999)

Rapid on/off cycling of cytokine production by virus-specific CD8+ T cells.
Nature 401: 6748: 76-9

Smeets TJ, Kraan MC, Galjaard S, Youssef PP, Smith MD, Tak PP (2001)

Analysis of the cell infiltrate and expression of matrix metalloproteinases and granzyme B in paired synovial biopsy specimens from the cartilage-pannus junction in patients with RA.

Ann Rheum Dis 60: 6: 561-5

Solomon GF, Segerstrom SC, Grohr P, Kemeny M, Fahey J (1997)

Shaking up immunity: psychological and immunologic changes after a natural disaster.

Psychosom Med 59: 2: 114-27

Soni A, Pepper GM, Wyrwinski PM, et al. (1995)

Adrenal insufficiency occurring during septic shock: incidence, outcome, and relationship to peripheral cytokine levels.

Am J Med 98: 3: 266-71

Sprent J, Tough DF (1994)

Lymphocyte life-span and memory.

Science 265: 5177: 1395-400

Stephoe A, Vögele L (1991)

Methodology of mental stress testing in cardiovascular research.

Circulation 83: II: 14-24

Sternberg EM (2001)

Neuroendocrine regulation of autoimmune/ inflammatory disease.

J Endocrinol 169: 3: 429-435

Sternberg EM (2006)

Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. *Nat*

Rev Immunol 6: 4: 318-28

Stoddard SL, Bergdall VK, Townsend DW, Levin BE (1986)

Plasma catecholamines associated with hypothalamically-elicited defense behavior.

Physiol Behav 36: 867-873

Straub RH, Dhabhar FS, Bijlsma JW, Cutolo M (2005)

How psychological stress via hormones and nerve fibers may exacerbate rheumatoid arthritis.

Arthritis Rheum 52: 16-26

Straub H, Härle P (2005)

Stress, Hormone und neuronale Signale bei rheumatoider Arthritis. Der negative Einfluss auf das chronische Entzündungsgeschehen.

Med Klin 100: 794-803

Takata H, Takiguchi M (2006)

Three memory subsets of human CD8⁺ T cells differently expressing three cytolytic effector molecules.

J Immunol 177: 7: 4330-40

Tews U, Schedlowski M (1999)

Psychological Methods.

In: *Schedlowski M, Tews U: Psychoneuroimmunology: An Interdisciplinary Introduction*. Kluwer Academic/ Plenum Publishers, New York, USA. Pp. 113-124**Titinchi S, Clark B (1984)**alpha₂-adrenoceptors in human lymphocytes: Direct characterization by [³H] yohimbine binding. *Biochem Biophys Res Commun* 121: 1-7**Trapani JA, Smyth MJ (2002)**

Functional significance of the perforin/granzyme cell death pathway.

Nat Rev Immunol 2: 735-747**Unsoeld H, Pircher H (2005)**

Complex Memory T-Cell Phenotypes Revealed by Coexpression of CD62L and CCR7.

Virology 4510–4513**Ursin H, Olf M (1993)**

Psychobiology of coping and defence strategies.

Neuropsychobiology 28: 1-2: 66-71**Vedhara K, Cox NK, Wilcock GK (1999)**

Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination.

Lancet 353: 9153: 627-31**Viswanathan K, Dhabhar FS (2005)**

Stress-induced enhancement of leukocyte trafficking into sites of surgery or immune activation.

Proc Natl Acad Sci U.S.A. 102: 16: 5808-13**Viswanathan K, Daugherty C, Dhabhar FS (2005)**

Stress as an endogenous adjuvant: augmentation of the immunization phase of cell-mediated immunity.

Int Immunol 17: 8: 1059-69**Wagner UG, Kurtin PJ, Wahner A, et al. (1998)**

The role of CD8+ CD40L+ T cells in the formation of germinal centers in rheumatoid synovitis.

J Immunol 161: 11: 6390-7**Watkins LR, Maier SF (2005)**

Immune regulation of central nervous system functions: from sickness responses to pathological pain.

J Intern Med 257: 2: 139-55**Webster JI, Tonelli L, Sternberg EM (2002)**

Neuroendocrine regulation of immunity.

Annu Rev Immunol 20: 125-63

Wherry EJ, Teichgraber V, Becker TC, et al. (2003)

Lineage relationship and protective immunity of memory CD8 T cell subsets.
Nat Immunol 4: 3: 225-34

Willemsen G, Carroll D, Ring C, Drayson M. (2002)

Cellular and mucosal immune reactions to mental and cold stress: associations with gender and cardiovascular reactivity.
Psychophysiology 39: 2: 222-8

Wills MR, Carmichael AJ, Weekes MP, et al. (1999)

Human virus-specific CD8⁺ CTL clones revert from CD45RO^{high} to CD45RA^{high} in vivo: CD45RA^{high}CD8⁺ T cells comprise both naive and memory cells.
J Immunol 162: 7080-7087

Wolint P, Betts MR, Koup RA, Oxenius A (2004)

Immediate Cytotoxicity But Not Degranulation Distinguishes Effector and Memory Subsets of CD8⁺ T Cells.
J Exp Med 199: 925-936

Wood PG, Karol MH, Kusnecov AW, Rabin BS (1993)

Enhancement of antigen-specific humoral and cell-mediated immunity by electric footshock stress in rats.
Brain Behav Immun 7: 121-134

Wright RJ (2005)

Stress and atopic disorders.
J Allergy Clin Immunol 116: 6: 1301-6

Wrona D (2006)

Neural-immune interactions: an integrative view of the bidirectional relationship between the brain and immune systems.
J Neuroimmunol 172: 1-2: 38-58

Zabel BA, Agace WW, Campbell JJ, et al. (1999)

Human G protein-coupled receptor GPR-9-6/CC chemokine receptor 9 is selectively expressed on intestinal homing T lymphocytes, mucosal lymphocytes, and thymocytes and is required for thymus-expressed chemokine-mediated chemotaxis.
J Exp Med 190: 1241-56

Zajac AJ, Blattman JN, Murali-Krishna K, et al. (1998)

Viral immune evasion due to persistence of activated T cells without effector function.
J Exp Med 188: 2205-2213

Zaph C, Uzonna J, Beverley SM, Scott P (2004)

Central memory T cells mediate long-term immunity to *Leishmania major* in the absence of persistent parasites.
Nat Med 10: 10: 1104-10

Zhang X, Nakajima T, Goronzy JJ, Weyand CM (2005)

Tissue trafficking patterns of effector memory CD4⁺ T cells in rheumatoid arthritis.
Arthritis Rheum 12: 3839-49

Zorrilla EP, Luborsky L, McKay JR, et al. (2001)

The relationship of depression and stressors to immunological assays: a meta-analytic review.
Brain Behav Immun 15: 3: 199-226

Abkürzungsverzeichnis

A	Ausgangswert (Messung am Ende der Ruhephase 1)
ACTH	Adrenocorticotropes Hormon
AK	Antikörper
APC	Antigenpräsentierende Zellen
B	Stresswert (Messung während der Belastungsphase)
BE	Blutentnahme
C	Erholungswert (Messung am Ende der Erholungsphase)
CBF	Campus Benjamin Franklin
CRH	Corticotropin Releasing Hormone
CTL	Cytotoxische T-Zellen
DC	Dendritische Zellen
DMSO	Dimethylsulfoxid
EDTA	Ethylendiamintertraessigsäure
FACS	Fluorescence activated cell sorting
FB	Fragebogen
FCS	Fötales Kälberserum (fetal calf serum)
FITC	Fluoresceinisothiocyant
HPA-Achse	Hypothalamic-pituitary-adrenal-Achse (Hypothalamus-Hypophysen-Nebennieren-Achsen)
JIA	Juvenile idiopathische Arthritis
MW	Mittelwert
n	Stichprobenumfang
n.s.	nicht signifikant
NK-Zellen	Natürliche Killerzellen
NKCA	Natürliche Killerzellaktivität
PBMC	peripherer mononukleäre Zellen
PBS	Phosphate buffered saline
PE	Phycoerythrin
PerCP	Peridiniumchlorophyll-Protein
PI	Propidiumjodid
prä	unter Ruhebedingungen (vor dem Belastungstest)
post	unter Ruhebedingungen (nach der Erholungsphase)
RA	Rheumatoide Arthritis
SD	Standardabweichung
SEM	Standardfehler der Mittelwerte („standard error of means“)
Sig	statistische Signifikanz
SNS	Sympathisches Nervensystem
STAXI	State Trait Anger Expression Inventory (State-Trait-Ärgerausdruckinventar)
Stress	unter Stressbedingungen (direkt nach dem Belastungstest)
T _{CM}	central memory T-cells (zentrale Gedächtnis-T-Zellen)
T _{EM}	effector memory T-cells (Effektor-Gedächtnis-T-Zellen)
T _{EMRA}	terminally differentiated effector T-cells (terminal differenzierte Effektor-T-Zellen)
T _{naive}	naïve T-cells (naive T-Zellen)

Eigene Publikationen

Originalpublikationen

Atanackovic D, Schnee B, Schuch G, Faltz C, Schulze J, Weber CS, Schafhausen P, Bartels K, Bokemeyer C, Brunner-Weinzierl MC, Deter HC (2006)

Acute psychological stress alerts the adaptive immune response: stress-induced mobilization of effector T cells.

J Neuroimmunol 176: 1-2: 141-52

Kurzartikel

Atanackovic D, Muzzolini J, Weber CS, Schnee B, Faltz C, Hegewisch-Becker S, Deter HC (2006)

Effects of Acute Psychological Stress on Virus-Specific and Skin-Homing T Cells.

Psychother Psych Med 56: 2

Zweiter Preis des Poster Awards der 25th European Conference on Psychosomatic Research, Berlin (2004) für:

Atanackovic D, Hegewisch-Becker S, Brunner M, Wagner M, Schnee B, Deter HC, Weber, CS (2004)

Acute psychological stress causes a redistribution of memory/effector T-cell subsets in humans.

J Psychosom Res 56: 581-673

Lebenslauf

Mein Lebenslauf wird aus Datenschutzgründen in der elektronischen Version meiner Arbeit nicht mit veröffentlicht.

Danksagung

Zuerst und vor allem danke ich meinem Doktorvater Herrn Prof. Hans-Christian Deter für die freundliche Überlassung des Themas und die Freiheit bei der Gestaltung dieser Arbeit.

Den Mitarbeitern der Abteilung für Psychosomatik des Campus Benjamin Franklin, insbesondere Miriam Rudat und Dr. Cora Weber, möchte ich für ihre ausdauernde konstruktive Kritik, stete Ermutigung und moralische Unterstützung danken.

Ganz besonders danke ich Herrn Dr. Djordje Atanackovic sowie den Mitgliedern seiner Arbeitsgruppe für den intensiven und anregenden Gedankenaustausch.

Des Weiteren möchte ich Frau PD Dr. Monika Brunner-Weinzierl und den Mitgliedern ihrer Arbeitsgruppe im DRFZ für die kollegiale Aufnahme, die gute Einarbeitung und die freundliche Hilfsbereitschaft bei der Durchführung des immunologischen Teils der vorliegenden Studie danken - insbesondere Karin Knieke, die immer ein offenes Ohr nicht nur bei wissenschaftlichen Fragestellungen hatte.

Für die freundliche Unterstützung bei der Bewältigung statistischer Fragestellungen danke ich Herrn PD Dr. Dr. Werner Hopfenmüller aus der Abteilung für Biometrie und Medizinische Epidemiologie des CBF.

Sehr herzlich danke ich meiner Mutter für ihre oftmals stillschweigende, jedoch immer zuversichtliche Unterstützung in jeglicher Hinsicht, ohne die meine Ausbildung und die Erstellung dieser Dissertationsschrift nicht möglich gewesen wären.

Meinem Bruder danke ich für seine Anwesenheit, nicht zuletzt in und vor der Bibliothek mit ablenkenden, ermutigenden und den Horizont erweiternden fachübergreifenden Gesprächen. Amit danke ich für seine unendliche Geduld, Friede für die vielen Milchkaffees und meinen Freunden für ihr Verständnis in den Zeiten meiner rezidivierenden geistigen und körperlichen Abwesenheit.

Erklärung

„Ich, Benjamin Schnee, erkläre, dass ich die vorgelegte Dissertationsschrift mit dem Thema: ‚Auswirkungen von kurzzeitigem psychischem Laborstress auf die Verteilung von T-Zell-Subpopulationen und Effektormechanismen des peripher zirkulierenden T-Zell-Pools‘ selbst verfasst habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopie anderer Arbeiten dargestellt habe.“

Datum

Unterschrift