EDITORIAL

SUBSTANCE P: AN INFLAMMATORY PEPTIDE

G.S. KATSANOS, A. ANOGEIANAKI, C. ORSO[1], S. TETÈ[2], V. SALINI[1], P.L. ANTINOLFI[3] and G. SABATINO[4]

Immunology Division, University of Chieti-Pescara, Chieti, Italy; [1]Orthopaedic Division, University of Chieti-Pescara, Chieti; [2]Dental School, University of Chieti-Pescara, Chieti; [3]Orthopaedics Division, University of Perugia, Perugia; [4]Paediatric Division, University of Chieti-Pescara, Chieti, Italy

Received March 19, 2008 – Accepted May 10, 2008

Substance P (SP) is involved in neurogenic inflammation and in the pathogenesis of several inflammatory diseases, demonstrating that there is a narrow interrelationship between the nervous system and immunity. Macrophage functions are altered in stress, therefore, since SP is a macrophage activator, its biological effect has been intimately linked to stress. In fact, SP enhances LPS-induced macrophage TNFα production from stressed animals and stimulates the production of IL-8 CXC chemokine response in a mast cell line *in vitro*. The stress-induced cytokines from macrophage also alter and contribute to inflammation. Understanding the pathophysiology of inflammation and the role of the chemical mediator SP may improve inflammation management.

Immune inflammation is a part of innate and adaptive immune response to microbes, antigens and cytokines (1-6). The migration of activated T lymphocytes to sites of inflammation is part of a general process of leukocyte recruitment (7-11). This process is due to the actions of several cytokines (12-17). Substance P (SP) was first discovered in 1931 and isolated by Leeman S. et al. in the 70's and was shown to be an undecapeptide (18-19). There is a good deal of evidence to support the hypothesis that SP is one of the most important neurotransmitters and neuromodulators present in the human brain (20-22). Its biological effect has been intimately linked to the pathophysiology of several relevant neurological and psychiatric disorders, such as migraine, asthma, nausea, inflammatory bowel syndrome, anxiety, depression and stress (23-25). For decades, research has demonstrated that chronic diseases characterized by dysregulation of inflammation are particularly susceptible to exacerbation by stress and emotion (23). Likewise, rates of depression and anxiety are overrepresented in individuals suffering from chronic inflammatory diseases. In recent years, substance P has been implicated in both pathophysiology of inflammatory disease and the pathophysiology of depression, anxiety and stress (23).

Perceived stress has long been allied with disturbances of the dynamic equilibrium established between the nervous, endocrine and immune systems, thus triggering or aggravating disease manifestation. For example, several common skin diseases are now acknowledged to be worsened by psychological stress, particularly immunodermatoses such as atopic dermatitis, psoriasis, seborrheic eczema, prurigo

Key words: Substance P, neurogenic inflammation, cytokines, T cells

Mailing address: Prof. G. Sabatino,
Paediatric Division,
University of Chieti-Pescara,
via dei Vestini,
Chieti, Italy
Tel: ++39 0871 358339
e-mail: sabatino@unich.it

1721-727 (2008)

nodularis, lichen planus, chronic urticaria, alopecia areata and pruritus sine materia (26). Pruritus is perhaps the most common symptom associated with the majority of these inflammatory skin diseases, and acute as well as chronic stress perceptions are recognized to trigger or enhance pruritus. A wealth of mediators released systemically or locally in the skin in response to stress increase sensory innervation, upregulate the production of other pruritogenic agents, perpetuate (neurogenic) inflammation and lower the itch threshold (27). This demonstrates that pathogenesis of atopic dermatitis involves the interactions of immune and neuroendocrine systems with SP participation.

Stress primarily exacerbates allergic dermatitis via SP-dependent cutaneous neurogenic inflammation and subsequent local cytokine shifting and should be considered as a therapeutic target. Recently, high levels of neurotrophic factors have been found in bronchial asthma. These factors include nerve growth factor, brain-derived neurotrophic factor, and leukemia inhibitory factor (28). Neurotrophic factors are first synthesized in bronchial epithelial cells, immune cells, and other cells in the airway; they are then taken up by the synapse and are finally transported to dorsal root ganglia (C7-T5). Increased neurotrophic factors in dorsal root ganglia promote the synthesis and release of SP. As a result, SP causes a series of reactions such as contraction of airway smooth muscles, secretion of mucous fluids, seepage of capillary vessels, release of mediators of inflammation, and aggravation of airway hyperreactivity, including macrophage activation and subsequent release of cytokines and chemokines (29-30). It is interesting to note that the anatomic locations of dorsal root ganglia (C7-T5) are similar to a series of acupuncture points in traditional Chinese medicine. It is hypothesized that dorsal root ganglia may be the targets of acupuncture in the treatment of asthma; in this process, acupuncture has an inhibitory effect on the uptake of neurotrophic factors, or it inhibits the synthesis and release of SP in dorsal root ganglia. As a result, airway neurogenic inflammation in asthma is relieved.

One of the most important capacities of every normal individual's immune system is its ability to recognize, respond and eliminate antigens (with cytokine production), a process that is not harmful for the individual (self), unless cytokine levels are out of the physiological range (31-33). Tolerance is an immunological unresponsiveness, and intolerance to self antigens is maintained by several mechanisms (34-36). Potentially, neuropeptides serve as the initial insult, resulting in loss of tolerance and autoimmune disease. A fascinating question regarding the pathogenesis of alopecia areata is the potential linkage with the brain. Potentially, neuropeptides serve as the initial insult resulting in loss of tolerance and autoimmune disease. Siebenharr et al. have demonstrated that SP fibers are increased in early lesions, and that SP treatment induces catagen follicles along with activated CD8+ T cells (37-39).

Sleep difficulty is one of the hallmarks of menopause. Following recent studies showing no cardiac benefit and increased breast cancer, the question of indications for hormonal therapy has become even more pertinent. Three sets of sleep disorders are associated with menopause: insomnia/depression, sleep disordered breathing and fibromyalgia (40). The primary predictor of disturbed sleep architecture is the presence of vasomotor symptoms. This subset of women has lower sleep efficiency and more sleep complaints. The same group is at higher risk of insomnia and depression. The "domino theory" of sleep disruption leading to insomnia followed by depression has the most scientific support. High SP and low serotonin have significant potential to affect sleep and mood. Treatment of sleep itself seems to improve; if not resolve fibromyalgia. Menopausal sleep disruption can exacerbate other pre-existing sleep and circadian disorders.

SP is a neuropeptide that is a neurotransmitter and a neuromodulator in the central and peripheral nervous system. There is a link between the immune system and neurogenic inflammation and this is surely influenced by SP (41). During the past 30 years SP has been identified as an important mediator in the development and progress of inflammation by binding to its high-affinity neurokinin-1 receptor (NK-1R). SP is known to have regulatory effects on nervous or non-nervous cells, including immune cells. Neurogenic inflammation encompasses a series of vascular and non-vascular inflammatory responses, triggered by the activation of primary sensory neurons and the subsequent release of

inflammatory neuropeptides, including SP (42). Topical application of exogenous SP enhances wound closure kinetics, suggesting that wounds which have insufficient SP levels to promote a neuroinflammatory response do not have a normal wound repair mechanism.

Several data demonstrate lesion grade dependence of below-level pain development and suggest chemokines as potential candidates for integrating inflammation and central neuropathic pain after spinal cord injury. Accumulating evidence on bone physiopathology has indicated that the skeleton contains numerous nerve fibers, and its metabolism is regulated by the nervous system (46-48). Until now, more than 10 neuropeptides have been identified in the bone. SP is a neuropeptide released from axons of sensory neurons, belongs to the tachykinin family and plays important roles in many physiological and pathological processes by acting as a neurotransmitter, neuromodulator, or trophic factor. It activates signal transduction cascades by acting on the neurokinin-1 receptor (NK(1)-R). Previous studies have confirmed that the SP-immunoreactive (IR) axons innervate bone and adjacent tissues, and that their density varies depending on the regions and physiological or pathological conditions. Over the past few decades, it has been found that SP takes part in the stimulation of bone resorption, and its receptors have been demonstrated to be located in osteoclasts (49). Notably, in studies of skeletal ontogeny, SP-IR axons have been shown to appear at an early stage, mostly coinciding with the sequence of long bone mineralization. These findings, together with data obtained from chemically or surgically targeted nerve deletions, strongly suggest that SP is a potent regulator of skeletal physiology. The specific distribution of SP-IR nerve fibers, the different amount of SP within regions, and the various levels of expression of NK(1)-R in targeted cells presumably are related to and participate in bone metabolism. It can be predicted that the indirect roles of SP through other cytokines are as important as its direct roles in bone metabolism. This new regulating pathway of bone metabolism would have enormous implications in skeletal physiology, and the relevant research might present curative potentials to a spectrum of bone diseases.

Recent studies suggest that neuropeptides, and specifically SP, may be involved in the injury processes, as mentioned before, that occur following acute insults to the brain such as stroke and trauma, and may be responsible, in part, for edema formation (40, 42-45). Levels of SP are increased following CNS injury, which is indicative of neurogenic inflammation, and this is associated with injury to the blood-brain barrier, the development of cerebral edema, cell death and functional deficits. Subsequent studies inhibiting neuropeptide release have consistently shown decreased cerebral edema and improved neurological outcome, while SP antagonists administered after the insult are efficacious in reducing post-stroke cerebral edema and neurological deficits.

The current review summarizes the evidence supporting the benefits of inhibiting neurogenic inflammation to treat CNS injury. Recent evidence has suggested that neuropeptides, and in particular SP, may play a critical role in the development of morphological injury and functional deficits following acute insults to the brain with consequent cyclooxygenase augmentation and cellular damage (50-54). Few studies, however, have examined the role of SP, and more generally, neurogenic inflammation, in the pathophysiology of traumatic brain injury and stroke.

Those studies that have been reported suggest that SP is released following injury to the CNS and facilitates the increased permeability of the blood brain barrier, the development of vasogenic edema and the subsequent cell death and functional deficits that are associated with these events. Inhibition of the SP activity, either through inhibition of neuropeptide release, or the use of SP receptor antagonists, have consistently resulted in profound decreases in edema formation and marked improvements in functional outcome (55).

The isolation of SP and the later discovery of its preferred neurokinin (NK)1 receptor, led to an intense research effort aimed at elucidating the biological role of SP, particularly within the central nervous system. This wide therapeutic potential triggered an unprecedented research effort, both pre-clinically and clinically, to identify appropriate NK1 receptor antagonists and transform them into effective drugs (56). Aprepitant, a selective high-affinity antagonist of human substance P/neurokinin

1 (NK1) receptors, is the active ingredient of EMEND which has recently been approved by the FDA for the prevention of chemotherapy-induced nausea and vomiting (CINV). Aprepitant undergoes extensive metabolism, primarily via CYP3A4 mediated oxidation. It is interesting that this drug is not renal excreted.

REFERENCES

1. Abbas AK, Lichtman AH. Cellular and Molecular Immunology. Elsevier Saunders Fifth Edition, Philadelphia 2005.
2. Allavena P, Sica A, Garlanda C, Mantovani A. The Yin-Yang of tumor-associated macrophages in neoplastic progression and immune surveillance. Immunol Rev 2008; 222:155-61.
3. Weiner HL. A shift from adaptive to innate immunity: a potential mechanism of disease progression in multiple sclerosis. J Neurol 2008; 255(S1):3-11.
4. Castellani ML, Bhattacharya K, Tagen M, Kempuraj D, Perrella A, De Lutiis M, Boucher W, Conti P, Theoharides TC. Anti-chemokine therapy for inflammatory diseases. Int J Immunopathol Pharmacol 2007; 20:447-453.
5. Di Lorenzo L, Vacca A, Corfiati M, Lovreglio P, Soleo L. Evaluation of tumor necrosis factor-alpha and granulocyte colony-stimulating factor serum levels in lead-exposed smoker workers. Int J Immunopathol Pharmacol 2007; 20:239-247.
6. Papoff P, Mancuso M, Barbàra CS, Moretti C. The role of terlipressin in pediatric septic shock: a review of the literature and personal experience. Int J Immunopathol Pharmacol 2007; 20:213-222.
7. Martin AL, Schwartz MD, Jameson SC, Shimizu Y. Selective regulation of CD8 effector T cell migration by the p110gamma isoform of phosphatidylinositol 3-kinase. J Immunol. 2008; 180(4):2081-8.
8. Ou R, Zhang M, Huang L, Flavell RA, Koni PA, Moskophidis D. Regulation of immune response and inflammatory reactions against viral infection by VCAM-1. J Virol 2008; 82(6):2952-65.
9. Rosati E, Mencarelli S, Magini A, Sabatini R, Tassi C, Orlacchio A, Coaccioli S, Frenguelli A, Marconi P, Emiliani C. Enhancement of lysosomal glycohydrolase activity in human primary B lymphocytes during spontaneous apoptosis. Int J Immunopathol Pharmacol 2007; 20:279-288.
10. Hauswirth AW, Sonneck K, Florian ST, Krauth MT, Böhm A, Sperr WR, Valenta R, Schernthaner G-H, Printz D, Fritsch G, Bühring H-J, Valent P. Interleukin-3 promotes the expression of e-npp3/cd203c on human blood basophils in healthy subjects and in patients with birch pollen allergy. Int J Immunopathol Pharmacol 2007; 20:267-278.
11. Madonna R, Massaro M, Pandolfi A, Consoli A, Caterina RD. The prominent role of p38 mitogen-activated protein kinase in insulin-mediated enhancement of VCAM-1 expression in endothelial cells. Int J Immunopathol Pharmacol 2007; 20:539-555.
12. Galkina E, Ley K. Leukocyte influx in atherosclerosis. Curr Drug Targets 2007; 8(12):1239-48.
13. Bell LV, Else KJ. Mechanisms of leucocyte recruitment to the inflamed large intestine: redundancy in integrin and addressin usage. Parasite Immunol 2008; 30(3):163-70.
14. D'Offizi G, Gioia C, Corpolongo A, Martini F, Paganelli R, Volpi I, Sacchi A, Tozzi V, Narciso P, Poccia F. An IL-15 dependent CD8 T cell response to selected HIV epitopes is related to viral control in early-treated HIV-infected subjects. Int J Immunopathol Pharmacol 2007; 20:473-485.
15. Ventura MT, Sanapo F, Calogiuri GF, Satriano F. Anaphylaxis induced by intramuscular betamethasone disodium phosphate: reflections on a clinical case. Int J Immunopathol Pharmacol 2007; 20:387-392.
16. Feliciani C, Ruocco E, Zampetti A, Toto P, Amerio Pa, Tulli A, Amerio P, Ruocco V. Tannic acid induces in vitro acantholysis of keratinocytes via IL-1α and TNF-α. Int J Immunopathol Pharmacol 2007; 20: 289-300.
17. Mayerhofer M, Aichberger KJ, Florian S, Valent P. Recognition-sites for microbes and components of the immune system on human mast cells: relationship to CD antigens and implications for host defense. Int J Immunopathol Pharmacol 2007; 20:421-434.
18. Leeman SE, Ferguson SL. Substance P: an historical perspective. Neuropeptides 2000; 34(5):249-54.
19. Boyd ND, MacDonald SG, Kage R, Luber-Narod J, Leeman SE. Substance P receptor. Biochemical

characterization and interactions with G proteins. Ann NY Acad Sci. 1991; 632:79-93.
20. Anisman H, Baines MG, Berczi I, et al. Neuroimmune mechanisms in health and disease: 1. Health. CMAJ 1996; 155(7):867-74.
21. Luger TA, Bhardwaj RS, Grabbe S, Schwarz T. Regulation of the immune response by epidermal cytokines and neurohormones. J Dermatol Sci 1996; 13(1):5-10.
22. Sluka KA. Pain mechanisms involved in musculoskeletal disorders. J Orthop Sports Phys Ther 1996; 24(4):240-54.
23. Chancellor-Freeland C, Zhu GF, Kage R, Beller DI, Leeman SE, Black PH. Substance P and stress-induced changes in macrophages. Ann NY Acad Sci 1995; 771:472-84.
24. Cohen PA, Gower AC, Stucchi AF, Leeman SE, Becker JM, Reed KL. A neurokinin-1 receptor antagonist that reduces intraabdominal adhesion formation increases peritoneal matrix metalloproteinase activity. Wound Repair Regen 2007; 15(6):800-8.
25. Karagiannides I, Kokkotou E, Tansky M, Tchkonia T, Giorgadze N, O'Brien M, Leeman SE, Kirkland JL, Pothoulakis C. Induction of colitis causes inflammatory responses in fat depots: evidence for substance P pathways in human mesenteric preadipocytes. Proc Natl Acad Sci USA 2006; 103(13):5207-12.
26. Misery L. Neuro-immuno-cutaneous system (NICS). Pathol Biol (Paris) 1996; 44(10):867-74.
27. Staniek V, Misery L. Substance P and human skin. Pathol Biol (Paris) 1996; 44(10):860-6.
28. Caddell JL. Evidence for magnesium deficiency in the pathogenesis of bronchopulmonary dysplasia (BPD). Magnes Res 1996; 9(3):205-16.
29. Paulus WJ. Paracrine coronary endothelial modulation of diastolic left ventricular function in man: implications for diastolic heart failure. J Card Fail 1996; 2(4S):155-64.
30. Koon HW, Pothoulakis C. Immunomodulatory properties of substance P: the gastrointestinal system as a model. Ann NY Acad Sci. 2006; 1088:23-40.
31. Zhu W, Mantione KJ, Kream RM, Cadet P, Stefano GB. Cholinergic regulation of morphine release from human white blood cells: evidence for a novel nicotinic receptor via pharmacological and microarray analysis. Int J Immunopathol Pharmacol 2007; 30:229-238.
32. Lavagno L, Ferrero E, Ortolan E, Malavasi F, Funaro A. CD157 is part of a supramolecular complex with CD11b/CD18 on the human neutrophil cell surface. J Biol Regul Homeost Agents 2007; 21:5-12.
33. Santagostino A, Saggia C, Migliora P et al. Prospective study on prognostic significance of DNA ploidy and Ki-67 expression in colorectoral cancer. J Biol Regul Homeost Agents 2007; 21:13-22.
34. Kingsley CI, Nadig SN, Wood KJ. Transplantation tolerance: lessons from experimental rodent models. Transpl Int 2007; 20(10):828-41.
35. Bocchietto E, Paolucci C, Breda D, Sabbioni E, Burastero SE. Human monocytoid THP-1 cell line versus monocyte-derived human immature dendritic cells as in vitro models for predicting the sensitising potential of chemicals. Int J Immunopathol Pharmacol 2007; 20: 259-266.
36. Garbuglia AR, Grasso F, Donà MG, Mochi S, Conti P, De Lutiis MA, Giorgi C, Iezzi T. TTV infection: role of IFNs, IL-28 and IL-29 cytokines, antiviral proteins. Int J Immunopathol Pharmacol 2007; 20: 249-258.
37. Ikeda Y, Takei H, Matsumoto C, Mase A, Yamamoto M, Takeda S, Ishige A, Watanabe K. Administration of substance P during a primary immune response amplifies the secondary immune response via a long-lasting effect on CD8+ T lymphocytes. Arch Dermatol Res 2007; 299(7):345-51.
38. Shim JY, Han Y, Ahn JY, Yun YS, Song JY. Chemoprotective and adjuvant effects of immunomodulator ginsan in cyclophosphamide-treated normal and tumor bearing mice. Int J Immunopathol Pharmacol 2007; 20:487-497.
39. Kalish RS. Clues from alopecia areata on the role of neuropeptides in the initiation of autoimmunity. J Invest Dermatol 2007; 127(6):1489-97.
40. Chung KF. Effects of nedocromil sodium on airway neurogenic mechanisms. J Allergy Clin Immunol 1996; 98:S112-6.
41. Thomson LM, Terman GW, Zeng J, Lowe J, Chavkin C, Hermes SM, Hegarty DM, Aicher SA. Decreased substance P and NK1 receptor immunoreactivity and function in the spinal cord dorsal horn of morphine-treated neonatal rats. J Pain 2008; 9(1):11-9.

42. Caudle RM, Mannes AJ, Keller J, Perez FM, Suckow SK, Neubert JK. Sensitization of spinal cord nociceptive neurons with a conjugate of substance P and cholera toxin. BMC Neurosci 2007; 10:8:30.
43. Gelardi M, Maselli del Giudice A, Fiorella ML, Soleti P, Di Gioacchino M, Conti CM, Fulcheri M, Doyle R, Ciprandi G. Quality of life in non-allergic rhinitis depends on the predominant inflammatory cell type. J Biol Regul Homeost Agents 2007; 22: 73-81.
44. Speranza L, Grilli A, Patruno A et al. Plasmatic markers of muscular stress in isokinetic exercise. J Biol Regul Homeost Agents 2007; 21:23-32.
45. Deepak P, Kumar S, Acharya A. IL-13 neutralization modulates function of type II polarized macrophages in vivo in a murine T-cell lymphoma. Eur J Inflamm 2007; 5:37-46.
46. Liu D, Jiang LS, Dai LY. Substance P and its receptors in bone metabolism. Neuropeptides. 2007; 41(5):271-83.
47. Ventura MT, Gelardi M, Di Gioia R, Buquicchio R, Accettura G, Tummolo RA, Arsioni A. Statistical evaluation and parameters of phlogosis in patients sensitized to cypress. J Biol Regul Homeost Agents 2007; 21:41-47.
48. Pollice R, Tomassini A, Malavolta M, Di Giovambattista E, Verni L, Roncone R, Conti CM, Casacchia M. Subjective and psychopathological response in patients under different antipsychotic treatments: are there differences in real clinical practice? J Biol Regul Homeost Agents 2007; 22: 83-91.
49. Sohn SJ. Substance P upregulates osteoclastogenesis by activating nuclear factor kappa B in osteoclast precursors. Acta Otolaryngol 2005; 125(2):130-3.
50. Lin Q, Li D, Xu X, Zou X, Fang L. Roles of TRPV1 and neuropeptidergic receptors in dorsal root reflex-mediated neurogenic inflammation induced by intradermal injection of capsaicin. Mol Pain 2007; 3: 30-39.
51. Anogianaki A, Negrev NN, Shaik YB et al. Capsaicin: an irritant anti-inflammatory compound. J Biol Regul Homeost Agents 2007; 21:1-4.
52. Cadoni S, Ruffelli M, Fusari S, de Pità O. Oral allergic syndrome and recombinant allergens rBet v 1 and rBet v 2. Eur J Inflamm 2007; 5:21-26.
53. Ciprandi G, Cirillo I, Troisi RM, Marseglia GL. Allergic subjects have more numerous respiratory infections and severe gastrointestinal infections than non-allergic subjects: preliminary results.. Eur J Inflamm 2007; 5:27.
54. Pannone G, Sanguedolce F, De Maria S, et al. Cyclooxygenase isozymes in oral squamous cell carcinoma: a real-time RT-PCR study with clinic pathological correlations. Int J Immunopathol Pharmacol 2007; 20:317-324.
55. Ro JY, Zhang Y, Nies M. Substance P does not play a critical role in neurogenic inflammation in the rat masseter muscle. Brain Res 2005; 1047(1):38-44.
56. Madsen JL, Fuglsang S.A randomized, placebo-controlled, crossover, double-blind trial of the NK1 receptor antagonist aprepitant on gastrointestinal motor function in healthy humans. Aliment Pharmacol Ther 2008; 27:609-15.