EDITORIAL

IMPACT OF NEUROPEPTIDE SUBSTANCE P AN INFLAMMATORY COMPOUND ON ARACHIDONIC ACID COMPOUND GENERATION

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There is much evidence that neuropeptide substance P is involved in neurogenic inflammation and is an important neurotransmitter and neurmodulator compound. In addition, substance P plays an important role in inflammation and immunity. Macrophages can be activated by substance P which provokes the release of inflammatory compounds such as interleukins, chemokines and growth factors. Substance P is involved in the mechanism of pain through the trigeminal nerve which runs through the head, temporal and sinus cavity. Substance P also activates mast cells to release inflammatory mediators such as arachindonic acid compound, cytokines/chemokines and histamine. The release of these chemical mediators is crucial for inflammatory response. Among these mediators there are prostoglandins and leukotrines. Here we review the impact of substance P on inflammatory compounds.

Kinins possess the capacity to release neurotransmitters such as substance P and a second wave of mediators: interleukin-1, tumour necrosis factor, interleukin-8, prostaglandins, and leukotrienes (1-4). Neuropeptides such as substance P (SP), neurokinin A, calcitonin gene-related peptide, vasoactive intestinal peptide, pituitary adenylate cyclase activating peptide, neuropeptide, and somatostatin are vasodilators, and some of them seem to be involved in neurogenic inflammation (5-7).

The 11-amino acid neuropeptide Substance P (SP) is released from nerve endings in many tissues, and belongs to a family of related peptides called tachykinins (8-10). Substance P was first isolated by Leeman S. et al. and it has been found to have an

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important neurotransmitter-neuromodulator effects and plays critical roles in inflammation and immunity (11-13). It is well known that SP is a product of the sensory ganglion cells, and it is transported to peripheral sites where it is stored and released on noxious stimulation (14-16). It is important to note that SP is found in high concentrations in the brain, gut, and lungs where it plays an important role in immunoregulation (17-19). SP can have a role in both innate and adaptive immunity (21-24). Therefore, neuropeptide SP is released from sensory nerves innervating the skin upon several stimulants exposure and acts via membrane-bound NK1 receptors (NK1R).

Since human lymphocytes express SP receptor, they enhance their proliferation when they are stimulated with mitogen *in vitro* (25-27). Activation of macrophages with mitogen is enhanced with SP which provokes immune activation and release of inflammatory compounds (28-31). In addition, mononuclear cells activated with SP cause cytokine release *in vitro* such as interleukins, chemokines and growth factors (32-34). Substance P was shown to induce and mediate inflammation, angiogenesis, infections, intestinal mucosal immunity and stress (35-37).

Substance P is able to activate several immune cells, such as T lymphocytes, mast cells, NK cells and macrophages (38-41). However, SP appear to be chemotactic for human lymphocytes rather than monocytes (42-46). Interaction between the peripheral nervous system, the immune system, and local cells is probably of great importance for the modulation of pain and inflammation (11, 47-50).

Substance P is involved in the mechanism for producing swelling and pain throughout the trigeminal nerve, which runs through the head, temple, and sinus cavity (51-56). Patients suffering from arthritis pain typically have elevated levels in their blood and in the synovial fluid of SP which is the key transmitter of pain to the brain (57-63). Neurogenic inflammation involves vasodilation and plasma protein extravasation in response to neural stimulation. Upon stimulation, sensory neurons release Substance P and other neuropeptides and activate neurokinin-1 receptors leading to plasma protein extravasation from post-capillary venules (64-67).

When the nerve fibers come in contact with Substance P, they react by swelling - an effect that causes headaches and sinus symptoms (68-72.). Neuropathic pain with a major cutaneous component may respond well to topical therapy with the Substance P depletor capsaicin to reduce elevated prostaglandin levels. Sensory neuropeptides may activate brain mast cells to release inflammatory mediators such as histamine, serotonin, arachidonic acid compound and *de novo* synthesized cytokines/ chemokines (73-77). It has been reported that the chemical mediators of inflammatory response, such as substance P, prostaglandins, leukotrienes (LTC4, LTD4, LTE4), histamine, C3a, C5a, bradykinin, PAF, and cytokines, increase vascular permeability (78-80).

The increase in vascular permeability, a fundamental phenomenon in trauma, anaphylaxis, or endotoxemia, might be mediated by PAF, LTs, PGs, substance P and amines such as histamine (81-82). Injury to a tissue provokes the release of inflammatory mediators that dilate arterioles and post-capillary venules and increase capillary permeability (83). In this case, the cells of the immune system cross the endothelial barrier and migrate to the specific site of injury. This migration is accomplished by the process of chemical signaling (chemotaxis) mediated by specific chemokines. However, previously discovered, there are also non-specific chemo-attractant compounds such as LTB4, prostaglandins, C3a, lipoxins (A and B), PAF, bacterial products, and cytokines (84-85).

It has been shown that substance P by itself causes an increase of synthesis of CC and CXC chemokines in inflammatory cells. Studies from our group found that SP is capable of activating mast cells and releasing IL-8 (CXCL8) (86-88). SP is a potent modulator of monocyte/macrophage function, causing the release of arachidonic acid compounds such as leukotrienes and prostaglandins along with other proinflammatory compounds, proteases (chymase and tryptase), histamine, and provokes transcription and translation of several different cytokines/chemokines such as tumor necrosis factor-alpha (TNF-alpha), macrophage inflammatory protein-1 (MIP-1) and GM-CSF, RANTES, MCP-1, and CXCL8 (89-90).

Several reports suggest that SP/NK-1R activates

two convergent proinflammatory signaling pathways, PKCs and PI3K-Akt, resulting in ERK1/2 and NF-kappaB activation and chemokine production. The SP-preferring receptor neurokinin-1 receptor (NK1R) has two forms: a full-length NK1R (NK1R-F) isoform and a truncated NK1R (NK1R-T) isoform, which lacks the terminal cytoplasmic 96-aa residues (91-93).

These observations support an important pro-inflammatory role for substance P, acting via NK1 receptors in acute inflammatory diseases and associated tissue injury. It has also been reported that knockout mice deficient in the preprotachykinin-A gene, the precursor gene for substance P, are also protected against acute inflammation and tissue injury (94-95). Blockade of the tachykinin NK1 receptor may therefore represent an important strategy in the treatment of patients with signs of severe neuro-inflammatory diseases. Moreover, knockout mice deficient in NK1 receptors are protected against inflammatory diseases (96).

In addition to being a mediator of pain, SP has been shown to play an important role in inflammatory states such as asthma, immune complex-mediated lung injury, experimental arthritis, and inflammatory bowel disease (97-99). Airway epithelial damage in asthma exposes sensory nerves which may become sensitized by inflammatory products, including prostaglandins and cytokines, so that neuropeptides are released via a local reflex trigger such as bradykinin, resulting in exaggerated inflammation (100). SP and other neuropeptides are released from airway sensory nerves upon exposure to irritant chemicals and endogenous agents including prostaglandins, histamine, and other compounds (101). The released neuropeptides are potent inducers of a cascade of responses, including vasodilatation, mucus secretion, plasma protein extravasation, leukocyte adhesion and activation, and bronchoconstriction (102-104). It as been reported that orally active neurokinin receptor antagonists could have a therapeutic potential in asthmatic patients. Prostaglandin E2 and leukotriene B4 (LTB4) are both present in the arthritic diseases and also the neuropeptides substance P (SP), and others have all been found at high levels in the synovial fluid (105).

SP and PGs are also involved in pain which is a complex phenomenon involving both neurophysiological and psychological components. Pathophysiological mechanisms involve neural pathways which include acetylcholine, serotonin, histamine, bradykinin, prostaglandins, and substance P. Karaki and Kuwahara reported that neurotransmitter-induced secretion in the intestine may be influenced by the tissue level of prostaglandin E2 (PGE2) (106). They conclude that the concentration of tissue PGE2 may indicate tissue alert level, and when this level elevates, PGE2 enhances ACh and SP-induced Cl- secretion, thus mediating massive fluid secretion for host defence.

On the other hand, spinal PGE(2) binds to receptors at presynaptic endings of primary afferent neurons (thus influencing synaptic release) and to receptors on postsynaptic spinal cord neurons. The administration of PGE(2) to the spinal cord surface produces changes of responsiveness of spinal neurons similar to peripheral inflammation, and spinal indomethacin to the spinal cord attenuates development of hyperexcitability significantly (107). PGE2 is involved in the development of pain and hyperalgesia/allodynia of the masseter muscle in patients with fibromyalgia, whereas local myalgia seems to be modulated by other, as yet unknown, mediators.

Inflammation induces neuroplastic changes in the spinal cord which alter nociceptive processing. This state of hyperexcitability is maintained during persistent inflammation. Several transmitters and mediators contribute to the generation and maintenance of inflammation-induced spinal hyperexcitability including, substance P, prostaglandins and others. Recent evidence suggests that spinal adaptations lead to increased activity of sensory neuropeptide, such as substance P, and its downstream signaling messengers derived from metabolism of arachidonic acid: prostaglandins, and lipoxygenase metabolites. Non-steroidal anti-inflammatory drugs (NSAIDs) provoke analgesia and antinociception mainly acting on the spinal cord, by inhibiting the synthesis of the expression of cyclooxygenase(COX)-1 and COX-2 and therefore prostaglandins. Several prostaglandins such as PGD2, PGE2, PGF2-alpha and PGI2 (prostacyclin) play an important role in the physiopathology of root ganglia and spinal cord. Substance P increases PG release.

Prostaglandins activate cAMP and protein kinase A pathway and bind to G-protein-coupled receptors located in intrinsic spinal neurons and acute and chronic inflammation, interleukins and spinal cord injury increase the expression of COX-2 and release of PGE_2 and PGI_2. Direct administration of PGs to the spinal cord causes hyperalgesia and allodynia, and some studies have shown an association between induction of COX-2, increased PG release and enhanced nociception (108). NSAIDs inhibits the COX-1 and COX-2 enzymes and have a potent anti-inflammatory effect. However, new COX-2 inhibitors may have a role in subjects for whom simple analgesia is inadequate.

The presence of mast cells and inflammatory cells may create a special environment in several tissue. Human mast cells bind IgE with high affinity to specific FcepsilonRI receptors and they express the receptor and activation sites for substance P. Both IgE-dependent stimulation by activating tyrosine kinases, and non-immunologic stimulation by activating G-proteins induce a characteristic compound exocytosis resulting in the liberation of the preformed mediators. However, in mast cells, the production of prostaglandin D2 and leukotriene C4, occurs only with IgE-dependent stimulation (109). In the light of these studies, we believe that substance P is important in understanding the pathophysiology of inflammation and immunity. This study suggests a potential interaction of SP and arachidonic acid compounds that requires further detailed investigation.

REFERENCES

1. Cleugh J, Gaddum JH. The stability of purified preparations of substance P. Experientia 1963; 19:72-3.
2. Shimizu Y, Dobashi K, Fueki N, Fueki M, Okada T, Tomioka S, Makino S, Mori M. Changes of immunomodulatory cytokines associated with omalizumab therapy for severe persistent asthma. J Biol Regul Homeost Agents 2011; 25:177-86.
3. Boyaci H, Pala A, Argun Bariş S, Başyigit I, Yildiz F, Ilgazli A. The effects of inhaled steroid and theophylline on systemic inflammation in COPD. Eur J Inflamm 2011; 9:241-8.
4. Yeh JL, Hsu JH, Hong YS, Wu JR, Liang JC, Wu BN, Chen IJ, Liou SF. Eugenolol and glyceryl-isoeugenol suppress LPS-induced iNOS expression by down-regulating NF-kappaB AND AP-1 through inhibition of MAPKS and AKT/IkappaBalpha signaling pathways in macrophages. Int J Immunopathol Pharmacol 2011; 24:345-56.
5. Shaw JE, Ramwell PW. Release of a substance P polypeptide from the cerebral cortex. Am J Physiol 1968; 215(1):262-7.
6. Salini V, Conti P. Inflammatory markers: serum amyloid A, fibrinogen and C-reactive protein – a revisited study. Eur J Inflamm 2011; 9:95-102.
7. Marotta F, Chui DH, Jain S, Polimeni A, Koike K, Zhou L, Lorenzetti A, Shimizu H, Yang H. Effect of a fermented nutraceutical on thioredoxin level and TNF-α signalling in cirrhotic patients. J Biol Regul Homeost Agents 2011; 25:37-45.
8. Krivoy W, Kroeger D. The neurogenic activity of high potency substance P. Experientia 1963; 19:366-7.
9. Sedriep S, Xia X, Marotta F, et al. Beneficial nutraceutical modulation of cerebral erythropoietin expression and oxidative stress: an experimental study. J Biol Regul Homeost Agents 2011; 25:187-194.
10. Tsoucalas G, Karamanou M, Androutsos G. Travelling through time with aspirin, a healing companion. Eur J Inflamm 2011; 9:13-16.
11. Horwitz DL. Pain. Compr Ther 1980; 6(2):3-6.
12. Ruiz-Pérez MV, Sánchez-Jiménez F, Quesada AR, Medina MA. A re-evaluation of the mitogenic effect of serotonin on vascular endothelial cells. J Biol Regul Homeost Agents 2011; 25:13-20.
13. Mirzaei K, Hossein-Nezhad A, Mokhtari F, Najmafshar A, Khoshniat Nikoo M. VISFATIN/NAMPT/PBCEF and cytokine concentration in multiple sclerosis patients compared to healthy subjects. Eur J Inflamm 2011; 9:31-37.
14. Lembeck F, Gamse R. Substance P in peripheral sensory processes. Ciba Found Symp 1982; (91):35-54.
15. Saggini A, Tripodi D, Maccauro G, et al. Tumor necrosis factor-alpha and mast cells: revisited study. Eur J Inflamm 2011; 9:17-22.
16. Bordignon V, Bultrini S, Prignano G, et al. High prevalence of latent tuberculosis infection in

autoimmune disorders such as psoriasis and in chronic respiratory diseases, including lung cancer. J Biol Regul Homeost Agents 2011; 25:213-20.

18. Hösli L, Hösli E, Zehntner C, Landolt H. Effects of substance P on neurones and glial cells in cultured rat spinal cord. Neurosci Lett 1981; 24(2):165-8.
19. Tarakanov I, Tikhomirova L, Tarasova N, Safonov V, Bialkowska M, Pokorski M. GABA representation in hypoxia sensing: a ventilatory study in the rat. J Biol Regul Homeost Agents 2011; 25:169-75.
20. Ciprandi G, De Amici M, Quaglini S, et al, Workgroup "Allergy Project". Prediction of allergy by total serum IgE measurements in infancy: a 10-year follow-up. Eur J Inflamm 2011; 9:199-203.
21. Fisher GH, Humphries J, Folkers K, Pernow B, Bowers CY. Synthesis and some biological activities of substance P. J Med Chem 1974; 17(8):843-6.
22. Mazzoccoli G, Carughi S, Sperandeo M, Pazienza V, Giuliani F, Tarquini R. Neuro-endocrine correlations of hypothalamic-pituitary-thyroid axis in healthy humans. J Biol Regul Homeost Agents 2011; 25:249-57.
23. Zizzi A, Aspriello SD, Rubini C, Goteri G. Peri-implant diseases and host inflammatory response involving mast cells: a review. Int J Immunopathol Pharmacol 2011; 24:557-66.
24. Guillén D, Millán O, Brunet M. *In vitro* studies of the immunomodulatory effects of statins alone and in combination with immunosuppressive drugs. Eur J Inflamm 2011; 9:117-124.
25. Yoshida M. The GABAergic systems and the role of basal ganglia in motor control. Adv Biochem Psychopharmacol 1981; 30:37-52.
26. Hossein-Nezhad A, Mirzaei K, Aslani S, Tootee A, Karimi F. MIF expression in induced peripheral blood mononuclear cells by vitamin D3 and its potential correlation with resting metabolic rate in obesity. Eur J Inflamm 2011; 9:125-134.
27. Pandolfi F, Cianci R, Casciano F, Pagliari D, De Pasquale T, Landolfi R, Di Sante G, Kurnick JT, Ria F. Skewed T-cell receptor repertoire: more than a marker of malignancy, a tool to dissect the immunopathology of inflammatory diseases. J Biol Regul Homeost Agents 2011; 25:153-161.
28. Naruishi K, Omori K, Maeda H, et al. Immune responses to *Porphyromonas gingivalis* infection suppress systemic inflammatory response in experimental murine model. J Biol Regul Homeost Agents 2011; 25:195-202.
29. Kokkas A, Goulas A, Stavrianos C, Anogianakis G. The role of cytokines in pulp inflammation. J Biol Regul Homeost Agents 2011; 25:303-311.
30. Wang JC, Sonnylal S, Arnett FC, De Crombrugghe B, Zhou X. Attenuation of expression of extracellular matrix genes with siRNAs to Sparc and Ctgf in skin fibroblasts of CTGF transgenic mice. Int J Immunopathol Pharmacol 2011; 24:595-601.
31. Maghbooli Z, Hossein-Nezhad A, Shirzad M, Behzadi H. The role of osteoprotegrin/ nuclear factor κb ligand in coronary collateral development Eur J Inflamm 2011; 9:57-64.
32. Terenius L. Biochemical mediators in pain. Triangle 1981; 20(1-2):19-26.
33. Marotta F, Naito Y, Padrini F, et al. Redox balance signalling in occupational stress: modification by nutraceutical intervention. J Biol Regul Homeost Agents 2011; 25:221-29.
34. Savastano S, Balato N, Gaudiello F, Di Somma C, Brancato V, Colao A, Ayala F, Tarantino G. Insulin-like growth factor-1, psoriasis, and inflammation: a ménage à trois? Eur J Inflamm 2011; 9:277-283.
35. Katayama Y, North RA. Does substance P mediate slow synaptic excitation within the myenteric plexus? Nature 1978; 274(5669):387-8.
36. Guarino F, Cantarella G, Caruso MA, Russo C, Mancuso S, Arcidiacono G, Cacciola RR, Bernardini R, Polosa R. Endothelial activation and injury by cigarette smoke exposure. J Biol Regul Homeost Agents 2011; 25:259-68.
37. Symeonidou I, Hatzistilianou M, Papadopoulos E, Dovas CI, Karagouni E, Pappa S, Pantzartzi CN, Kourelis A, Frydas S. Susceptibility and resistance to canine leishmaniosis is associated to polymorphisms of the canine TNF-α gene. Eur J Inflamm 2011; 9:23-29.
38. Mudge AW. Effect of chemical environment on levels of substance P and somatostatin in cultured sensory neurones. Nature 1981; 292(5825):764-7.
39. Esposito G, Rossi F, Matteini P, Puca A, Albanese A, Sabatino G, Maira G, Pini R. Present status and new perspectives in laser welding of vascular tissues. J Biol Regul Homeost Agents 2011; 25:145-152.

40. Cantarini L, Iacoponi F, Lucherini OM, et al. Validation of a diagnostic score for the diagnosis of autoinflammatory diseases in adults. Int J Immunopathol Pharmacol 2011; 24:695-702.
41. Ciprandi G, De Amici M, Berardi L, Vignini M, Marseglia G. Serum IgE for Bet v 1 in patients affected by atopic dermatitis. Eur J Inflamm 2011; 9:205-207.
42. Phillis JW, Limacher JJ. Substance P excitation of cerebral cortical Betz cells. Brain Res 1974; 69(1):158-63.
43. Pesce M, Speranza L, Franceschelli S, Ialenti V, Patruno A, Febo MA, De Lutiis MA, Felaco M, Grilli A. Biological role of interleukin-1β in defensive aggressive behavior. J Biol Regul Homeost Agents 2011; 25:323-329.
44. De Amici M, Villani MA, Milanesi E, Rossini B, Barco S, Gerletti M, Ciprandi G. Adverse reactions to anaesthetics prevented by the use of specific laboratory tests Eur J Inflamm 2011; 9:79-81
45. Tarantino G, Colao A, Capone D, et al. Circulating levels of cytochrome c, gamma-glutamyl transferase, triglycerides and unconjugated bilirubin in overweight/obese patients with non-alcoholic fatty liver disease. J Biol Regul Homeost Agents 2011; 25:47-56.
46. Cernysiov V, Mauricas M, Girkontaite I. Leucocyte infiltration in lymphoid organs and peritoneal cavity upon immunization: dependence on circadian rhythmicity and melatonin 24-h profile. Eur J Inflamm 2011; 9:219-29.
47. Battelli MG, Ravaioli M, Musiani S, Scicchitano V, Grazi GL, Bolognesi A. Increased serum level of xanthine oxidoreductase in liver transplanted patients. J Biol Regul Homeost Agents 2011; 25:77-84.
48. Silambarasan G, Ramanathan T, Nabeel MA, Kalaichelvan VK, Kathiresan K, Balasubramanian T. Anti-inflammatory activity of the marine cyanobacterium *trichodesmium erythraeum* against carrageenan-induced paw oedema in wistar albino rats. Eur J Inflamm 2011; 9:53-56.
49. Altorjay I, Veréb Z, Serfozo Z, et al. Anti-TNF-alpha antibody (infliximab) therapy supports the recovery of eNOS and VEGFR2 protein expression in endothelial cells. Int J Immunopathol Pharmacol 2011; 24:323-35.
50. Giordano N, Papakostas P, Pecetti G, Nuti R. Cytokine modulation by endothelin-1 and possible therapeutic implications in systemic sclerosis. J Biol Regul Homeost Agents 2011; 25:487-92.
51. Konishi S, Otsuka M. Excitatory action of hypothalamic substance P on spinal motoneurones of newborn rats. Nature 1974; 252(5485):734-5.
52. Foltran F, Berchialla P, Bernasconi S, Grossi E, Gregori D, Street ME. A systems biology approach: new insights into fetal growth restriction using Bayesian Networks. J Biol Regul Homeost Agents 2011; 25:269-77.
53. Tsoupras AB, Chini M, Tsogas N, Mangafas N, Demopoulos CA, Lazanas MC. *In vivo* effects of a *Ginkgo biloba* extract on platelet activating factor metabolism in two asymptomatic HIV-infected patients. Eur J Inflamm 2011; 9:107-16
54. Cassano N, Mastrandrea V, Principi M, Loconsole F, De Tullio N, Di Leo A, Vena GA. Anti-tumor necrosis factor treatment in occult hepatitis B virus infection: a retrospective analysis of 62 patients with psoriatic disease. J Biol Regul Homeost Agents 2011; 25:285-289.
55. Tammaro A, Narcisi A, Persechino S, De Marco G, Camplone G. Contact allergy to disperse blue dye in goggles for swimming-bath. Eur J Inflamm 2011; 9:83-84.
56. Mazzoccoli G, Sothern RB, De Cata A, Giuliani F, Fontana A, Copetti M, Pellegrini F, Tarquini R. A timetable of 24-hour patterns for human lymphocyte subpopulations. J Biol Regul Homeost Agents 2011; 25:387-95.
57. Jessell TM, Iversen LL. Inhibition of substance P release from the isolated rat substantia nigra by GABA. Br J Pharmacol 1977; 59(3):486P.
58. Sancilio S, Di Giacomo V, Quaglietta AM, et al. TRAIL promotes a pro-survival signal in erythropoietin-deprived human erythroblasts through the activation of an NF-κB/IκBα pathway. J Biol Regul Homeost Agents 2011; 25:375-86.
59. Zhu J-S, Xu Z-P, Song M-Q, Zhang Q. Effect of oxymatrine combined with low dose 5-FU on lymphatic vessel and microvascular endothelial cell growth of gastric cancer in a severe combined immunodeficient mouse orthotopic implantation

model. Eur J Inflamm 2011; 9:45-51.
60. Mazzoccoli G, Giuliani F, Sothern RB. A method to evaluate dynamics and periodicity of hormone secretion. J Biol Regul Homeost Agents 2011; 25:231-8.
61. Carlesimo M, Narcisi A, Orsini D, Cortesi G, Abruzzese C, Giovagnoli S, Giubettini M, Camplone G. A rare case of sarcoidosis and morphea. Eur J Inflamm 2011; 9:297-9.
62. Malerba M, Ragnoli B, Salameh M, Sennino G, Sorlini ML, Radaeli A, Clini E. Sub-clinical left ventricular diastolic dysfunction in early stage of chronic obstructive pulmonary disease. J Biol Regul Homeost Agents 2011; 25:443-451.
63. Tammaro A, Narcisi A, Persechino S, De Marco G, Camplone G. Contact allergy to disperse blue dye in goggles for swimming-bath. Eur J Inflamm 2011; 9:83-84
64. Helke CJ. Neuroanatomical localization of substance p: implications for central cardiovascular control. Peptides. 1982; 3(3):479-83.
65. Mazzoccoli G, Carughi S, Sperandeo M, Pazienza V, Giuliani F, Greco A. Alteration of circadian rhythmicity of CD3+CD4+ lymphocyte subpopulation in healthy aging. J Biol Regul Homeost Agents 2011; 25:405-16.
66. Dozio E, Malavazos AE, Dogliotti G, Goggi S, Galliera E, Solvimene U, Magni P, Costa E, Morricone L, Corsi MM. Asymmetric dimethylarginine: relationship with circulating biomarkers of inflammation and cardiovascular disease risk in uncomplicated obese women. Eur J Inflamm 2011; 9:249-255.
67. Masuelli L, Pompa G, Fabrizi M, et al. Patients with periimplantitis, unlike those with a healthy peri-implant microenvironment, display antibodies to more than one heat shock protein (HSP 27, HSP 65 and HSP 90) linear epitope. Eur J Inflamm 2011; 9:257-67.
68. Barbeau A, Rondeau DB, Jolicoeur FB. Behavioral effects of substance P in rats. Int J Neurol 1980; 14(2-4):239-52.
69. Migliore A, Massafra U, Bizzi E, Vacca F, Martin-Martin LS, Granata M, Tormenta S, Laganà B. Efficacy and safety profile of intra-articular administration of Jointex® in patients suffering from symptomatic hip osteoarthritis: an open, prospective study with a 12-month follow-up. Eur J Inflamm 2011; 9:269-76.
70. P ollice R, Bianchini V, Marola V, et al. Post-traumatic and psychiatric symptoms among young earthquake survivors in primary care camp hospital. Eur J Inflamm 2011; 9:39-44.
71. Chatzovoulos P, Tsoupras AB, Samiotaki M, Panayotou G, Demopoulos CA, Dotsika E. PAF metabolic enzymes and PAF-like activity in *L. infantum* and *L. major* promastigotes. Eur J Inflamm 2011; 9:231-9.
72. Angelini A, Centurione L, Sancilio SA, et al. The effect of the plasticizer diethylhexyl phthalate on transport activity and expression of P-glycoprotein in parental and doxo-resistant human sarcoma cell lines. J Biol Regul Homeost Agents 2011; 25:203-11
73. Coccaro EF, Lee R, Owens MJ, Kinkead B, Nemeroff CB. Cerebrospinal fluid **substance P**-like immunoreactivity correlates with aggression in personality disordered subjects. Biol Psychiatry 2012; 72(3):238-43.
74. Mazurek U, Owczarek A, Nowakowska-Zajdel E, Wierzgoń J, Grochowska-Niedworok E, Kokot T, Muc-Wierzgoń M. Statistical analysis of differential gene expression in colorectal cancer using CLEAR-test. J Biol Regul Homeost Agents 2011; 25:279-83.
75. Di Paola R, Mazzon E, Paterniti I, Impellizzeri D, Bramanti P, Cuzzocrea S. Apocynin, a plant-derived drug, might be useful in the treatment of myocardial ischemia reperfusion injury in rat hearts. Eur J Inflamm 2011; 9:169-74.
76. Scaramuzzo L, Raffaelli L, Spinelli MS, Damis G, Maccauro G, Manicone PF. Orthopaedic and dental abnormalities in osteogenesis imperfecta: a review of the literature. J Biol Regul Homeost Agents 2011; 25:313-21.
77. Menghini L, Leporini L, Scanu N, Pintore G, La Rovere R, Di Filippo ES, Pietrangelo T, Fulle S. Effect of phytochemical concentrations on biological activities of cranberry extracts. J Biol Regul Homeost Agents 2011; 25:27-35.
78. Veda P. Why are neutrophils polymorphonuclear? Eur J Inflamm 2011; 9:85-93
79. Galliera E, De Girolamo L, Randelli P, Volpi P, Dogliotti G, Quaglia A, Banfi G, Cabitza P, Corsi MM, Denti M. High articular levels of the

angiogenetic factors VEGF and VEGF-receptor 2 as tissue healing biomarkers after single bundle anterior cruciate ligament reconstruction. J Biol Regul Homeost Agents 2011; 25:85-91.

80. Scaramuzzo L, Manicone PF, Graci C, Muratori F, Spinelli MS, Damis G, Raffaelli L, Maccauro G. Morphological modifications in osteoarthritis: a scanning electron microscopy study Eur J Inflamm 2011; 9:73-78
81. Gaudino G, Fasolo A. Substance P-related peptides in the hypothalamus of amphibia. Cell Tissue Res 1980; 211(2):241-50.
82. Zanna P, Maida I, Turpin Sevilla MC, et al. Molecular characterization of novel melanoma cell lines. J Biol Regul Homeost Agents 2011; 25:239-47.
83. Romano G, Barbagli G, Lazzeri M. The use of topical hyaluronic acid and silver sulfadiazine (Altergen®) in patients undergoing two-stage anterior urethroplasty with oral mucosal graft. Eur J Inflamm 2011; 9:175-83.
84. D'Alimonte I, Nargi E, Mastrangelo F, et al. Vascular endothelial growth factor enhances *in vitro* proliferation and osteogenic differentiation of human dental pulp stem cells. J Biol Regul Homeost Agents 2011; 25:57-69.
85. Kourelis TV, Moustakakis MN, Silk R, Pharm D, Boruchov A, Bilgrami SF. Decitabine for acute myeloid leukemia in a patient undergoing hemodialysis. Eur J Inflamm 2011; 9:289-292.
86. Fehér E, Wenger T. Ultrastructural immunocytochemical localization of substance P in the cat small intestine. Anat Anz 1981; 150(1-2):137-43.
87. Germano V, Picchianti Diamanti A, Ferlito C, Podestà E, Salemi S, Migliore A, D'Amelio R, Laganà B. Cyclosporine A in the long-term management of systemic lupus erythematosus. J Biol Regul Homeost Agents 2011; 25:397-403.
88. Aslani S, Hossein-Nezhad A, Mirzaei K, Maghbooli Z, Asgarabad SN, Karimi F. Tandem repeats of the CATT element of macrophage migration inhibitory factor gene may predict gestational diabetes mellitus severity. Eur J Inflamm 2011; 9:193-197.
89. Negrev N, Tashev R, Radev R, Anogeianaki A, Ivanova M. Hormones of hypothalamic-pituitary-thyroid axis are significant regulators of synthesis and secretion of vitamin K-dependent plasma coagulation factors. J Biol Regul Homeost Agents 2011; 25:21-26.
90. Riccioni G, Scotti L, Di Ilio E, Bet al. Lycopene and preclinical carotid atherosclerosis. J Biol Regul Homeost Agents 2011; 25:435-441.
91. Dalgliesh CE, Toh CC, Work TS. Fractionation of the smooth muscle stimulants present in extracts of gastro-intestinal tract. Identification of 5-hydroxytryptamine and its distinction from substance P. J Physiol 1953; 120(3):298-310.
92. Mosconi G, Colombo D, Graziani E, Franceschelli N, Roi GS, Totti V, Nanni Costa A, Stefoni S. Physical performance in kidney transplanted patients: a study on desert trekking. J Biol Regul Homeost Agents 2011; 25:417-425.
93. Zhang C-Y, Shao S-H, Chen X, Shi Y-L. Anti-frostbite effects of *prunus tomentosa thunb* total flavone Eur J Inflamm 2011; 9:65-71.
94. Verratti V, Brunetti L, Tenaglia R, et al. Physiological analysis of 8-Iso-PGF2 alpha: a homeostatic agent in superficial bladder cancer. J Biol Regul Homeost Agents 2011; 25:71-76.
95. Borrione P, Spaccamiglio A, Rizzo M, Termine A, Chierto E, Campostrini N, Quaranta F, Di Gianfrancesco A, Pigozzi F. Urinary hepcidin identifies a serum ferritin cut-off for iron supplementation in young athletes: a pilot study. J Biol Regul Homeost Agents 2011; 25:427-34.
96. Rigante D, Zampetti A, Bersani G, Candelli M, Piras A, Rendeli C, Antuzzi D, Feliciani C, Stabile A. Serum interleukin-18 in children with Henoch-Schönlein purpura: a promising marker of disease activity. Eur J Inflamm 2011; 9:157-168.
97. Binici DN, Güneş N, Kayataş K, Pişkinpaşa N. The effects of interferon-α2b on intestinal flora in peritoneal fibrosis. Eur J Inflamm 2011; 9:135-139.
98. Luppi F, Covi M, Velluti G, Spagnolo P, Fabbri LM, Richeldi L. Co-trimoxazole effect on human alveolar macrophages of AIDS patients. J Biol Regul Homeost Agents 2011; 25:461-464.
99. Karam WG, Rady A, Abdallah Hajj Hussein I, et al. Cytology and clinical spectrum of sexually transmitted infections in Lebanese women as revealed by Pap smear: a cross-sectional study from 2002-2006. J Biol Regul Homeost Agents 2011; 25:453-9.

100. Berardi D, De Benedittis S, Scoccia A, Perfetti G. Evaluation of neridronate on the osseointegration process of endeous titanium implants in animal models. Eur J Inflamm 2011; 9:141-9.
101. Kasperska-Zajac A, Czecior E, Grzanka A, Machura E, Misiolek M. The blood urokinase system in patients with seasonal allergic rhinitis and concomitant seasonal asthma during pollen season. Eur J Inflamm 2011; 9:285-88.
102. Betto P, Cerimele S, Rassu M, Fornasa CV, Di Pietro M, Sessa R. Cutaneous infection of *Nocardia altamirensis*: the first case report. Eur J Inflamm 2011; 9:301-303.
103. Dahamsheh Z, Bellomo RG, Saggini R, Barassi G, Saggini A. The prevalence of rheumatoid arthritis in the south of Jordan. Eur J Inflamm 2011; 9:293-5.
104. Belloli L, Carlo-Stella N, Ughi N, Marasini B. Cancer in Italian patients with systemic sclerosis. Eur J Inflamm 2011; 9:151-6.
105. Abdel-Latif AA. Regulation of arachidonate release, prostaglandin synthesis, and sphincter constriction in the mammalian iris-ciliary body. Prog Clin Biol Res 1989; 312:53-72.
106. Karaki SI, Kuwahara A. Regulation of intestinal secretion involved in the interaction between neurotransmitters and prostaglandin E2. Neurogastroenterol Motil 2004;16 S1:96-9.
107. Schaible HG, Ebersberger A, Von Banchet GS. Mechanisms of pain in arthritis. Ann NY Acad Sci 2002; 966:343-54.
108. Vanegas H, Schaible HG. Prostaglandins and cyclooxygenases [correction of cycloxygenases] in the spinal cord. Prog Neurobiol 2001; 64(4):327-63.
109. Church MK, Clough GF. Human skin mast cells: in vitro and in vivo studies. Ann Allergy Asthma Immunol 1999; 83(5):471-5.