



MECHANISM PAPER

The substance P cascade

Dwight Jennings, DDS, MICCMO · Alameda, California

Elevated Substance P (elevated in ASD) Elevated in Neurogenic Inflammatory Disorders (headaches, seizures, eczema, autoimmune disorders, IBS, etc.) iv; GI disturbance as it regulates motility Causes Hypersensitivity of all sensory neurons = faulty sensory function Faulty response to sensory input=loss of homeostasis=chronic illness Pain propensity, multiple chemical sensitivity, and hyperacusis, light hypersensitivity, etc. Down regulation of Nerve Growth Factor=difficult to make new neural connections Loss of catecholamine production = behavioral and psychiatric disorders Degeneration of neural crest derived tissues = Neurodegenerative disorders (NGF necessary for the health and maintenance of neural crest derivatives) = Parkinson's, Alzheimer, dementia, multiple sclerosis, cerebral palsy, etc. Possible cause of lack of growth of head in Down's Syndrome Loss of sympathetic neurons to stomach=digestive disorders Modulation of bone marrow stem cell differentiationvii, and platelet aggregationviii, modulation of immune and hematopoietic functions = immune dysfunction Blood dyscrasias, mononucleosis, leukemia, multiple forms of cancer Increases cell membrane permeabilityix= metabolic disequilibrium Increase viral infection propensity (i.e. HIV proliferation)

©2009 Dwight Jennings, DDS

i Definition Craniomandibular dysfunction: a condition in which the teeth do not relate the maxillary and mandibular bones in the same relationship as where the muscles suspending the jaw want the jaw to be. This requires the jaw muscles to accommodate to the tooth position, thus causing the jaw muscles and trigeminal nerve to become hypertonic/hyperactive. This is a very common condition in modern man.

ii Substance P: From Wikipedia In the field of neuroscience, substance P (SP) is a neuropeptide: an undecapeptide that functions as a neurotransmitter and as a neuromodulator which alters the excitability of the dorsal horn ganglion (pain responsive neurons).[1][2] It belongs to the tachykinin neuropeptide family. Substance P is released from the terminals of specific sensory nerves. It is a protein found in the brain and spinal cord, and is associated with some inflammatory processes in the joints. Its function is to cause pain, particularly in arthritis, low back pain and fibromyalgia. Function Substance P is one of the important complex mechanisms involved in pain perception. The sensory function of substance P is thought to be related to the transmission of pain information into the central nervous system. Substance P coexists with the excitatory neurotransmitter glutamate in primary afferents that respond to painful stimulation.[11] SP has been associated in the regulation of mood disorders, anxiety, stress,[12] reinforcement,[13] neurogenesis,[14] respiratory rhythm,[15] neurotoxicity, nausea/emesis,[16] pain and nociception.[17] Substance P and other sensory neuropeptides can be released from the peripheral terminals of sensory nerve fibers in the skin, muscle and joints. It is proposed that this release is involved in neurogenic inflammation which is a local inflammatory response to certain types of infection or injury.[18] The regulated function of SP also involves the regulation of its high-affinity receptor, NK-1. Because of importance of substance P in perception of pain in animals, applying receptor antagonists may have important therapeutic applications in the treatment of a variety of stress-related illnesses, in addition to



their potential as analgesics. Vomiting The vomiting center in the brainstem contains high concentrations of substance P and its receptor, in addition to other neurotransmitters such as choline, histamine, dopamine, serotonin, and opioids. Their activation stimulates the vomiting reflex. Different emetic pathways exist, and substance P/NK1R appears to be within the final common pathway to regulate vomiting.[19] Substance P antagonist (SPA) aprepitant is available in the market in the treatment of chemotherapy-induced nausea / emesis. Pain

Substance P is involved in nociception, transmitting information about tissue damage from peripheral receptors to the central nervous system to be converted to the sensation of pain. It has been theorized that it plays a part in fibromyalgia. Capsaicin has been shown to reduce the levels of Substance P probably by reducing the number of C-fibre nerves or causing these nerves to be more tolerant. Thus, Capsaicin is clinically used as an analgesic and anti-inflammatory agent to relieve pain associated with arthritis and many types of neuralgia. A role of substance P and NKA in nociception is suggested by the reduction in response thresholds to noxious stimuli by central administration of NK1 and NK2 agonists. Based on recent studies, it was proposed that NK1, and possibly the NK2 receptor antagonists could be developed as analgesic drugs. It has been studied that the mice carrying a disruption of the gene encoding SP/NKA, show severely reduced nociceptive pain responses when the stimuli are moderate to intense. Pain behaviors induced by mechanical, thermal and chemical stimulation of somatic and visceral tissues were reduced in the mutant mice lacking SP/NKA. However, it has been proposed that the importance of SP and NKA in animal's pain response apply only to a certain 'window' of pain intensities and when the intensity of the pain stimuli is further increased, the responses of the knockout mice is not severely different from the wild-type mice.[11] Cellular growth Substance P has been known to stimulate cellular growth in cell culture,[20] and it was shown that Substance P could promote wound healing of non-healing ulcers in humans.[21] It has also been shown to reverse diabetes in mice.[22][23] Vasodilation Substance P also has effects as a potent vasodilator. Substance P-induced vasodilatation is dependant on nitric oxide release.[24] Substance P is involved in the axon reflex-mediated vasodilatation to local heating and wheal and flare reaction. It has been shown that vasodilatation to substance P is dependent on the NK1 receptor located on the endothelium. In contrast to other neuropeptides studied in human skin, substance P-induced vasodilatation has been found to decline during continuous infusion. This possibly suggest an internalization of neurokinin-1 (NK1).[25] As is typical with many vasodilators, it also has bronchoconstrictive properties, administered through the non-adrenergic, non-cholinergic nervous system (branch of the vagal system). Eczema High levels of BDNF and Substance P have been found associated with increased itching in eczema.[26][27] iii : Autism. 2002 Sep;6(3):315-28.

Urinary peptides in Rett syndrome.

Solaas KM, Skjeldal O, Gardner ML, Kase FB, Reichelt KL.

Institute of Pediatric Research, The National Hospital, University of Oslo, Norway.

Rett syndrome is a neuro-developmental disorder related to autistic behavior. Persons with autism have previously been found to have hyperpeptiduria. We here report a significantly higher level of peptides in the first fasting morning urine from 53 girls with Rett syndrome (both classical and congenital) compared with 53 healthy girls. This elevation in urinary peptides was similar to that in 35 girls with infantile autism.



As in persons with autism, the individual levels of urinary peptides in the Rett syndrome group varied, and about a fifth were within the normal range. Levels of peptides were lower in girls with classic Rett syndrome than in girls with congenital Rett syndrome. This may be due to different etiological causes or to active and stagnant phases of the disease. Urine from girls with Rett syndrome was found to have higher frequency and higher levels of some urinary peptides that may cause inhibition of brain maturation and epilepsy

iv Definition of Neurogenic Inflammatory Disorders: From Wikipedia Neurogenic inflammation is a general term used to describe the local release of inflammatory mediators from afferent neurons such as substance P and calcitonin gene-related peptide. This process appears to play an important role in the pathogenesis of numerous diseases including asthma, fibromyalgia, eczema, rosacea, psoriasis and migraine. Author's Note: Autoimmune disorders are also associated with elevated substance P. Substance P levels are also disturbed in neurodegenerative disorders.

v Definition of Nerve Growth Factor: From Wikipedia Nerve growth factor (NGF), is a small secreted protein which induces the differentiation and survival of particular target neurons (nerve cells). It is perhaps the prototypical growth factor, in that it is one of the first to be described — that work by Rita Levi-Montalcini and Stanley Cohen was rewarded with a Nobel Prize. While "nerve growth factor" refers to a single factor,[1] "nerve growth factors" refers to a family of factors also known as neurotrophins.[2] Function NGF is critical for the survival and maintenance of sympathetic and sensory neurons. NGF is released from the target cells, binds to and activates its high affinity receptor (TrkA), and is internalized into the responsive neuron. There are some data that show that NGF can be

transported from the axon tip to soma, but it is unclear if this is necessary for effective cell signalling; in fact there are data showing that it is not[citation needed]. What is clear is that NGF binding and activation of TrkA is required for NGF-mediated neuronal survival and differentiation. Receptor binding mechanism Main article: Nerve growth factor receptor NGF binds at least two receptors on the surface of cells which are capable of responding to this growth factor, TrkA (pronounced "Track A") and the LNGFR (for "low affinity nerve growth factor receptor"). History Stanley Cohen and Rita Levi-Montalcini, at the time faculty members at Washington University in St Louis, won the 1986 Nobel Prize in Physiology or Medicine for their discovery of NGF and other growth factors.[3][4][5] Cultural and medical significance In 2005, Italian scientists at University of Pavia found that a protein molecule known as the nerve growth factor (NGF) has high levels when people first fall in love, but these levels return to as they were after one year. Specifically, four neurotrophin levels, i.e. NGF, BDNF, NT-3, and NT-4, of 58 subjects who had recently fallen in love were compared with levels in a control group who were either single or already engaged in a long-term relationship. The results showed that NGF levels were significantly higher in the subjects in love than as compared to either of the control groups.[6][7][8] It has also been tied to Alzheimer's disease.[9][10][11] Pietro Calissano has suggested that nerve growth factor may contribute to increased longevity and mental capacity.[12] Centenarian Rita Levi-Montalcini has been taking a daily solution in the form of eye drops, and has stated that her brain is more active now than it was four decades ago. Interactions Nerve growth factor has been shown to interact with TrkA[13][14][15] and Low affinity nerve growth factor receptor.[13][14]

Catecholamine From Wikipedia



Catecholamines are sympathomimetic[1] "fight -or-flight" hormones that are released by the adrenal glands in response to stress.[2] They are part of the sympathetic nervous system . They are called catecholamines because they contain a catechol group, and are derived from the amino acid tyrosine .[3] The most abundant catecholamines are epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine , all of which are produced from phenylalanine and tyrosine . Catecholamines are water -soluble and are 50% bound to plasma proteins, so they circulate in the bloodstream. Tyrosine is created from phenylalanine by hydroxylation by the enzyme phenylalanine hydroxylase . (Tyrosine is also ingested directly from dietary protein). It is then sent to catecholamine -secreting neurons. Here, many kinds of reactions convert it to dopamine, to norepinephrine, and eventually to epinephrine.[4]

Location Catecholamines are produced mainly by the chromaffin cells of the adrenal medulla and the postganglionic fibers of the sympathetic nervous system . Dopamine , which acts as a neurotransmitter in the central nervous system , is largely produced in neuronal cell bodies in two areas of the brainstem: the substantia nigra and the ventral tegmental area . **Synthesis** Dopamine is the first catecholamine to be synthesised from steps shown. Norepinephrine and epinephrine, in turn, are derived from further modifications of dopamine. It is important to note that the enzyme dopamine hydroxylase requires copper as a cofactor (not shown) and DOPA decarboxylase requires PLP . **Function** Two catecholamines, norepinephrine and dopamine , act as neuromodulators in the central nervous system and as hormones in the blood circulation. The catecholamine norepinephrine is a neuromodulator of the peripheral sympathetic nervous system but is also present in the blood (mostly through "spillover" from the synapses of the sympathetic system). High catecholamine levels in blood are associated with stress , which can be induced from psychological reactions or environmental stressors such as elevated sound levels , intense light , or low blood sugar levels .

Extremely high levels of catecholamines (also known as catecholamine toxicity) can occur in central nervous system trauma due to stimulation and/or damage of nuclei in the brainstem , in particular those nuclei affecting the sympathetic nervous system . In emergency medicine , this occurrence is widely known as catecholamine dump . Extremely high levels of catecholamine can also be caused by neuroendocrine tumors in the adrenal medulla , a treatable condition known as pheochromocytoma . High levels of catecholamines can also be caused by monoamine oxidase A deficiency. This is the gene responsible for degradation of these neurotransmitters and thus increases the circulation of them considerably. It occurs in the absence of pheochromocytoma, neuroendocrine tumors, and carcinoid syndrome , but it looks similar to carcinoid syndrome such as facial flushing, aggression, and ADHD . [6][7] **Effects** Catecholamines cause general physiological changes that prepare the body for physical activity (fight -or-flight response). Some typical effects are increases in heart rate , blood pressure , blood glucose levels, and a general reaction of the sympathetic nervous system . Some drugs, like tolcapone (a central COMT -inhibitor), raise the levels of all the catecholamines. **Function in plants** "They have been found in 44 plant families, but no essential metabolic function has been established for them. They are precursors of benzo[c]phenanthridine alkaloids , which are the active principal ingredients of many medicinal plant extracts. CAs have been implicated to have a possible protective role against insect predators, injuries, and nitrogen detoxification. They have been shown to promote plant tissue growth, somatic embryogenesis from in vitro cultures, and flowering . CAs inhibit indole -3-acetic acid oxidation and enhance ethylene biosynthesis. They have also been shown to enhance synergistically various effects of gibberellins ."[8] **Structure** Catecholamines have



the distinct structure of a benzene ring with two hydroxyl groups, an intermediate ethyl chain, and a terminal amine group. Degradation They have a half -life of approximately a few minutes when circulating in the blood. Monoamine oxidase (MAO) is the main enzyme responsible for degradation of catecholamines. Amphetamines and MAOIs bind to MAO in order to i nhibit its action of breaking down catecholamines. This is primarily the reason why the effects of amphetamines have a longer lifespan than those of cocaine and other substances. Amphetamines not only cause a release of

dopamine , epinephrine , and norepinephrine into the blood stream but also suppress re - absorption.

vii J Neuroimmunol. 2003 May;138(1 -2):65 -75. Crosstalk between neurokinin receptors is relevant to hematopoietic regulation: cloning and characterization of neurokinin -2 promoter. Bandari PS , Qian J , Oh HS , Potian JA , Yehia G , Harrison JS , Rameshwar P . Department of Medicine, UMDNJ -New Jersey Medical School, MSB, Rm. E -579, 185 South Orange Avenue, Newark, NJ 07103, USA. Neurokinin (NK) -1 and NK -2 receptors regulate hematopoiesis by interacting with neurotransmitters that belong to the tachykinin. This report studies the relationship between NK -1 and NK -2 in primary human bone marrow (BM) stroma, which supports hematopoiesis. Use of NK receptor antagonists and deficient stromal cells indicate that the neurotransmitter, substance P (SP), could exert dual hematopoietic effects (inhibitory or stimulatory), depending on the interacting receptor and crosstalk between NK -1 and NK-2. Cloning and identification of the minimal promoter for NK -2 and comparison with NK-1 promoter showed that the hematopoietic functions of NK receptors involve receptor crosstalk and the particular cytokine (IL -3, GM-CSF, TGF -beta or IL -1alpha). Crosstalk between NK -1 and NK -2 adds to communication within neural -hematopoietic axis.

viiiBlood. 2004 Aug 15;104(4):1058 -65. Epub 2004 May 6. Tachykinins regulate the function of platelets. Graham GJ, Stevens JM , Page NM , Grant AD , Brain SD , Lowry PJ , Gibbins JM . School of Animal and Microbial Sciences, The University of Reading, Whiteknights, Reading, Berkshire, RG6 6AJ, UK. Evidence has been mounting for peripheral functions for tachykinins, a family of neuropeptides including substance P (SP), neurokinin A, and neurokinin B, which are recognized for their roles in the central and peripheral nervous system. The recent discovery of 4 new members of this family, the endokinins (EKA, B, C, and D), which are distributed peripherally, adds support to the notion that tachykinins have physiologic/endocrine roles in the periphery. In the present study we report a fundamental new function for tachykinins in the regulation of platelet function. We show that SP stimulates platelet aggregation, and underlying this is the intracellular mobilization of calcium and degranulation. We demonstrate the presence of the

tachykinin receptors NK1 and NK3 in platelets and present evidence for the involvement of NK1 in SP-mediated platelet aggregation. Platelets were found to contain SP-like immunoreactivity that is secreted upon activation implicating SP-like substances in the autocrine/paracrine regulation of these cells. Indeed, NK1 -blocking antibodies inhibited aggregation in response to other agonists. Of particular note is the observation that EKA/B cross-react in the SP immunoassay and are also able to stimulate platelet activation. Together our data implicate tachykinins, specifically SP and EKA/B, in the regulation of platelet function. PMID: 15130944



Postepy Hig Med Dosw (Online). 2009 Mar 2;63:106 -13. Links [Substance P as a regulatory peptide of hematopoiesis and blood cell functions] [Article in Polish] Adamus M . Zakład Hematologii Eksperymentalnej, Instytut Zoologii Uniwersytetu Jagiellońskiego, Poland. SP is an undecapeptide that belongs to the family of related neurokinins termed tachykinins. SP is one of the mediators responsible for the neural-immune/hematopoietic cross-talk. It is released from the nerve fibers of the autonomic and enteric nervous systems in lymphoid organs and is also produced by the resident, stromal or hematopoietic cells. SP stimulates the production of hematopoietic cytokines (e.g. IL-1, IL-3, IL-6, SCF, GM-CSF) by bone marrow stromal cells. It enhances the proliferation of bone marrow progenitors, both directly by binding to progenitor's receptors and indirectly by interacting with marrow stromal cells. SP can also modulate immune and hematopoietic functions like phagocytosis, immunoglobulin production, lymphocyte proliferation and platelet aggregation. SP fragments derived from endopeptidase activity could also exert immune and hematopoietic regulation. The biological effects of SP are mediated through interactions with certain G protein-coupled receptors: the neurokinin (NK) receptors. Different studies have shown that NK receptors are localized on immune-competent cells, including monocytes/macrophages, neutrophils, mast cells, dendritic cells and T or B lymphocytes, bone marrow stromal cells and hematopoietic progenitors. The disturbance of the neural-hematopoietic-immune axis may be implicated in hematological malignancies. SP seems to be important in the neoplastic transformation of bone marrow, leading to the development of acute leukaemia in children; myelofibrosis and also metastases to bone marrow of solid tumors in early stages of these diseases.

ix AIDS. 1998 Dec 24;12(18):2377 -85. HIV-1 gp120 increases the permeability of rat brain endothelium cultures by a mechanism involving substance P. Annunziata P , Cioni C , Toneatto S , Paccagnini E . Institute of Neurological Sciences, University of Siena, Italy. **OBJECTIVE:** To analyse whether an HIV-1 envelope protein might play a role in damaging the blood-brain barrier as a fundamental step in the early invasion of the central nervous system by HIV-1. **DESIGN:** Analysis of permeability of rat brain endothelium cultures to albumin, to assess the functional integrity of the vascular component of the blood-brain barrier. **METHODS:** Rat brain endothelium cultures prepared by cerebral microvessels were exposed to recombinant gp120IIIB on microporous membranes and passage of biotin-labelled albumin was analysed. Scanning electron microscopy was used to analyse cell culture morphology. Some cultures were preincubated with N-nitro-L-arginine methyl ester (L-NAME), a selective inhibitor of nitric oxide synthase, or with spantide, a selective substance P antagonist. **RESULTS:** HIV-1 gp120 increased the permeability of rat brain endothelial cells to albumin in a dose-dependent manner. Scanning electron microscopy revealed profound gp120-induced alterations in cell morphology accounting for the increased permeability to macromolecules. These alterations were neutralized by anti-gp120 monoclonal antibody but not by isotype control antibody or L-NAME. By contrast, spantide and anti-substance P polyclonal antibody completely blocked the gp120-induced increase in albumin permeability. Control cultures exposed to measles virus nucleoprotein showed an increase in permeability that was not blocked by spantide. Brain endothelial cells, exposed to gp120, displayed cell surface immunoreactivity for substance P, suggesting that substance P is secreted by brain endothelium in response to gp120 stimulation and binds to brain endothelial cells through a receptor-mediated mechanism. **CONCLUSIONS:** These findings suggest a role for substance P in the gp120-induced increase in permeability of brain endothelium. PMID: 9875575 ©2009 Dwight Jennings, DDS