Vasoactive Peptides in the Skin

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The vascular effects of endogenous substances can be easily studied in the skin. Early in this century, vasoregulation was shown to be dependent on innervation. Peptidergic transmitters have been shown to co-exist and co-transmit along with noradrenaline and acetylcholine, sometimes being responsible for non-adrenergic-noncholinergic responses. This review summarizes recent information on vasoregulatory effects of neuropeptides such as substance P (SP), neurokinin A (NKA), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating peptide (PACAP), neuropeptide Y (NPY), and somatostatin. All these peptides are vasodilators, and some of them seem to be involved in neurogenic inflammation. Some vasoactive peptides and other vasoactive molecules, such as nitric oxide (NO) and histamine, can originate both from nerves and cells and are crucially involved in vasoregulation. Other cell-derived peptides and molecules, such as bradykinin, endothelins, and prostaglandins, may contribute to neurogenic inflammation. All the peptides and molecules described also exist in other organs such as the brain, heart, lung, pancreas, and gastrointestinal tract. The effect of neuropeptides seems to vary from one organ or tissue to another, e.g., NPY is a potent vasoconstrictor in cardiac and cerebral vascular beds but acts as a vasodilator when it occurs in the skin. The presence of mast cells and inflammatory cells may create a special environment in the skin. Key words: neuropeptides/neurotransmitters/histamine/prostaglandins. Journal of Investigative Dermatology Symposium Proceedings 2:49–55, 1997

The skin protects the body from noxious agents in the environment. Nerve fibers in the skin provide the chemical mediators that enable blood vessels and other structures to respond to external stimuli. In 1901 Bayliss showed that stimulation of primary afferent nerve fibers will evoke vasodilatation in the skin. The term 'axon reflex' was introduced to describe the conjunction of afferent (orthodromic) and efferent (anti-dromic) conduction of impulses (Bayliss, 1901). The afferent function of sensory nerves is to signal the presence of nociceptive stimuli to the central nervous system, where they will be interpreted as pain, itch, etc. Their efferent function is to contribute to the local defense against harmful (nociceptive) stimuli. Neuropeptides are involved in both these functions (Lembeck and Holzer, 1979).

The skin is also supplied with parasympathetic and sympathetic nerve fibers. Blood vessels and sweat glands are regulated by sympathetic fibers. Most post-ganglionic sympathetic nerves release noradrenaline (NA), which may act on either α- or β-adrenoceptors. The sympathetic fibers that supply sweat glands are cholinergic. Parasympathetic stimulation has little effect on blood vessels, except in certain restricted areas such as the bluish area of the face and neck. In many organ systems, autonomic nervous transmission cannot be completely blocked by drugs that abolish responses to acetylcholine or noradrenaline. The term nonadrenergic noncholinergic transmission was coined to denote the involvement of additional chemical mediators. Sensory neurons and nerve fibers form another important part of the peripheral nervous system. The axon reflex in human skin depends on the release of neuropeptides from sensory C-fibers and on the mobilization of histamine from nerve-associated mast cells (Foreman and Jordan, 1983). Among the neuropeptides that occur in sensory nerve endings are substance P (SP) and calcitonin gene-related peptide (CGRP). Other agents, such as the peptide bradykinin, which is derived from plasma proteins, and prostaglandins, which originate from tissue cells, are known to cause or enhance the axon reflex owing to their ability to excite or sensitize C-fibers. There is much evidence to suggest that additional factors released from vascular endothelial cells, such as endothelin and nitric oxide (NO), may act as vasoactive mediators. Endothelin is a very potent vasoconstrictor peptide, whereas NO is a vasodilator.

Data accumulated during the past decade suggest that neurons release more than one transmitter (i.e., co-transmission) (Burnstock, 1987). Thus, NA has been shown to co-exist with neuropeptide Y (NPY) in sympathetic nerve terminals. Such co-existence has also been shown for acetylcholine and vasoactive intestinal peptide (VIP) in parasympathetic nerve fibers. What can co-transmission achieve that cannot be achieved with a single transmitter? One possibility is that the two mediators operate differently, one participating in processes that occur within milliseconds, and the other in slower processes. Another possibility is that the ratio of the two mediators released may vary, for instance, with the stimulation frequency. This is the case with NA and NPY at sympathetic nerve terminals, the release of NPY being less than that of NA at low stimulus frequencies but increasing with increasing frequency (Sjärne, 1989). A third possibility is that one of the co-existing mediators (e.g., the peptide) may be removed or inactivated more slowly than the other (e.g., acetylcholine or NA),
thus reaching targets further away from the site of release and producing more long-lasting effects.

The aim of this review is to provide an updated comprehensive analysis of the effects and mechanisms of action of various vasoactive peptides and other vasoactive molecules in the skin. These substances elicit a wide range of responses in many types of cells including neurons, smooth muscle, vascular endothelium, exocrine gland cells, mast cells, and cells of the immune system. The classification into nerve-derived and cell-derived messengers is not strict, as some molecules such as nitric oxide (NO) and histamine can originate both from cellular and neural structures, whereas tachykinins, mainly originating from neurons of the dorsal root ganglia, may be synthesized in non-neural structures such as endothelial cells (Linnick and Moskowitz, 1989), eosinophils, and macrophages (Weinstock and Blum, 1990).

**NERVE-DERIVED VASOACTIVE PEPTIDES**

Regulatory peptides normally consist of five to 40 amino acid residues, and the peptide precursors are produced in the nerve cell bodies. The precursor protein is packaged into granules/vesicles in the Golgi area, and the active peptide is generated through proteolysis in the secretory organelle, being ready for release by the...
The Tachykinins (Substance P and Neurokinin A) Substance P (SP) was first discovered by von Euler and Gaddum in 1931 and its structure of 11 amino acids was published in 1970. SP is encoded by the same gene as neurokinin A (NKA), which consists of ten amino acid residues. Differential splicing of the RNA transcript results in the production of two mRNAs and two precursor proteins, one of which includes both peptides and the other includes SP only. How the splicing process is controlled is not well understood, but it is clearly an important regulatory mechanism. Tachykinin receptors are of three subtypes: NK₁, NK₂, and NK₃ receptors (Maggi et al., 1993). Although each tachykinin has some affinity for all three receptor subtypes, SP mainly activates the NK₁ receptor.

SP was put forward as a putative neurotransmitter in sensory nerves after the finding of large amounts of SP in the dorsal horn of the spinal cord (Lembeck et al., 1979). The distribution of SP has been established using immunohistochemistry and immunocytochemistry. SP is present in primary sensory nerves that have their cell bodies in the spinal and trigeminal ganglia (Sundler et al., 1985). SP has strong vasoactive effects causing vasodilatation and profound hypotension.

SP is thought to be involved as a mediator in sensory processes of various types, including nociception and inflammation (Lynn, 1992). In the skin, SP-immunoreactive nerve fibers are distributed as single scattered fibers just beneath the epithelium or penetrating into it. They sometimes occur as bundles of fibers in the deeper layers and sometimes as single fibers running either close to blood vessels or freely in the connective tissue. Generally, SP fibers are few or moderate in number except, for instance, in the skin of fingertips where they are numerous and sometimes ramify within the corpuscles of Meissner in the papillae. SP-containing nerve fibers are also known to form a network around sweat glands and blood vessels. Simultaneous demonstration of CGRP and SP has revealed their co-existence in spinal nerve cell bodies and in a population of subepithelial nerve fibers (Wallengren et al., 1987).

Intradermal injection of SP produces flare, wheal, and itch (Hägermark et al., 1978). There is regional variation in the flare response, which is most pronounced on the torso and less at remote distal locations, whereas wheal is most manifest on the upper aspect of the foot and on the flexor surface of the upper arm (Fig 1) (Wallengren et al., 1992). The itch is most intense on the foot and the nape of the neck, indicating that the itch does not correlate to the flare response (Wallengren et al., 1992). The flare response diminishes with increasing age and in conditions of physical stress, and its magnitude varies with the time of day, whereas the wheal response appears to be independent of circadian rhythm (Wallengren et al., 1992).

SP is known to release mast-cell histamine in vitro. The depletion of histamine from dermal mast cells by compound 48/80 greatly reduces the flare response to SP (Foreman and Jordan, 1983), suggesting that the flare is dependent upon histamine (Fig 2A). It has therefore been postulated that, during the axon reflex, mobilized SP does not evoke vasodilatation directly but through the release of mast-cell histamine (Foreman and Jordan, 1983). Moreover, SP-evoked flare is dependent upon an axon reflex, because pre-treatment of the skin with lidocaine greatly diminishes the response (Foreman and Jordan, 1983) (Fig 2A). Conceivably, exogenous SP releases histamine, which in turn stimulates sensory nerve fibers to release tachykinins and CGRP. The end result reflects the combined direct vascular effects of histamine, tachykinins, and other bioactive agents released from mast cells and sensory nerve fibers. The SP-evoked wheal, on the other hand, is only moderately affected by pre-treatment with compound 48/80 and local anesthetics (Fig 2D). Thus, the wheal response seems to be largely due to a direct local effect of the injected SP (Foreman et al., 1983).

NKA, first isolated from the porcine spinal cord (Kimura and Kangawa, 1983), was later shown to activate NK₁ receptors (Maggi et al., 1993). It was found to co-exist with SP in primary sensory neurons. Like SP, NKA is also active with regard to gall bladder contraction, protein extravasation, hypotension, and bronchial smooth muscle spasm (Tatemoto et al., 1985). NKA is less potent than SP in inducing flare and itch in human skin. The poor itch and flare response to NKA may reflect its weak histamine-releasing ability. Nonetheless, the flare evoked by NKA is reduced by pre-treatment with compound 48/80 (by about 50%) and is virtually abolished by the local anesthetic lidocaine (Fig 2B) (Wallengren and Håkanson, 1987). It is therefore conceivable that, like SP, NKA acts via sensory fibers and mast cells. The wheel-inducing capacity of NKA is similar to that of SP (Fig 2E), although SP is more effective in inducing flare (Wallengren and Håkanson, 1987).

SP, NKA, and CGRP are thought to be released concomitantly from sensory nerve fibers in response to physical or chemical irritation. It appears that SP effectively mobilizes histamine from local mast cells. The histamine released will excite sensory nerve fibers causing the release of more SP (together with NKA and CGRP), and this positive feedback mechanism continues to be operative, possibly until all ramifications of the nerve have become
engaged in axon reflexes and until available pools of the neuropeptides have been exhausted.

**CGRP**

CGRP, a 37-amino acid peptide, is encoded by the same gene that codes for calcitonin and was discovered by Amara and colleagues in 1982. Differential splicing allows cells to produce either pro-calcitonin (expressed in thyroid C-cells) and/or pro-CGRP (expressed in many neurons and in thyroid C-cells) from the same gene.

The CGRP receptors have not yet been cloned. There is pharmacologic evidence, however, supporting the existence of several receptors (for review see Poyner, 1995).

CGRP has been found in sensory neurons in the trigeminal ganglion and in the spinal ganglia. It co-exists with SP and NKA in sensory nerve cell bodies (Sundler et al., 1985). CGRP is the most abundant of all neuropeptides in human skin and is often found to be co-localized with SP (Wallengren et al., 1987). In the skin, CGRP-immunoreactive nerve fibres are distributed as single scattered fibers just beneath and sometimes penetrating into the epithelium. Occasionally CGRP-positive nerve fibers form fiber bundles in the deeper layers, whereas single fibers run either close to blood vessels or around sweat glands. The density of CGRP-IR fibers is generally moderate, although it is quite high in the skin of fingertips, particularly in the papillae. Based on the abundance of CGRP-containing fibers, we propose that CGRP is an important messenger molecule in the sensory nervous system. In human skin, CGRP induces slowly developing local reddening (duration of several hours) (Wallengren and Häkanson, 1987) (Fig 3). The CGRP-evoked erythema does not seem to be mediated by mast-cell histamine or by C-fiber tachykinins, as it is not suppressed by pre-treatment with mepyramine or compound 48/80 or by lidocaine treatment. The long-lasting and widespread vascular effects of CGRP may reflect a gradual diffusion of the peptide, which conceivably exerts direct effects on blood vessels. Although SP and CGRP may be released concomitantly from the same C-fibers, they seem to differ from each other in their duration of action, CGRP being more long-lasting. In the immediate phase of inflammation, it is likely that SP and histamine, by inducing triple response, play crucial parts. The CGRP-evoked erythema continues to develop as the effects of SP and histamine subside. Hence CGRP may be expected to play a greater part in subsequent stages of inflammation. Clinical inflammatory reactions are usually more prolonged than the rapidly developing flare and wheal reactions, which can be induced experimentally, and hence resemble the action of CGRP more than that of SP. When injected concomitantly, SP is found to shorten the duration of the reddening induced by CGRP (Brain and Williams, 1988). NKA does not shorten the duration of the CGRP response. Local elimination of mast cells in the skin by treatment with compound 48/80 causes SP to lose its ability to shorten the duration of CGRP-evoked erythema. These observations suggest that an SP-evoked release of proteolytic enzymes from mast cells may result in accelerated degradation of CGRP (Brain and Williams, 1988).

**VIP**

VIP was isolated from porcine intestine by Said and Mutt in 1970 and structurally characterized by the same authors 4 years later (Mutt and Said, 1974). VIP consists of 28 amino acids and belongs to the same family of neuropeptides as secretin and glucagon. Recent reports have identified two distinct VIP receptors, VIP1 and VIP2, which are members of a family of G-protein-linked receptors (for a review see Harmar and Lutz, 1994).

VIP has received its name because of its hypotensive actions and because of its potent vasodilatory activity in the splanchnic, coronary, and pulmonary vascular beds where it is present in nerve structures (Said and Mutt, 1970). VIP and acetylcholine co-exist in post-ganglionic parasympathetic nerve fibers. In the skin, VIP-containing nerve fibers are distributed preferentially in the deeper parts of the dermis in perivascular nerve fibers (Wallengren et al., 1987). In eccrine sweat glands, VIP-containing fibers seem to innervate glandular cells (Hartschuh et al., 1983). VIP relaxes the smooth muscle of blood vessels and has been suggested to be involved in the regulation of vasodilatation and sweat gland function. The amount of VIP in skin varies from one region to another, the richest supply occurring in perioral and digital skin. VIP induces histamine-dependent flare and wheal when injected intradermally (Fjellner and Hagermark, 1981). VIP is found at high concentrations in fluid from spontaneous blisters in inflamed skin (Wallengren et al., 1987).

**Pituitary Adenylate Cyclase-Activating Peptide (PACAP)**

PACAP was discovered in 1989 and consists of two forms, one with 36 amino acid residues, the other with 27. Both peptides arise from a common precursor and belong to the same family as VIP (for review see Warren et al., 1992). Although several receptors that interact with both PACAP and VIP have been described, the PACAP type 1 receptor seems to be highly specific for PACAP (review see Harmar and Lutz, 1994).

PACAP is a powerful activator of adenylyl cyclase and seems to regulate hormone production and secretion in the pituitary gland, thyroid gland, gastrointestinal tract, and the cardiovascular and endothelium-independent vasodilatation. It has been found to stimulate the secretion of NPY and catecholamines (May and Braas, 1995).

The supply of PACAP in human skin is scant, but it occurs in blister fluid from inflamed skin (Wallengren J, Wang Z, Häkanson R, unpublished observations). In human skin PACAP induces a slowly developing erythema resembling that induced by CGRP (Wallengren J, Häkanson R, unpublished observations). In the skin of the rat, PACAP-positive nerve fibers are found as free nerve endings near hair follicles (Wallengren J, Sundler F, unpublished observations), a distribution similar to that of VIP and CGRP (Wallengren et al., 1987). PACAP can be partly eliminated (to 75%) from the nerve fibers of the rat skin by capsaicin (Wallengren J, Häkanson R, Sundler F, unpublished observations). From available information it appears that PACAP is a constituent of C-fiber neurons (together with SP and CGRP) and of parasympathetic neurons and fibers (together with VIP and sometimes with NPY).

**NPY**

NPY consists of 36 amino acid residues and has been found in neuronal elements in both brain and periphery. It was first isolated from bovine brain by Tatemoto and co-workers in 1982. Numerous NPY receptors have been identified. The binding properties of two of the NPY receptors (Y1 and Y2) have been described in some detail (Hashim and Tadepalli, 1995).

Because many nerve cell bodies in the sympathetic ganglia have been found to store NPY, it has been suggested that noradrenergic sympathetic neurons contain NPY (Lundberg et al., 1982). NPY is known to co-exist with NA in peripheral adrenergic neurons and to enhance various adrenergically mediated functions (Sundler et al., 1984). A dense supply of NPY-immunoreactivity fibers is found in the respiratory tract, heart, gut, pancreas, and the urogenital tract (Sundler et al., 1986). In these vascular beds the vasoconstrictor response to exogenous noradrenaline is greatly enhanced by NPY (Edvinsson et al., 1984).

In the skin, NPY fibers occur mainly in the deeper portions of the dermis, mostly around blood vessels and occasionally in association with sweat glands and hair roots (Wallengren et al., 1987). We have found that concomitant intracutaneous injection of NPY and NA in equimolar concentrations decreases the bleeding induced by NA given alone (Wallengren J, Häkanson R, Möller H, unpublished observations), suggesting that in the skin the two substances do not act synergistically. The observed cutaneous vasodilatation is in agreement with the paradoxical increase in cutaneous microvascular blood flow reported by Hashim and Tadepalli in 1995. The flare induced by intracutaneous injection of NPY is probably mediated by histamine, as NPY releases histamine from cutaneous mast cells (Emadi-Khiav et al., 1995). NPY is found in fluid from spontaneous blisters in inflamed skin (Wallengren et al., 1987). NPY occurs together with NA in sympathetic fibers and together with VIP in a subpopulation of parasympathetic fibers. If NPY participates in the neurogenic inflammation in the skin, it
probably does so as a transmitter released from sympathetic nerve fibers together with NA.

**Somatostatin** Somatostatin consists of 14 or 28 amino acid residues. It was first discovered by Brazeau and colleagues in 1973 in hypothalamus. Specific receptors for somatostatin are expressed on normal and activated monocytes, and on lymphocytes, but not on granulocytes and red blood cells (Hiruma et al, 1990).

Somatostatin was subsequently demonstrated in the gastrointestinal tract, and it was shown to be a highly potent inhibitor of peptide hormone release and cell proliferation (Brazeau et al, 1973). Somatostatin is localized to neurons in the spinal ganglia (10% of the nerve cell bodies are somatostatin-immunoreactive) and to nerve fibers in the dorsal horn of the spinal cord. In the skin somatostatin occurs at small concentrations and with a distribution similar to that of SP (Johansson and Vaalasti, 1987). In normal human skin, the concentration of somatostatin is so low that it cannot be detected by immunostaining (Wallengren et al, 1987). Intracutaneous injection of somatostatin induces flare and wheal that are fainter than that induced by SP. The two peptides given in equimolar doses act synergistically producing a greater flare response than either of them does alone. Somatostatin is found in blister fluid from inflamed skin (Wallengren et al, 1987), which suggests that it functions as an inflammatory mediator.

**CELL-DERIVED VASOACTIVE PEPTIDES AND MOLECULES**

**Nitric Oxide (NO)** Furchgott and Zawadzki reported in 1980 that endothelial cells are required for the acetylcholine-evoked relaxation of arterial smooth muscle. Acetylcholine acting on muscarinic receptors was shown to release a substance, which they called endothelium-derived relaxing factor. In 1982 Palmer and co-workers showed this substance to be nitric oxide, a short-lived free radical (for a review see Snyder, 1992). Nitric oxide appears to be a second messenger acting within the cell or neuron in which it is formed. The hypotensive action of kinins was first discovered by two French surgeons, Abelous and Bardier, in 1909. Bradykinin was purified in 1956 by Andrade and Roch e Silva. It exists in the circulation at very low concentrations. The precursors of bradykinin, kallikreins, and pre-kallikreins are released from exocrine glands (pancreas, kidney, intestine, salivary, and sweat glands) upon stimulation by the autonomic nervous system (for review see Regoli and Barabe, 1980). Bradykinin is a powerful stimulant of C-fibers and induces triple response upon intradermal injection (Greaves and Shuster, 1967). The intensity of the response to bradykinin varies from one skin region to another and diminishes with age. The flare response is triggered by axon reflexes and the release of mast-cell histamine (Wallengren and Häkanson, 1992). Repeated injection of bradykinin induces tachyphylaxis, which is reversed 8 wk after the last injection of bradykinin (Wallengren and Häkanson, 1992). The wheal induced by bradykinin cannot be inhibited by a non-peptide neurokinin1 (NK1) receptor antagonist, which effectively inhibits SP- and NKA-induced weal (Wilsoncroft et al, 1994).

**Prostaglandins** In the 1960s Bergström and Samuelsson isolated two prostaglandins (PGE2 and PGF2α) and determined their 20-carbon fatty acid structure. Additionally three prostaglandins, all with the same carbon skeleton (prostanoid acid), were defined later. Five main prostanoid receptors have been defined, one each for the natural prostaglandins (EP-receptor for PGE2, DP-receptor for PGD2, and IP-receptor for PGI2).

Prostaglandins are generated de novo from arachidonic acid by cyclo-oxygenase activity. PGE2 is produced mainly by macrophages and neutrophils, PGD2 mainly by mast cells and basophils, and PGI2 by the endothelium. The prostaglandins differ in their actions. PG12 is a vasodilator that acts synergistically with NO in relaxing vascular smooth muscle; it also inhibits platelet aggregation. PGE2 relaxes smooth muscle and acts as a bronchodilator and enhancer of cutaneous permeability. Intracutaneous injection of PGE2 induces an indurated erythema with pseudopodia, a reaction resembling that of CGRP but of shorter duration. The PGE2 response is partly (to 30%) dependent on axon reflexes and release of mast-cell histamine (Wallengren and Häkanson, 1992). The PGE2-induced vasodilation in the skin potentiates histamine-, serotonin-, and bradykinin-evoked edema and itch (Williams and Morley, 1973). Indomethacin blockade of prostaglandin synthesis inhibits the flare response to SP by approximately 40% and inhibits the flare response to bradykinin by 70%. (Wallengren and Häkanson, 1992b). These findings suggest that prostaglandins interfere with the neurogenic mechanisms responsible for inflammation in the skin. Nonsteroidal
anti-inflammatory drugs have not proved to be effective in the treatment of skin diseases (Greaves, 1987).

**Histamine** Most of the early studies on the biologic action of histamine were performed by Lewis in the 1920s and Dale in the 1930s. Specific histamine receptors, of three types (H₁, H₂, and H₃), have been defined. H₁-receptors are found in human airways and skin, H₂-receptors in the gastrointestinal tract, and H₃-receptors are mainly associated with neural tissue at pre-synaptic sites. Histamine is 2-(4-imidazolyl)-ethylamine, formed from histidine by histidine decarboxylase. At the cellular level, it occurs mainly in mast cells and basophils. Non–mast-cell histamine occurs mainly in the brain where it may serve as transmitter in histaminergic neurons. Histamine was the first substance found to induce the triple response, as demonstrated by Lewis in 1927. The histamine-evoked flare reaction is almost abolished by local anesthetics (Wallengren and Häkanson, 1987) (Fig 2C). The part played by histamine in neurogenic inflammation is still a matter of debate. It is generally agreed that histamine is released in response to noxious stimulus. The crucial question is whether histamine participates in the progressive spread of the flare, by activating sensory nerve endings to release neurogenic mediators (e.g., tachykinins) followed by further histamine release (reinforcement). This cascade of responses has been termed the ‘axon response’ (Lembeck and Holzer, 1979), to distinguish it from the classic ‘axon reflex.’ The latter concept implies that the spread of the flare is mainly dependent on the anti-dromic passage of impulses. That the flare is limited by the extent of the collateral network was initially demonstrated by Bayliss (for review see Foreman and Jordan, 1983). The question of the function of histamine and its interaction with C-fibers in neurogenic inflammation has been thoroughly investigated using capsaicin as an experimental tool.

**CAPSAICIN**

Capsaicin is the active agent in hot pepper of the genus capsicum. Chemically, capsaicin is trans-8-methyl-N-vanillyl-6-nonenamide. It was introduced to pharmacology by Jancso and collaborators in 1979, to distinguish it from the classic ‘axon reflex.’ The latter concept implies that the spread of the flare is mainly dependent on the anti-dromic passage of impulses. That the flare is limited by the extent of the collateral network was initially demonstrated by Bayliss (for review see Foreman and Jordan, 1983). The question of the function of histamine and its interaction with C-fibers in neurogenic inflammation has been thoroughly investigated using capsaicin as an experimental tool.

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