Ann. Rev. Pharmacol. Toxicol. 1988. 28:123–40

PHARMACOLOGY OF DYNORPHIN

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INTRODUCTION

Both opioid receptors and their natural ligands, the endogenous opioids, exist in multiple forms in the central nervous system. Opioid receptors include μ (selective for morphine-like ligands), δ (enkephalins) and κ (ethylketocyclazocine) (1, 2); still other receptor types may exist, either in brain or in peripheral tissues (3, 4), as well as subtypes for μ (5, 6) and κ (7) receptors. The endogenous opioid peptides can also be grouped into three major classes, members of which have distinct precursors and distinct though overlapping distributions in the central nervous system: the enkephalins, β-endorphin and related compounds, and the dynorphins (8).

The temptation is to view each of the major ligand classes as selective for one of the major receptor types, and some evidence supports this conclusion. β-endorphin has high affinity for μ receptors, enkephalins for δ receptors, and dynorphin for κ receptors (2, 9). However, each of these ligands has significant affinity for more than one receptor type (2, 10, 11), and their widespread CNS distribution (12) makes it unlikely that the action of any of them in vivo is confined exclusively to one kind of receptor.

This conclusion appears to be particularly true for the dynorphins, a series of peptides derived from the precursor prodynorphin (proenkephalin B). Unlike either the enkephalins or the endorphins, many members of this endogenous opioid class interact with high affinity with all three major opioid receptor types found in the brain (10, 11). They are also nearly unique among endogenous opioids in that they are not analgesic in the brain (13), though they may be in the spinal cord (14, 15).

In this article, we review what is known about the physiological, pharmacological, and behavioral characteristics of the dynorphins. Special focus

0732-0582/88/04190123$02.00

will be on the 17 amino acid peptide dynorphin A(1–17) and its 13 amino acid fragment dynorphin A(1–13), as these were the first dynorphins isolated (16) and are currently the best characterized. Because of the enormous volume of relevant studies and strict page limitations, this review emphasizes information at the expense of interpretation.

IN VIVO EFFECTS OF DYNORPHIN

Analgesia and Modulation of Analgesia

BRAIN A classic property of opioid agonists is their ability to induce analgesia in mammals. A striking feature of dynorphin, however, is its lack of analgesic activity when injected in the mammalian brain,—an observation confirmed in many laboratories (9, 13, 17). In those few instances where analgesia has been reported, it has generally been observed only with very high doses of dynorphin (18) or only on certain kinds of tests (19, 20). In fact, since dynorphin can induce various motor effects in animals (see below), it is often necessary to use an analgetic test that does not require the animal to move, such as vocalization.

Dynorphin's lack of analgetic effect was initially ascribed to rapid degradation by peptidases present in vivo (9). However, it was subsequently reported that the peptide has other, modulatory effects under these conditions; it antagonizes morphine or β-endorphin induced analgesia in naive animals, while potentiating it in tolerant ones (13, 21). The antagonism has also been observed with the des-Tyr fragment of dynorphin (2–17), a likely metabolite of dynorphin (22), but the potentiation has not, suggesting that it is a property of the intact peptide. Dynorphin also modulates the respiratory and thermoregulatory effects of morphine (see below).

The ability of dynorphin to potentiate morphine analgesia in morphine-tolerant animals suggests that while not analgesic itself, the peptide can nevertheless substitute for morphine in tolerant/dependent animals, and this was directly demonstrated in studies with rats (23), monkeys (24), and human heroin addicts (25). In rats, moreover, termination of dynorphin administration resulted in no withdrawal signs (23). Should this finding be replicable in humans, it would obviously have enormous clinical potential.

In conclusion, pharmacological evidence suggests that dynorphin-(1–17) and -(1–13) may play primarily a modulatory role in the brain. Since they decrease opioid potency in naive animals while increasing it in tolerant ones, we have suggested that these peptides might act as a "set point" mechanism, holding opioid sensitivity within a fairly narrow range (26). In fact, anatomical studies indicate considerable overlap between the central nervous system distribution of dynorphins and other opioids, in areas such as the hippocampus, hypothalamus, pituitary, striate, and spinal cord (27–33).

Though no one, to our knowledge, has demonstrated colocalization of dynorphin and another opioid within the same neuron, these different peptides could conceivably be released by different neuron terminals onto a common postsynaptic site.

The modulatory effects of dynorphin might also be brought into play through regulation of prodynorphin processing. This dynorphin precursor also contains several leucine-enkephalin sequences, and some studies suggest that in parts of the brain, some of the latter opioid may be derived from prodynorphin, rather than from proenkephalin (34, 35). Thus, through the processing steps, the proportions of enkephalin and dynorphin could be directly regulated in a given brain region.

SPINAL CORD While evidence does not support a direct role of dynorphin in analgesia in the brain, the situation in the spinal cord may be different. Several investigators have reported that dynorphin-(1–13) is analgesic when injected intrathecally, with a potency equal to or greater than that of morphine (14, 15, 20, 36–38). Tolerance has been reported to develop upon chronic infusion of the peptide (26). Analgesia has also been reported for intrathecal administration of dynorphin B-(1–29) (39) and dynorphin A-(1–9) (40).

Contrasting results, however, were reported by Stevens & Yaksh (41). Like other investigators, this group observed that dynorphins given intrathecally at high doses induced flaccid paralysis (see below). When doses of dynorphin-(1–17) or (1–13) were used below this level, no antinociceptive activity could be detected using three different analgesic tests: tail flick, hot-plate, and writhing. This study thus points up again the great difficulty in dissociating analgetic and motor effects of putative opioids in commonly used tests.

Another piece of evidence suggesting that dynorphin may not be analgesic in the spinal cord is the inability of investigators to demonstrate its interaction with a known opioid receptor type. On the basis of the relatively low potency of naloxone in blocking dynorphin's action, as well as lack of cross-tolerance with morphine, most investigators agree that dynorphin does not act primarily through μ (morphine-like) receptors at this level. Some investigators have reported that dynorphin has κ agonist properties in the spinal cord (36, 39), consistent with its action as a κ agonist in in vitro tissue systems (see below). However, these studies were conducted by blocking dynorphin's effects with a relatively nonselective κ antagonist, or by comparing its effects with those of a nonselective κ agonist.

Jhamandas et al, in contrast, reported that dynorphin's pharmacological profile in the spinal cord differed from that of U-50,488H, one of the most highly specific κ agonists currently known (38). Both dynorphin-(1–13) and dynorphin-(1–8) induced a biphasic response, with antinociception present 24 hr after administration; in contrast, U-50,488H induced a monophasic re-

sponse, and antinociception was not present after 24 hours. In addition, both dynorphins enhanced analgesia induced by intrathecal morphine, while U-50,488H had no effect. Thus, in this study the dynorphins and U-50,488H appeared to be acting on different receptors. Stevens & Yaksh (41) came to a similar conclusion.

In conclusion, the evidence that dynorphin has analgesic properties in the spinal cord is somewhat better than that for the brain, yet it is still controversial. In addition to the negative results reported by Stevens & Yaksh (41), the evidence to date indicates that dynorphin is not interacting with any of the three major opioid receptor types. Furthermore, the enhancement of morphine analgesia by dynorphin observed in the study by Jhamandas et al (38) suggests that, as in the brain, dynorphin at the spinal level may be modulating opioid analgesia, rather than directly inducing it.

Motor Effects

Dynorphin has pronounced effects on the mammalian motor system, which were noted in some of the earliest studies of this peptide. When injected intracerebroventricularly or into other brain regions in high doses, both dynorphin-(1–17) and -(1–13) induced barrel rotation in rats (17, 18, 42–44). However, some investigators have found that these effects were not blocked by naloxone (17), and that they were also induced by the non-opioid dynorphin fragment (6–17) (17, 44). Thus, opioid receptors may not be involved.

When given intrathecally, on the other hand, dynorphin at high doses induces flaccid paralysis (15, 41, 43, 45). Most of these investigators reported that this effect was not antagonized by naloxone and thus appeared to be mediated by non-opioid mechanisms. This conclusion was further supported by the fact that a non-opioid C-terminal fragment of dynorphin was also active in this system (45).

Cardiovascular Effects

Several investigators have shown that dynorphin, like other opioids, lowers blood pressure and heart rate (46–48). In these studies, dynorphin-(1–17) or (1–13) was administered directly into hypothalamic nuclei, or other brain regions. Kiang & Wei (49) reported that dynorphin-(1–13), given intravenously, also enhanced the effect of morphine on these parameters.

However, in a study in which opioid agonists were administerd into the ventral lateral medulla, opioids either increased or decreased these parameters, depending on the site of injection (50). Injection of morphiceptin, DADLE, β-endorphin or dynorphin into pressor regions in every case decreased blood pressure and heart rate, while injection into depressor regions increased these parameters.

Further evidence for a role of dynorphin in regulating the cardiovascular

system was provided by Feuerstein et al (51), who reported differences between spontaneously hypertensive rats and normal controls in levels of dynorphin-(1–13) or -(1–8) in some brain regions.

Dynorphin also has peripheral effects on the circulatory system. Kannan & Seip (52) reported that this peptide relaxed rat superior mesenteric arteries, an effect blocked by naloxone. Wei et al (53) found that dynorphin inhibits neurogenic plasma extravasation. A possible mechanism for peripheral effects is suggested by the recent identification of dynorphin B in nerve fibers serving brain blood vessels (54).

Respiration

One of the best-characterized and most undesirable side effects of morphine and many other opioid agonists is respiratory depression. Though it has no effect on respiration by itself, dynorphin-(1–13) enhanced morphine's depression of this function in morphine-naive animals (55), while having the opposite effect in morphine-tolerant animals, where it antagonized morphine's action.

This pattern of opposite modulatory effects on morphine in naive and tolerant animals is thus like that observed with opioid analgesia (see above), but opposite in direction. As we have pointed out before (26), these modulatory effects should further enhance the clinical potential of dynorphin, as it should reduce the side effects of opioids in the dependent animal, even as it enhances the analgetic effect.

Temperature Control

Dynorphin also has modulatory effects on opioid control of body temperature. Morphine has a pronounced hypothermic effect 30–60 minutes after administration, while dynorphin administerd alone has a slight hyperthermic effect. When given together with morphine, however, it potentiates the latter's hypothermia (56).

Evidence also exists that temperature changes can alter brain levels of dynorphin. Morley et al (57) found that when rats were kept at 4° C for 2 hr, hypothalamic levels of dynorphin were decreased. Taken together with the modulatory effects of dynorphin on body temperature, these results suggest that temperature-induced changes in dynorphin levels may act as a feedback system in thermo-regulation.

Feeding Behavior

Considerable evidence implicating opioid systems in feeding behavior has accumulated in recent years (58, 59). Generally speaking, opioid agonists such as morphine stimulate food intake, while antagonists such as naloxone suppress it. Several investigators have reported that dynorphins also stimulate

food intake (57, 59–62). Morley & Levine (60) found that fragments of dynorphin-(1–17) as short as (1–10) shared this effect, as does the specific κ agonist U-50,488H.

However, one recent study found that neither acute nor chronic infusion of dynorphin-(1–13) had any effect on food intake in either normal or genetically obese rats (63). The finding with obese animals agrees with an earlier study by Morley et al (64), who found that κ agonists had little effect on feeding behavior of obese mice.

Several studies have also reported effects of feeding on dynorphin levels in the brain. Nizielski et al (65) studied ground squirrels, hibernating mammals that undergo periods of both hyperphagic (excess eating) and hypophagic (starvation) behavior prior to the winter. They found that dynorphin levels in several brain regions increased during the hypophagic phase. Other investigators have reported alterations in dynorphin levels in specific brain regions in rats during food deprivation (66, 67).

Hormonal Effects

The derivation of β-endorphin from adrenocorticotropic hormone (ACTH) was an early clue that it and other endogenous opioids might be involved in hormonal regulation. Several studies have shown that both μ and κ type opioids increase prolactin (PRL) levels and decrease luteinizing hormone (LH) levels (68–71). Dynorphin-(1–13) given icv or intravenously has similar effects (72–74) and has also been reported to suppress oxytocin release in lactating rats (75); these effects were reversed by naloxone.

A link between dynorphins and LH is also suggested by similar effects on their anterior pituitary levels as a result of castration. Molineaux et al (76) reported that castration of rats resulted in a short-term decrease in anterior pituitary levels of dynorphin A and B, which was reversed by testosterone; after a month, pituitary levels of dynorphins in the castrated animals had risen to more than twice that of controls. Ovariectomy also resulted in a long-term increase in anterior pituitary dynorphin levels, but no short-term decrease was observed. Castration or ovariectomy has similar effects on pituitary LH levels.

Dynorphin also has been shown to induce hormone secretion in some isolated tissue systems. Guaza et al (77) reported that dynorphin-(1–17) increased ACTH-stimulated steroid secretion in rat adrenocortical cells in vitro. Ishizuka et al (78) reported that dynorphin inhibited, glucose mediated insulin secretion from rat pancreas in vitro.

Finally, the involvement of dynorphins in the action of certain hormones is supported by studies demonstrating their colocalization in certain tissues. Thus, dynorphin-(1–13), LH, and FSH have been found together in anterior pituitary cells (79–81); dynorphin and vasopressin are colocalized in

hypothalamic cells (82); and dynorphin and substance P in nonmammalian striate (83).

Trauma

A great deal of evidence has implicated β-endorphin in the response to stress (84). More recently, dynorphins have also been shown to be involved. In an early study, Millan et al (85) reported that foot shock in rats resulted in an increase in dynorphin in hypothalamus and a decrease in anterior pituitary; there were also decreases in part of the spinal cord. Yaksh et al (86) reported evidence that dynorphin-(1–13) was released from rat spinal cord by bilateral stimulation of sciatic nerves or of the hind paws. As discussed earlier, studies in which stress was induced by food deprivation or low temperature also resulted in altered dynorphin levels, in cortex and hypothalamus, respectively.

Dynorphin levels are also altered by chronic stress. Millan et al (87) reported that chronic pain resulted in increases in dynorphin in anterior pituitary, thalamus, and spinal cord. Faden et al (88, 89) found that immunoreactive dynorphin levels in the spinal cord rose following local injury, with the increases limited to the site of the injury and correlated in magnitude with the severity of the injury. Specificity of the effect was suggested by the lack of changes in enkephalin levels.

Some evidence also suggests that dynorphin may play a role in the inflammation response. Sydbom & Terenius (90) reported that dynorphin induced histamine release from rat mast cells in a dose-dependent fashion; Chahl & Chahl (91) found that dynorphin induced plasma extravasation. However, in both of these studies, the effects of dynorphin were not blocked by naloxone; this suggests mediation through non-opioid receptors.

Opioids have been implicated in the response to brain injury, in particular, to stroke. Several laboratories have reported that in both experimental animals and human patients, morphine exacerbates the response to stroke, while antagonists such as naloxone can prolong survival and in some cases, improve neurological deficits (92–95). Baskin et al (96) then found that treatment of stroked cats with dynorphin also prolonged survival. Some changes in opioid binding were also observed, which were reversed by the dynorphin treatment (97).

Finally, several studies have shown that dynorphin has anticonvulsant activity. Przewocka et al (98) reported that dynorphin, as well as β-endorphin and morphine, antagonized the convulsant effects of pentylenetetrazol. They also reported an increase in pituitary dynorphin levels during amygdaloid kindling (99), while Lason et al (100) observed an initial decrease, followed by an increase, in hippocampal dynorphin levels during kindling. Garant & Gale (101) reported that dynorphin-(1–13) and other opioids attenuated ECS-

induced seizures when infused into the substantia nigra. Hong et al (102) reported that daily ECS treatment increased dynorphin-(1–8) in hypothalamus and decreased it in hippocampus.

Immunomodulation

In recent years, a growing body of evidence has indicated that endogenous opioids are closely connected with function of the immune system. Opioid receptors have been detected on lymphocytes and other immune cells (103, 104), and both endogenous and alkaloid opioid ligands affect the activity of a wide variety of immune functions, including proliferation of lymphocytes (105, 106), natural killer cell activity (107, 108), mononuclear cell chemotaxis (109), and lymphokine release (110). In many cases, however, controversy exists over whether the effect is naloxone-reversible, as well as whether an enhancement or suppression occurs of the immune function.

Dynorphin has not been tested in any of the above studies except for that on chemotaxis, where its effects were similar to those of β-endorphin and enkephalins. However, dynorphin has been implicated in tumor formation. Vaswani et al (111) found that dynorphin levels in the pituitary and the hypothalamus decreased during the formation of mammary tumors in rats. Changes in the levels of some other endogenous opioids were also detected in certain brain regions. High levels of dynorphin-(1–17) and dynorphin-(1–8) have been reported in tumor tissue (112).

IN VITRO EFFECTS OF DYNORPHIN

Effects on Neuronal Activity

Dynorphin, like other opioids, affects the activity of individual neurons in many regions of the CNS. One of the best studied systems is the hippocampus, which can be examined in vitro as well as in vivo. Using either preparation, investigators have demonstrated both excitatory and inhibitory effects of dynorphin-(1–17) on spontaneous and evoked activity (113–118). These effects are usually antagonized by naloxone, though a few investigators have reported that inhibitory actions are not (114, 116). Some evidence suggests that the excitatory effects may be mediated through μ or δ receptors, while the inhibitory effects are mediated through κ receptors (118, 119).

The effects of dynorphins on other CNS areas have not been as extensively studied. MacMillan & Clarke (120) found that dynorphin inhibited spontaneous activity in hypothalamic arcuate neurons in vitro, though less so than other opioids tested. Sutor & Zieglgansberger (121) found both depolarizing and hyperpolarizing effects, and increases and decreases in EPSPs, in neocortical neurons in vitro. Lavin & Garcia-Munoz (122) found that when

dynorphin was injected into the substantia nigra in vivo, it produced long-lasting inhibition of firing rates.

Werz & MacDonald (123, 124) reported that dynorphin and other opioid peptides decreased the calcium-dependent action potential duration of dorsal root ganglion cells grown in culture. The effect was blocked by naloxone. Dynorphin appeared to act on receptors different from those of other opioids, for its effects were not blocked by K^+ channel blockers, and dynorphin had effects on some neurons that were not affected by other opioids.

Effects on Peripheral Tissue Contractility

Dynorphin's opioid activity was first demonstrated by its ability to inhibit electrically induced contractions in peripheral tissues such as the mouse vas deferens and guinea pig ileum (16). Subsequent studies demonstrated that it interacted selectively with κ-type opioid receptors in these tissues (9, 125–127) and also in the rabbit vas deferens (128). One of these groups reported that dynorphin blocked neurotensin-induced contractile activity in the guinea pig ileum (129) and concluded that dynorphin receptors can modulate cholinergic activity.

The guinea pig ileum contains dynorphin, but its role in vivo is not known. However, Schulz et al (130) recently reported that administration of opioid agonist or antagonist to guinea pigs resulted in a dose- and time-dependent increase in dynorphin levels in the ileum. An increase in high molecular weight precursors of dynorphin was also observed, suggesting that the effect was to increase synthesis of dynorphin.

MOLECULAR BASIS OF DYNORPHIN'S ACTION

Dynorphin Interaction with Specific Opioid Receptor Types in Vitro

Opioid receptors are now recognized to belong to several distinct classes; at least three different types—μ (morphine); δ (enkephalin); and κ (ethylketocyclazocine)—are present in mammalian brain. As discussed earlier, dynorphin-(1–17) and -(1–13) act as κ agonists in the guinea pig ileum and possibly in the spinal cord. However, their action in the brain is more complex; unlike κ agonists, they are not analgesic but do have modulatory actions on the analgesia induced by other opioids.

Consistent with this in vivo profile, in vitro binding studies using brain tissue have demonstrated that dynorphin interacts with κ receptors but also with μ and δ receptors (9–11, 131). The δ activity is particularly prominent in the shorter dynorphins, such as (1–8), but is also found in (1–13) and (1–17).

Despite this relative nonselectivity, James & Goldstein (11) have argued that dynorphin's affinity is highest for κ receptors and that therefore the latter

are probably most relevant to its physiological interactions. The protection experiments on which they base this conclusion are open to question, however, as the concentrations of selective ligands used to protect specific sites should in fact have been sufficiently high to protect all sites completely. Furthermore, of course, even if the estimated affinities of dynorphin for μ, δ, and κ receptors that they have calculated are correct, they do not necessarily indicate that dynorphin in vivo interacts primarily with κ receptors. The action of any endogenous ligand depends not only on its affinity for particular receptors but on the availability of those receptors. In rat brain, κ receptors are greatly outnumbered by μ and δ receptors (132).

In addition to the three major opioid receptor types known to be present in brain the possibility exists that dynorphin may also interact with another, as yet unidentified, site. This idea is supported by evidence that many of dynorphin's actions, including modulation of analgesia (13), intrathecal analgesia (38), motor effects (17, 18, 43–45), and inhibition of neuronal firing (114, 116) may not be mediated through μ, δ, or κ opioid receptors. Furthermore, we have found that ^{3}H-dynorphin binding to brain membranes is not completely displaced by any unlabelled ligand except dynorphin, even at micromolar concentrations (A. P. Smith, unpublished data).

The basis of dynorphin's unusual ability to bind with high affinity to multiple opioid receptors is not known, but it may involve interaction with lipids. Much evidence indicates that lipids play a role in opioid binding to receptors (133–135), and recently it has been shown that acidic lipids such as cerebroside sulfate can induce the formation of α helix in opioid peptides such as β-endorphin as well as dynorphin-(1–17) and (1–13) in solution (136, 137). The dynorphin-lipid complexes are especially stable, and this may be due to the presence of several basic (lysine) residues in the C-terminal portion of the peptide.

Further support for this notion has been provided by Schwyzer (138, 139). On the basis of structure-activity relationships of a series of dynorphin fragments, as well as studies of dynorphin-(1–13) interaction with lipid bilayers, he has proposed that dynorphin receptors possess, in addition to a "message" site (presumably protein-bound) interacting with the N-terminus, an "address" site consisting of both membrane surface charges and the hydrophobic interior of the lipid bilayer. According to Schwyzer's model, dynorphin's basic terminus makes it uniquely able to interact with κ sites, while still retaining the μ and δ affinity found in other opioid peptides.

Possible Second Messenger Systems

Very little is known about the possible second messengers with which dynorphin receptors may interact. Its effects on neuronal activity, discussed above, suggest that dynorphin receptors may be coupled to ion channels. In support

of this, Cherubini & North reported that dynorphin inhibits transmitter release in the guinea pig ileum by depressing calcium conductance (140). They were able to distinguish this mechanism from that activated by μ and δ opioids, which increased potassium conductance (141).

Except for one report that dynorphin inhibits Ca^{++}-ATPase in rat erythrocyte membranes (142), this opioid has not been directly linked with other second messenger systems. However, in view of its high affinity for μ and δ opioid receptors, one would presume that it could inhibit adenylate cyclase, an effect observed with δ opioids in neuroblastoma-glioma hybrid cells (143) and the mammalian striate (144), and μ opioids in a pituitary tumor cell line (145). Furthermore, radiation inactivation experiments suggest that GTP-binding proteins, which mediate inhibition of adenylate cyclase, may be associated with all three major opioid receptor types (146).

GTP-binding proteins have been implicated not only in adenylate cyclase inhibition (147) and in calcium and potassium ion channels (148, 149), but in polyphosphoinositide (PI) turnover (150, 151), suggesting still another possible second messenger for opioid action. Since the PI system is thought to be involved in intracellular calcium mobilization (152), dynorphin effects on calcium levels might reflect action through this system. However, there is little direct evidence of opioid effects on PI turnover, though some preliminary work is consistent with this conclusion (153).

SUMMARY AND CONCLUSIONS

Like other opioids, the dynorphins play a role in a wide variety of physiological parameters, including pain regulation, motor activity, cardiovascular regulation, respiration, temperature regulation, feeding behavior, hormone balance, and the response to shock or stress. The dynorphins are unusual if not unique, however, in that they frequently modulate the activity of other opioids, rather than having direct effects themselves. Thus, they are not analgesic in brain, yet they antagonize opioid analgesia in naive animals and potentiate it in tolerant animals. They have little or no effect by themselves on temperature regulation or respiration, but they enhance the acute effects of morphine on these parameters. Their beneficial effects on stroke are like those of opioid antagonists rather than like agonists.

Consistent with such a wide variety of physiological effects, the dynorphins bind to all three of the major opioid receptor types in brain, μ, δ, and κ, though they exhibit some preference toward κ sites. They also seem to interact with other physiologically relevant sites; though on the basis of their sensitivity to des-Tyr fragments of dynorphin and/or their insensitivity to naloxone, these sites have been termed "non-opioid". No second messenger systems have been directly associated with dynorphin binding, but several likely candidates exist.

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