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Antinociceptive Properties of Fadolmidine (MPV-2426), a Novel α_2-Adrenoceptor Agonist

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ABSTRACT

Fadolmidine (MPV-2426) is a novel α_2-adrenoceptor (α_2-AR) agonist developed for spinal analgesia. It is highly selective for α_2-ARs, but it lacks subtype selectivity. Due to its pharmacokinetic properties, it only poorly penetrates blood-brain barrier or spreads from the site of injection within the central nervous system. By intrathecal (i.t.) administration to laboratory animals, fadolmidine produces dose-dependent antinociception in healthy controls and in models of inflammatory, postoperative and neuropathic pain. Fadolmidine has been effective against various submodalities of pain such as heat pain, mechanical pain, and visceral pain. In general, the antinociceptive potency of fadolmidine, i.t., was equal to that of dexmedetomidine. At antinociceptive i.t. doses fadolmidine did not suppress motoneurons or responses to innocuous stimulation. It produced no hemodynamic depression and considerably less sedation than dexmedetomidine. By peripheral administration fadolmidine had no or only a weak antinociceptive action, except following nerve injury, particularly that of the postganglionic sympathetic nerve fibers. Together these experimental animal studies indicate that i.t. administration of fadolmidine provides a segmentally restricted treatment of somatic and visceral pain, with only minor cardiovascular and sedative side effects. Additionally, peripheral administration of fadolmidine might provide a selective treatment for some hypersensitivity states that involve dysfunction of the sympathetic nervous system.

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ROLE OF α_2-ADRENOCEPTORS IN ANTINOCICEPTION

It is well established that α_2-adrenoceptor (α_2-AR) agonists have antinociceptive properties (10,21,36). Studies in subtype selective α_2-AR knockout animals have shown that the α_{2A}-AR is of critical importance for antinociception induced by synthetic α_2-AR agonists (7,11,12,15,16,29) and for feedback inhibition of pain induced by norepinephrine, the endogenous ligand for α_2-ARs (16). Additionally, there is evidence indicating that the α_{2C}-AR may contribute to pain regulation (6).

α_2-ARs are located at various levels of pain pathways from the periphery to the brain. Under physiological conditions, activation of peripheral α_2-ARs does not produce any significant changes in pain-related responses. Under pathophysiological conditions, however, activation of peripheral α_2-ARs produced conflicting results that varied from aggravation of pain to antinociception (27,32). The pain modulatory action of α_2-ARs has been most extensively studied in the spinal cord. There is strong evidence indicating that activation of α_2-ARs suppresses ascending nociceptive signals at the spinal cord level and that a significant part of antinociception induced by systemically administered α_2-AR agonists may be explained by an action at the spinal cord level (21,36). α_2-ARs in the spinal cord are located on central terminals of primary afferent nociceptive nerve fibers as well as on neurons of the spinal dorsal horn. On the central terminals of primary afferent nociceptive nerve fibers, the predominant α_2-AR subtype is α_{2A} (29). Based on their location, the α_{2A}-ARs may presynaptically inhibit the nociceptive signals arriving through the superficial laminae of the spinal dorsal horn. This concept is supported by neurochemical (14) and electrophysiological evidence (8,20). Subtype α_{2C} of the α_2-AR is found on axonal endings of excitatory spinal dorsal horn interneurons (17). The spinal interneurons with axon terminals containing the α_{2C}-AR innervate nociceptive spinal dorsal horn neurons with verified ascending projections to the medulla (17). This anatomical finding suggests that the α_{2C}-ARs on the axonal endings of excitatory spinal interneurons might contribute to pain modulation by inhibiting release of excitatory amino acids that activate pain-relay neurons, although this hypothesis still lacks experimental evidence. Additionally, descending noradrenergic pathways have direct synaptic contacts with cell bodies of the spinothalamic tract neurons in the spinal dorsal horn (33). The direct noradrenergic innervation of cell bodies of spinothalamic tract neurons provides an anatomical basis for α_2-adrenergic postsynaptic inhibition of pain-relay neurons at the spinal cord level.

The role of supraspinal α_2-ARs in pain regulation is still partly controversial, since both pro- and antinociceptive effects have been described following microinjections of α_2-AR agonists into various brain sites (21,26). The variability in results between laboratories can possibly be explained by genetic differences in the noradrenergic innervation in different strains of animals (2). Another potential source of confounding results is the low selectivity of some previously used α_2-adrenergic compounds. Thirdly, activation of α_2-ARs in the locus coeruleus nucleus produces sedation that may significantly influence behavioral assessment of pain (4). However, since sedation, but not the spinal antinociception induced by a systemically administered α_2-AR agonist was reversed following microinjection of an α_2-AR antagonist in the locus coeruleus, sedation does not explain the spinal antinociceptive effects of α_2-adrenergic compounds (24). The preservation of the spinal antinociceptive effect induced by a systemically administered α_2-AR agonist following spinal transection also indicates that supraspinal mechanisms are not critical for the spinal

antinociceptive action of α_2-adrenergic compounds (25,28). It should be noted that although supraspinal α_2-ARs are not critical for the spinal antinociception, supraspinally located α_2-ARs may have an important role in regulating supraspinally mediated components of pain responses, such as the emotional component of pain (21). Since the supraspinal α_2-ARs have only a limited role in antinociception, but are involved in the mediation of most side effects, selective activation of spinal α_2-ARs might provide a clinically useful method for the treatment of pain in some pathophysiological conditions.

GENERAL PHARMACOLOGICAL CHARACTERISTICS OF FADOLMIDINE

Fadolmidine (MPV-2426) is a novel α_2-adrenoceptor (α_2-AR) agonist developed for spinal analgesia at Orion Pharma, Finland (13). Its chemical name is 3-(1H-imidazol-4-yl-methyl)-indan-5-ol hydrochloride. The binding affinity ([^{3}H]rauwolscine displacement) of fadolmidine for α_2-ARs has been determined in membranes of Shionogi S115 cells that have been transfected with α_{2A}-, α_{2B}-, or α_{2C}-ARs. In this test model fadolmidine had high affinity (K_i values of 1.0, 1.7, 2.1 nM for α_{2A}-, α_{2B}-, and α_{2C}-ARs, respectively) and full agonist efficacy at all three subtypes of α_2-ARs (13). In rat vas deferens, fadolmidine inhibited electrically-evoked isometric contractions dose-dependently resulting in a pD_2-value of 8.2 and intrinsic activity of 0.75 (13). These results indicate that fadolmidine is a highly efficient α_2-AR agonist, but lacks subtype selectivity.

PHARMACOKINETIC PROPERTIES AS A CAUSE OF SEGMENTALLY RESTRICTED EFFECTS

Fadolmidine only poorly penetrates blood-brain barrier. This is indicated by the finding that bioavailability of fadolmidine in the cerebrospinal fluid is 7% by epidural administration and only 0.17% by intravenous administration (5). Also, unlike some other α_2-AR agonists such as clonidine and dexmedetomidine, fadolmidine, by i.v. or s.c. administration, has only little, if any antinociceptive, hypotensive or sedative effects (5,23,32). This finding is in line with the concept that following peripheral administration fadolmidine poorly penetrates blood brain barrier. Also, if administered directly into the brain or spinal cord, fadolmidine spreads less extensively than either clonidine or dexmedetomine. This concept is supported by the finding that after i.t. administration at the lumbar spinal cord level the antinociceptive effect of fadolmidine, but not that of dexmedetomine, is segmentally restricted to the lower half of the body (19,23). Furthermore, when drugs are administered i.t. at equianalgesic doses to the lumbar spinal cord, supraspinally mediated sedative effect of fadolmidine is considerably weaker than that of clonidine or dexmedetomidine (13,30,34). In line with this, fadolmidine produces significantly less sedation when microinjected one to two mm rostral to the locus coeruleus than in the locus coeruleus itself. No such injection site-dependent difference has been observed with dexmedetomidine (35). When injected unilaterally in the locus coeruleus, the sedative effect by fadolmidine was weaker than that produced by an equimolar dose of dexmedetomidine (35). This difference in the sedative potency can be explained by a more effective spreading of

dexmedetomidine than of fadolmidine and consequent activation of α_2-ARs also in the contralateral locus coeruleus, leading to a stronger sedation than a unilateral activation (31).

ANTINOCICEPTIVE EFFICACY OF FADOLMIDINE UNDER PHYSIOLOGICAL CONDITIONS

Table 1 lists i.t. doses of fadolmidine that were antinociceptive under various experimental conditions. By i.t. administration fadolmidine produced a dose-dependent attenuation of heat-induced tail and limb withdrawal responses in control rats (13,19,34). Depending on the intrathecal dose of fadolmidine, the onset of antinociception was less than five min, the maximum effect was reached within 30 min, and the duration of antinociception was up to two hours (34; Fig. 1). The i.t. ED_{50} of fadolmidine in a tail-flick assay was 0.7 μg/rat (13). It should be noted, however, that as with other analgesic compounds, the antinociceptive efficacy of fadolmidine increases with a decrease in the intensity of the noxious test stimulus (19). Also other experimental procedures, that concurrently activate nociceptive nerve fibers, may attenuate antinociceptive efficacy of fadolmidine, as well as that of other drugs (30). The thermal antinociceptive potency of fadolmidine (at or near the segment of its i.t. administration) was equal to that of dexmedetomidine, whereas fadolmidine-induced antinociception at a distant site was weaker than that induced by dexmedetomidine (19,34). This was obviously due to a more limited spread of fadolmidine. Atipamezole, a selective α_2-AR antagonist, reversed the thermal antinociceptive effect induced by fadolmidine (19,34). At an antinociceptive dose fadolmidine did not influence the non-nociceptive H-reflex indicating that the antinociceptive effect is selective (19).

Fadolmidine, i.t., was effective also against mechanically induced pain in sheep (5) and against colorectal distension-induced response of the presumed pain-relay neurons in the rat spinal dorsal horn (22). In sheep the ED_{50} of fadolmidine, i.t., against mechanically evoked pain was 49 μg/animal, and the time course of antinociceptive action was similar

TABLE 1. The lowest intrathecally administered fadolmidine doses that produced a significant antinociceptive effect in the adult rat

Experimental condition	Noxious test	Fadolmidine dose (μg/rat)	Ref.
Controls	Heat/paw	3	19
	Heat/tail	3	19
Postoperative hyperalgesia	Mechanical/hindpaw	3	18
Neuropathy	Heat/tail	1	23
	Heat/paw	3	23
	Noxious mechanical/paw	1	23
	Innocuous mechanical/paw	10	23
Visceral pain	controls	10	22
	visceral inflammation	3	22

to that against heat-induced pain in control rats (see above). In the rat, fadolmidine and clonidine were equipotent against visceral pain (22; Fig. 2B).

Table 2 lists systemically administered doses of fadolmidine that were effective at varying experimental conditions. In contrast to its effects by i.t. administration, s.c. or i.v. fadolmidine had only very weak, if any, antinociceptive effect in animals (5,23,32). In this

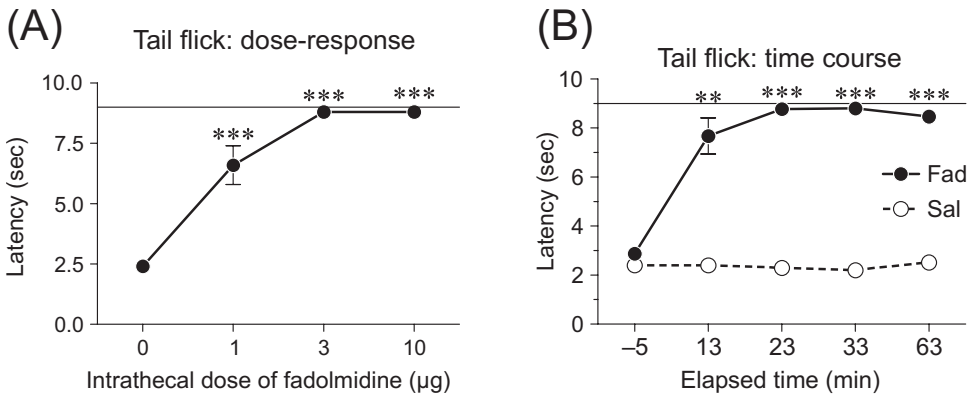

Fig. 1. The dose-response (A) and the time course (B) of the antinociceptive effect induced by i.t. administered fadolmidine (Fad) or saline (Sal) in the tail-flick test in the rat. The error bars represent S.E.M. ($n = 5$, except in the Sal-group of graph B $n = 4$). In B, the i.t. administrations were performed at time point 0, and the i.t. dose of fadolmidine was 10 µg/animal. The cutoff latency of 9 s is indicated by a horizontal line. ** $p < 0.01$, *** $p < 0.005$ (Tukey's test; reference the Sal = 0 group in A and the corresponding pre-injection value in B). Adapted from ref. 23.

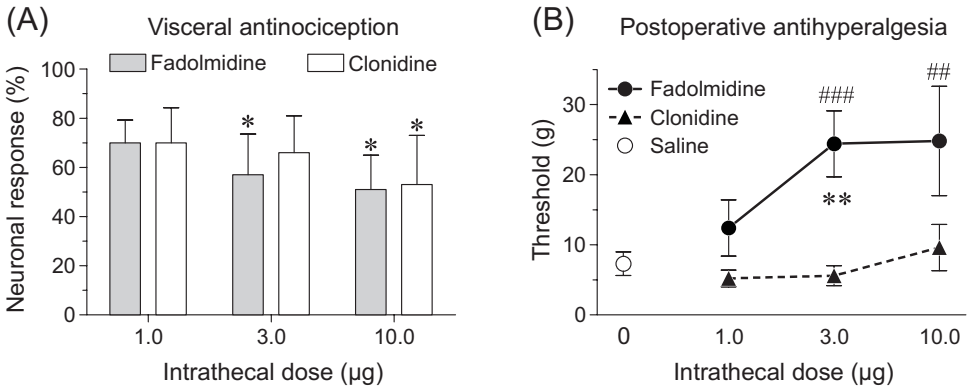

Fig. 2. Comparison of the antinociceptive effects induced by i.t. administered fadolmidine and clonidine. A) Colorectal distension-induced responses in nociceptive spinal dorsal horn neurons of the rat were equally attenuated by i.t. administration of fadolmidine and clonidine. This finding indicates that fadolmidine and clonidine have an equipotent visceral antinociceptive effect. B) I.t. administration of fadolmidine had a stronger mechanical antihyperalgesic effect in a rat model of postoperative hyperalgesia than i.t. administration of clonidine. In both graphs, the error bars represent S.E.M. ($n = 4$–6 in A, and $n = 5$–14 in B). $^{*/\#}p < 0.05$, $^{**/\#\#}p < 0.01$, $^{***/\#\#\#}p < 0.005$ (Tukey's test; in A the reference is the corresponding pre-drug response, in B the reference is the Saline group (*) or the corresponding pre-fadolmidine group (#)). In A, 100% represents the corresponding pre-drug response. Graph A is adapted from ref. 22 and graph B from ref. 18.

respect fadolmidine differs from dexmedetomidine or clonidine, since these drugs had significant antinociceptive effects also by systemic administration (23,32).

ANTINOCICEPTIVE EFFECT OF FADOLMIDINE IN MODELS OF INFLAMMATION

The effect of i.t. fadolmidine has been studied in a rat model of somatic inflammation induced by intraplantar injection of carrageenan (34). A strong hypersensitivity to mechanical and heat stimulation of the carrageenan-treated paw develops within a couple of hours mimicking inflammatory hyperalgesia in clinical patients. Fadolmidine, i.t., induced a dose-dependent attenuation of inflammatory hyperalgesia and this antihyperalgesic effect was equipotent with that induced by dexmedetomidine. The maximal effect of fadolmidine against thermal hyperalgesia developed earlier than the maximal effect against mechanical hypersensitivity (15 vs. 30–45 min, respectively; 34).

The efficacy of intrathecally administered fadolmidine has been studied also against visceral inflammation in the rat (22). In animals with experimentally induced inflammation of the colon, colorectal distension evoked stronger responses in nociceptive spinal dorsal horn neurons indicating development of visceral hyperalgesia. The visceral pain response was attenuated by fadolmidine, i.t. This effect was of the same percentile magnitude in animals subjected to visceral inflammation as in controls (22). Since inflamed animals had a higher baseline response, the visceral antinociceptive effect (when counted as a decrease in the number of nerve impulses) was actually stronger in animals subjected to visceral inflammation.

EFFICACY OF FADOLMIDINE IN A MODEL OF POSTOPERATIVE PAIN

The antinociceptive effect of fadolmidine against postoperative pain was studied in a rat model of postoperative hyperalgesia induced by a skin incision (1). On the first two

TABLE 2. The lowest doses of systemically administered fadolmidine that produced a significant antinociceptive effect in rats

Experimental condition	Noxious Test	Fadolmidine dose (μg/rat)	Refs.
Controls	Heat/tail	>300	23, 32
	Noxious mechanical/paw	>300*	23, 32
Neuropathy	Heat/tail	300	32
	Noxious mechanical/paw	>300	32
	Innocuous mechanical/paw	300	32
Sympathectomy	Heat/tail	30	32
	Noxious mechanical/paw	100	32

* >300 μg/kg indicates that this dose was the highest dose used and it was not sufficient to produce a significant effect.

postoperative days animals have a marked hypersensitivity to mechanical stimulation of the skin adjacent to a wound. This mechanical hyperalgesia was dose-dependently attenuated by fadolmidine, i.t. The antihyperalgesic effect induced by fadolmidine was of equal magnitude as that induced by dexmedetomidine, and considerably stronger than that induced by clonidine (18; Fig. 2A). The onset of significant mechanical antihyperalgesia induced by fadolmidine, i.t., was longer (>15 min; 18) than the onset of fadolmidine-induced thermal antinociception in control animals (<15 min; 19,34) or the onset of dexmedetomidine-induced mechanical hyperalgesia (18). Fadolmidine-induced mechanical antihyperalgesia was completely reversed by yohimbine, an α_2-AR antagonist with a non-imidazoline structure, indicating that fadolmidine-induced effects are not due to action on imidazoline receptors but due to action on α_2-ARs (18). By peripheral administration fadolmidine did not attenuate postoperative hyperalgesia at the site of skin incision (18). Thus, the attenuation of postoperative hyperalgesia is due rather to spinal than a peripheral action of fadolmidine.

EFFICACY OF FADOLMIDINE IN AN EXPERIMENTAL MODEL OF NEUROPATHIC HYPERSENSITIVITY

In humans, nerve injury may induce chronic (neuropathic) pain and hypersensitivity. Unilateral ligation of two spinal nerves in the rat provides a highly reproducible and stable experimental animal model for studying nerve injury-induced hypersensitivity (9). Hypersensitivity to mechanical and thermal stimulation of the hindlimb, ipsilaterally to the nerve ligation, develops within a few days, and reaches the maximum in 10–14 days, while hypersensitivity may last for months. Fadolmidine, i.t., has been shown to be effective in alleviating thermal and mechanical hypersensitivity in rats with a spinal nerve ligation-induced neuropathy (23,34). This antihyperalgesic effect of fadolmidine was equal to that of dexmedetomidine. The ascending nociceptive signals to the rostroventromedial medulla of neuropathic and control rats were also attenuated by i.t. fadolmidine indicating that the attenuation of behavioral pain responses in neuropathic animals was due to attenuation of ascending sensory (pain) signals (23).

By systemic administration fadolmidine at doses up to 300 μg/kg had a weak antinociceptive effect in neuropathic animals and was ineffective in healthy controls (23,32). Spontaneous activity in the dorsal root proximal to the spinal nerve injury was not influenced by systemic administration of fadolmidine (32). The antinociceptive efficacy of peripherally administered fadolmidine was increased by sympathectomy (32; Fig. 3). This finding suggests that the increase in peripheral antinociceptive action of fadolmidine in spinal nerve injured animals may, at least partly, depend on a concomitant injury of the sympathetic nerves. These findings suggest that fadolmidine might provide a selective peripheral treatment for those hypersensitivity conditions that involve dysfunction of the sympathetic nervous system and are sensitive to peripheral suppressant effects of α_2-AR agonists (3).

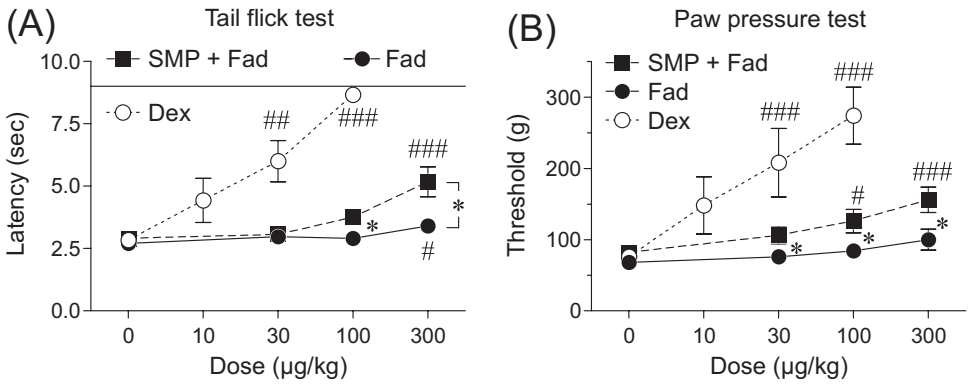

Fig. 3. Comparison of the antinociceptive effects of fadolmidine (Fad) and dexmedetomidine (Dex) following s.c. administration in rats with a spinal nerve ligation-induced neuropathy. A) Assessment of thermal pain sensitivity in the tail. B) Assessment of mechanical hyperalgesia in the neuropathic hindlimb. In both tests, dexmedetomidine produced a considerably stronger antinociceptive effect than fadolmidine. This difference may be explained by a more efficient penetration of blood brain barrier by dexmedetomidine. Fadolmidine had very little, if any, effect in neuropathic animals, unless the animals were chemically sympathectomized (SMP) with 6-hydroxydopamine. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.005$ (Tukey's test; reference: the corresponding pre-drug value). $^{*}p < 0.05$ (Student's *t*-test; difference between the corresponding values in the two fadolmidine-treated groups). Cutoff latency of 9 s indicated by a horizontal line in graph A. The error bars represent S.E.M. ($n = 7$–8). Adapted from ref. 32.

SEDATIVE AND CARDIOVASCULAR SIDE EFFECTS OF FADOLMIDINE

Sedation induced by α_2-AR agonists is mainly due to their action at α_2-ARs of the locus coeruleus in the pontomesencephalic junction (4). Since fadolmidine only poorly penetrates blood-brain-barrier and only slowly spreads within the central nervous system, peripherally administered fadolmidine induced very little, if any, sedation in the rat (32). By intrathecal administration to the rat fadolmidine induced considerably less sedation than dexmedetomidine (13,30,34). This result may be explained by differences in the spread of the drug from the site of administration at the lumbar level to the locus coeruleus in the brainstem. In sheep, by i.t. administration fadolmidine at antinociceptive doses produced no changes in systemic or central arterial blood pressures, or in heart rate (5). These findings indicate that sedative and cardiovascular side effects of fadolmidine are weaker than those of dexmedetomidine or clonidine, and that fadolmidine may provide selective spinal analgesia with little, if any, side effects.

CONCLUSIONS

Due to its pharmacokinetic properties fadolmidine, i.t., provides a more targeted and at least as potent treatment of segmentally restricted pain and hyperalgesia than some older α_2-AR agonists such as dexmedetomidine or clonidine (Table 3). Moreover, by i.t. administration fadolmidine produces considerably less cardiovascular and sedative side effects than either clonidine or dexmedetomidine. Additionally, by peripheral administration

TABLE 3. The main properties of fadolmidine as an analgesic

- Developed for intrathecal treatment of pain
- Highly selective for α_2-ARs but no subtype selectivity
- Segmentally restricted antinociception following i.t. administration
- Minor sedative and cardiovascular side effects following i.t. administration
- Antinociceptive potency at least equal to that of dexmedetomidine and clonidine
- Antinociception in inflammatory and neuropathic conditions at least as strong as in controls
- A selective peripheral treatment for pain that is suppressed by peripheral α_2-ARs

fadolmidine may provide a selective treatment for those pain conditions that are suppressed by peripheral α_2-ARs.

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