

Antidepressants as analgesics: an overview of central and peripheral mechanisms of action

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Antidepressants, given systemically, are widely used for the treatment of various chronic and neuropathic pain conditions in humans. In animal studies, antidepressants exhibit analgesic properties in nociceptive, inflammatory and neuropathic test systems, with outcomes depending on the specific agent, the particular test, the route of administration and the treatment method used. Although early studies focused on central (i.e., supraspinal, spinal) actions, more recent studies have demonstrated a local peripheral analgesic effect of antidepressants. These peripheral actions raise the possibility that topical formulations of antidepressants may be a useful alternative drug delivery system for analgesia. Antidepressants exhibit a number of pharmacological actions: they block reuptake of noradrenaline and 5-hydroxytryptamine, have direct and indirect actions on opioid receptors, inhibit histamine, cholinergic, 5-hydroxytryptamine and *N*-methyl-D-aspartate receptors, inhibit ion channel activity, and block adenosine uptake. The involvement of these mechanisms in both central and peripheral analgesia produced by antidepressants is considered. Data illustrating the preclinical peripheral analgesic actions of antidepressants are presented, as are some aspects of the mechanisms by which these actions occur.

Administrés de façon systémique, les antidépresseurs sont fréquemment utilisés pour le traitement de diverses douleurs chroniques et neuropathiques chez les êtres humains. Au cours d'études sur les animaux, les antidépresseurs montrent des caractéristiques analgésiques dans les systèmes de tests nociceptifs, inflammatoires et neuropathiques : les résultats dépendent de l'agent en cause, de l'épreuve, de la voie d'administration et de la méthode de traitement. Même si les premières études portaient avant tout sur des effets centraux (c.-à-d. susrachidien, rachidien), des études plus récentes ont démontré un effet analgésique périphérique local des antidépresseurs. Ces effets périphériques évoquent la possibilité que des formulations topiques d'antidépresseurs constituent un système de remplacement utile pour l'administration d'analgésiques. Les antidépresseurs ont certains effets pharmacologiques : ils bloquent le recaptage de la noradrénaline et de la 5-hydroxytryptamine; ils ont des effets directs et indirects sur les récepteurs des opioïdes; ils inhibent les récepteurs des histamines, des agents cholinergiques, de la 5-hydroxytryptamine et du *N*-méthyl-D-aspartate; ils inhibent l'activité des canaux ioniques et bloquent le captage de l'adénosine. On étudie ces mécanismes dans l'analgésie centrale et périphérique produite par les antidépresseurs. On présente des données illustrant les effets analgésiques périphériques précliniques des antidépresseurs, tout comme certains aspects des mécanismes qui produisent ces effets.

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Analgesic properties of antidepressants

In animal studies, antidepressants have been administered primarily by systemic routes (i.e., intraperitoneal, subcutaneous, intravenous, oral) to mimic oral intake in humans. Intrinsic activity obtained with such approaches has been variable, with outcomes depending on the specific agent used, the particular test, dose, route of administration and dosing schedule (acute v. chronic) (see Eschalier et al.¹ for review). More recent studies using inflammatory and nerve injury models of persistent pain, which are of greater relevance to human chronic pain conditions, have demonstrated consistent analgesic activity with antidepressants.²⁻⁹ With the focus of antidepressant actions as psychotropic agents being in the brain, a number of studies have administered antidepressants into the cerebral ventricles and have observed central analgesic actions directly.¹⁰⁻¹² Antidepressants have also been administered spinally¹³⁻¹⁵ to produce analgesia. In general, the efficacy observed following supraspinal administration is greater than that following spinal injections, with the latter being limited by motor effects when doses are increased.

An additional peripheral site of action for antidepressants received some consideration, but no evidence for such an action was observed using the carrageenan inflammation model.¹⁶ More recently, the peripheral application of antidepressants produced analgesia in the formalin test,^{17,18} a model of persistent pain that involves elements of both inflammation and central sensitization.¹⁹ Thus, the coadministration of a number of antidepressants with formalin produces a marked suppression of phase 2 flinching (Fig. 1A), as well as biting-licking behaviours (Fig. 1B). Phase 1 flinching behaviours also are suppressed by antidepressants.¹⁷ Such actions are clearly mediated by a local mechanism because an injection of effective doses into the contralateral paw is without effect (Fig. 1). Local antinociceptive actions are also observed in the spinal nerve ligation model⁹ (Fig. 2), a model of nerve-injury-induced pain.²⁰ Electrophysiological studies have provided additional evidence for a peripherally mediated action of antidepressants in visceral pain.²¹

The clear expression of a local antinociceptive or analgesic action with antidepressants raises the possibility that this class of agents could be given topically and may be useful as peripherally acting analgesics in humans. There is considerable interest in the development of topical analgesics, in general, for the relief of

both acute and chronic pain; this approach allows for the delivery of effective concentrations of drug at or near the site of origin of the pain and produces fewer side effects because of comparatively lower systemic drug levels. To date, capsaicin, lidocaine and non-steroidal anti-inflammatory drugs are available as topical pain treatments.²²⁻²⁴ However, the success of some of these has been limited, and there is a need for other effective therapies. Antidepressants may potentially represent an alternative class of agents to be developed in this regard. Interestingly, 2 recent randomized placebo-controlled studies indicated that topical doxepin, whose primary indication is for relief of pruritis associated with eczema,²⁵ can relieve symptoms of neuropathic pain.^{26,27} Both studies report significant peripheral analgesic actions with doxepin. The degree of pain relief is not further enhanced by combining it with capsaicin.²⁷

Mechanisms of action

Antidepressants, as a class, include diverse structures and represent several phases of development (e.g., tricyclic, tetracyclic and heterocyclic antidepressants, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors).²⁸ The earliest focus, with regard to mechanism of action, was the ability of antidepressants to inhibit biogenic amine reuptake; interest subsequently developed in altered biogenic amine receptor sensitivity after the chronic alteration of biogenic amine levels in the synapse.²⁹ It has, however, become increasingly apparent that this class of drugs exhibits diverse pharmacological properties, with individual agents within a class exhibiting such effects to variable degrees, and this may account for differing specific pharmacological profiles between agents. Pain is a complex neurobiological phenomenon, with a diversity of neurochemical factors contributing to both peripheral and central pain-signalling mechanisms. Accordingly, a range of antidepressant actions may contribute to the mechanisms by which pain suppression occurs. The contribution of these mechanisms to central and peripheral analgesia will be considered separately.

Central pain mechanisms

NA and 5-HT

Given the importance of central noradrenaline (NA)

and 5-hydroxytryptamine (5-HT) pathways to pain modulatory systems, interactions with these systems were an early focus of attention. Both α -adrenoceptor³⁰⁻³² and 5-HT receptor antagonists³³ inhibit antinociception mediated by antidepressants in various

tests. Similarly, depletion of central NA systems with α -methyl-*p*-tyrosine^{11,34,35} and 5-HT systems with *p*-chlorophenylalanine^{11,34,35} inhibits antinociception by antidepressants. There have been few studies in which microinjections of antagonists or neurotoxins

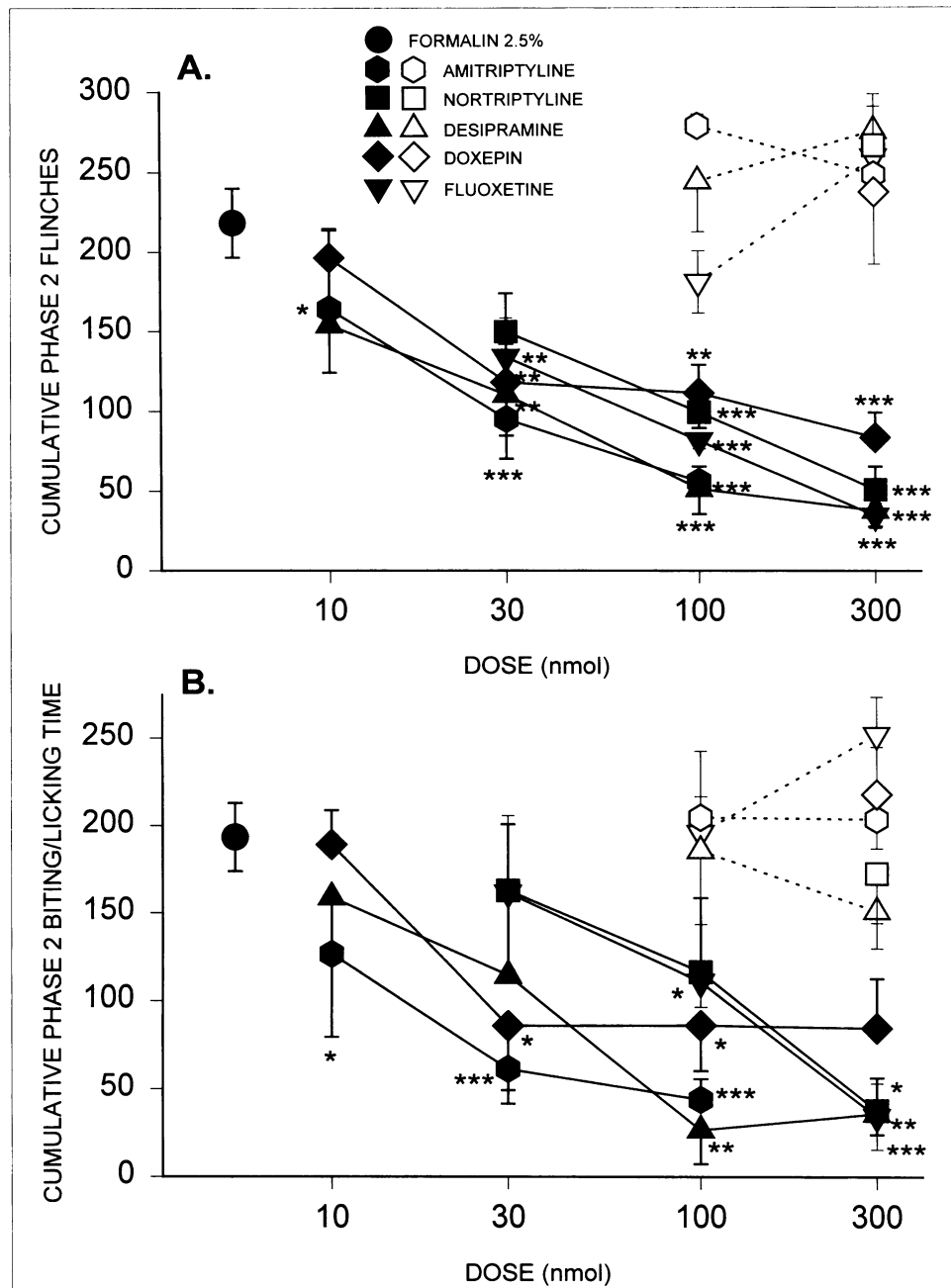


Fig. 1: Coadministration of antidepressants with formalin 2.5% produces a dose-related suppression of phase 2 flinching (A) and biting-licking (B) behaviours (solid symbols). Open symbols represent injection into the contralateral paw to control for potential systemic mediated actions. Data for amitriptyline, desipramine and fluoxetine are from Sawynok et al,^{17,18} with permission; data for nortriptyline and doxepin are previously unpublished. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with formalin group ($n = 6$ for latter 2 drugs).

into specific brain regions have been used to discriminate the involvement of particular central amine projection pathways in antidepressant actions. However, bulbospinal projection pathways, which have been implicated in endogenous pain-suppressing mechanisms for some time,³⁶ have received direct attention. Lesions of the dorsolateral funiculus through which such pathways course have been shown to inhibit analgesia produced by clomipramine.³⁷ Within the spinal cord, activation of both NA and 5-HT receptors produces analgesia,^{38,39} and NA and 5-HT mechanisms interact significantly.⁴⁰ A clearer understanding of the involvement of bulbospinal pathways in antidepressant actions would result from experiments in which antidepressants were administered systemically or to supraspinal sites, while selective amine antagonists or amine-depleting agents were administered to spinal sites.

Opioids

Studies have shown that analgesia by antidepressants can be inhibited by naloxone, an opioid receptor antagonist^{5,32,33,41,42} and enhanced by enkephalinase inhibitors.⁴² Antidepressants can displace opioids from binding sites in acute radioligand binding assays,⁴³ whereas chronic antidepressant administration can modify opioid receptor densities⁴⁴ and increase endogenous opioid levels in certain brain regions.^{45,46} It appears that antidepressants may interact both directly and indirectly with endogenous opioid systems to produce analgesia.

Other receptor systems

Antidepressants interact with α -adrenoceptors, as well as histaminic, cholinergic muscarinic, cholinergic nicotinic and 5-HT receptors^{47,48} in an inhibitory manner,

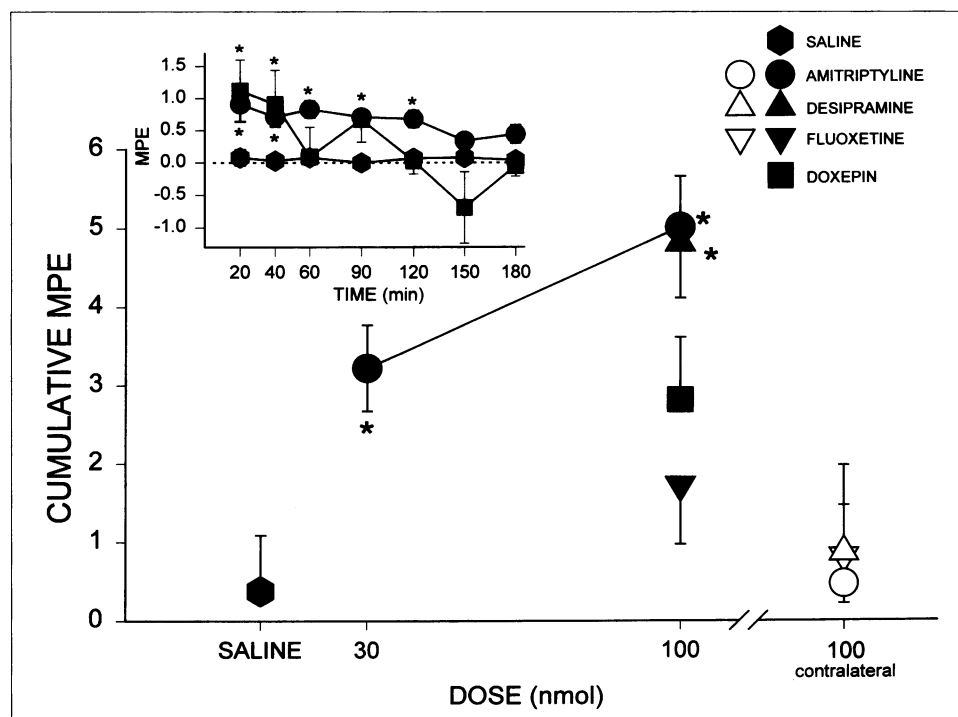


Fig. 2: Anti-hyperalgesic effect of antidepressants injected into the rat hindpaw ipsilateral to ligation of the L5 and L6 dorsal nerves (solid symbols). Data for the inset time course are expressed as a maximum possible effect (MPE) for reversal of thermal hyperalgesia by amitriptyline and doxepin (100 nmol), or in the body of the figure, as a cumulative score to the end of the time course or return to baseline. Note that an MPE of 1.0 in the inset signifies a complete reversal of thermal hyperalgesia. Open symbols represent injection into the contralateral paw to control for systemically mediated actions. Data for amitriptyline, desipramine and fluoxetine are from Esser and Sawynok⁷ and Sawynok et al,¹⁸ with permission; data for doxepin are previously unpublished. * $p < 0.05$, ** $p < 0.01$, * $p < 0.001$ compared with saline group ($n = 9$ for doxepin group).**

and some of these actions contribute to side effects. Thus, with amitriptyline for example, antihistaminic effects can produce sedation, antimuscarinic effects can produce dry mouth and constipation and anti-adrenergic effects can contribute to orthostatic hypotension.⁴⁹ Many of these systems can also modulate pain mechanisms by central actions. However, for cholinergic systems, agonist actions for both muscarinic and nicotinic systems produce antinociceptive actions;⁵⁰ because the nature of the antidepressant interaction with these systems is inhibitory, it is unlikely that such actions are involved. Enhanced central activity of 5-HT and NA systems generally produces analgesia, so blockade of these actions by antidepressants is unlikely to contribute substantially to analgesic properties.

Excitatory amino acids

Among other mechanisms, persistent pain involves central sensitization, a process in which excitatory amino acid (EAA) receptors contribute significantly.^{19,51} Antidepressants can bind to the *N*-methyl-D-aspartate (NMDA) receptor complex^{52,53} and reduce intracellular Ca^{2+} accumulations induced by NMDA,⁵⁴ whereas chronic exposure to antidepressants alters NMDA receptor binding.⁵⁵ Although the spinal administration of antidepressants inhibits NMDA-induced spinal hyperalgesia,^{15,56,57} and this has been proposed as a significant mechanism of spinal analgesia, some observations argue against this hypothesis. In the formalin model, spinal administration of EAA receptor antagonists consistently inhibits flinching behaviours.^{58,59} Some inhibition of flinching behaviours by spinal amitriptyline has been reported,⁵⁷ but we (Sawynok and Reid, unpublished data) and others⁶⁰ have observed that both systemically and spinally administered amitriptyline actually enhances flinching behaviours and suppresses biting-licking behaviours. In the spinal nerve ligation model, spinal administration of EAA antagonists suppresses allodynia,⁵⁹ yet spinal amitriptyline has no⁹ or only weak anti-allodynic activity.⁵⁷ There are thus differences in the pharmacological profile of EAA antagonists and antidepressants in these two models of persistent pain. Although an EAA mechanism may contribute to analgesia, it appears not to be the only mechanism involved.

Adenosine

Biochemical studies have reported that antidepressants

can inhibit the uptake of adenosine into neuronal preparations.⁶¹ Adenosine, acting at both spinal and supraspinal sites, can produce analgesia,⁶² and appears to be a significant mediator of analgesic properties of antidepressants, as methylxanthine adenosine receptor antagonists inhibit analgesia produced by systemically administered antidepressants in both nociceptive^{63,64} and neuropathic pain models.⁶⁵

Ion channels

Antidepressants can inhibit Na^+ , Ca^{2+} and K^+ channel activity in neuronal preparations at micromolar concentrations.⁶⁶ Given that other inhibitors of Na^+ channels (e.g., anticonvulsant drugs and local anesthetics)^{7,65} and blockers of Ca^{2+} channels^{68,69} exhibit analgesic properties in models of persistent pain, such actions might contribute to antidepressant-mediated analgesia. Inhibitory actions of antidepressants are seen at L-type Ca^{2+} channels,⁷⁰ whereas analgesic properties are exhibited with selective N-type Ca^{2+} channel blockers.⁶⁹ Interactions with ion channels, in general, are difficult to implicate definitively in antidepressant actions because, although mimicry of an action by agents known to produce a particular pharmacological effect is a necessary condition, it does not establish causality. One study does provide more definitive data. Thus, central administration of an antisense oligonucleotide to a particular K^+ channel has been shown to inhibit analgesic actions of amitriptyline and desipramine.⁷¹ The approach of selectively removing specific targets using molecular techniques would be of particular value in more definitively implicating ion channels in the actions of antidepressants.

Peripheral pain mechanisms

Because the peripheral action of antidepressants has only recently been recognized, there are less data exploring the potential contribution of the various actions of antidepressants to peripheral activity. However, certain mechanisms can be implicated or discounted.

NA and 5-HT

The block of NA and 5-HT reuptake by antidepressants would enhance amine availability at peripheral nerve terminals. Both NA and 5-HT have pain-facilitating actions mediated by α_1 - or α_2 -adrenoceptors^{72,73} and

5-HT₁, 5-HT₂, 5-HT₃, and 5-HT₄ receptors^{74,75} on peripheral sensory nerve terminals. The inhibition of reuptake of these amines is therefore unlikely to account for peripheral analgesia produced by antidepressants. Although a block of 5-HT receptors and α -adrenoceptors¹⁷ may potentially account for analgesia, when established receptor antagonists were evaluated in the formalin test, phentolamine (nonspecific α_1 - and α_2 -adrenoceptor antagonist), propranolol, ketanserin, tropisetron and GR 113808A (antagonists at 5-HT₁, 5-HT₂, 5-HT₃ and 5-HT₄ receptors, respectively) produced inhibitory responses that were less potent than those produced by amitriptyline (Fig. 3). Even if such agents had exhibited a greater potency in this respect, it would still be difficult to definitively implicate these mechanisms in antidepressant actions because, again, it is a necessary but not a sufficient condition. Such evidence would require, for example, an evaluation of antidepressant actions in knockout animals in which the gene for a particular receptor has been deleted or the use of antisense oligonucleotides which target production of particular receptors.

Opioids

Peripheral opioid receptors and their pain-suppressing actions are particularly prominent in inflammation.⁷⁶ This raises the possibility that the opioid-mimicking or

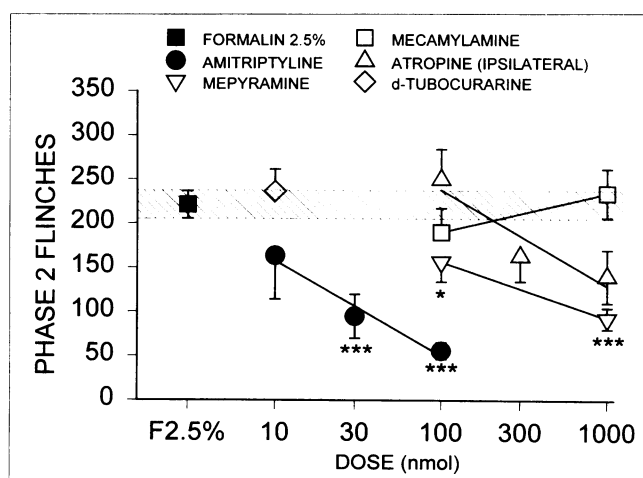


Fig. 3: Effects of coadministration of noradrenaline and serotonin receptor antagonists with formalin 2.5% on flinching behaviours produced by formalin. Data for amitriptyline and phentolamine are from Sawynok et al¹⁷ and for 5-HT antagonists, from Doak and Sawynok,⁷⁵ with permission. * $p < 0.05$, ** $p < 0.01$, * $p < 0.001$ compared with formalin controls.**

enhancing properties of antidepressants noted earlier may be involved in peripheral analgesia. In an electrophysiological study of visceral afferents, antidepressant activity that was clearly peripherally expressed was blocked by naloxone, implicating opioid mechanisms in the peripheral action.²¹ However, when amitriptyline was administered locally to the rat hind-paw, no block with naloxone was obtained.¹⁷

Other receptors

Given that both histamine and acetylcholine can facilitate peripheral pain signalling,⁷⁷ the ability of antidepressants to block such actions might contribute to peripheral analgesia. To consider this possibility, established receptor antagonists for these systems were evaluated. However, mepyramine (histamine H₁ receptor antagonist), atropine (muscarinic receptor antagonist) and mecamlamine (neuronal nicotinic receptor antagonist) were less active than amitriptyline or inactive against flinching behaviours (Fig. 4). *d*-Tubocurarine (muscle nicotinic receptor antagonist) was lethal at doses beyond that depicted in Fig. 4. These results make it unlikely that these mechanisms are essential to peripheral analgesia, although again, definitive evidence would require the use of molecular techniques to specifically inactivate a particular receptor target.

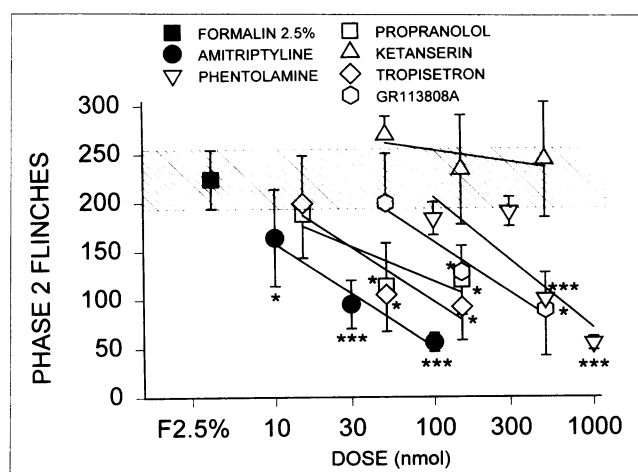


Fig. 4: Effects of coadministration of histamine and cholinergic receptor antagonists with formalin 2.5% on flinching behaviours produced by formalin. Data for mepyramine are from Sawynok et al,¹⁷ with permission; data for cholinergic receptor antagonists are previously unpublished. * $p < 0.05$, ** $p < 0.01$, * $p < 0.001$ compared with formalin controls ($n = 6$ per group for cholinergic receptor antagonists).**

EAA antagonists

Recently, it was reported that the peripheral administration of a number of EAA receptor antagonists produces peripheral analgesia in the formalin test.^{78,79} However, such a mechanism may not account entirely for the peripheral antidepressant actions as the activity with EAA antagonists was restricted to biting-licking behaviours, with no effect observed on flinching behaviours,^{78,79} while antidepressants clearly reduce both behaviours^{17,18} (Figs. 1A and 1B).

Adenosine

The ability of methylxanthines to block antinociception mediated by systemically administered antidepressants led us to determine whether caffeine could alter peripheral analgesia by antidepressants. Coadministration of caffeine with amitriptyline reduces the action of amitriptyline in both the formalin¹⁸ and spinal nerve ligation tests,⁶⁵ but does not alter the activity of desipramine in either test.¹⁸ Adenosine thus contributes to analgesia produced by some, but not all, antidepressants. Peripherally, adenosine produces analgesia through the activation of adenosine A₁ receptors on the sensory nerve terminal.⁶² Adenosine A₁ receptors appear to be involved in the action of amitriptyline, as a selective adenosine A₁ receptor antagonist reduces the antinociceptive action of amitriptyline.¹⁷

Ion channels

The peripheral application of Na⁺ channel blockers, such as local anesthetics⁸⁰ and anticonvulsant drugs,⁸¹ produces a locally mediated analgesia in persistent pain models and raises the possibility that such actions might contribute to antidepressant-mediated analgesia. However, given that there is no change in normal paw reactions after the local administration of amitriptyline, a local anesthetic action may not be primarily involved in the analgesia.⁹ However, following sensitization or nerve injury, a change in Na⁺ channel function or expression in sensory neurons⁸² may allow for this action to be expressed.

Conclusions

Antidepressants are complex drugs that exert multiple

pharmacological actions. This multiplicity of actions contributes to their efficacy in relieving depression at central sites, in producing analgesia at supraspinal, spinal and peripheral sites, as well as to side effects at multiple sites. Within a class, different specific agents exert these actions to differing degrees, and this accounts for their somewhat differential profiles of action and side effects. Central biogenic amine, opioid and adenosine systems are clearly implicated in mechanisms of analgesia following the systemic administration of antidepressants as antagonism of these systems inhibits analgesia. However, it is more difficult to definitively implicate other systems or mechanisms in antidepressant-mediated analgesia because, although many agents with particular pharmacological actions may mimic the action of antidepressants, mimicry alone does not necessarily establish involvement or causality. To further our understanding of specific mechanisms in analgesia, studies using animals with selective deletions of particular cellular targets (e.g., receptors, ion channels) using molecular techniques may be needed. Finally, given the multiplicity of antidepressant actions, it may well be that it is this very property that confers antidepressants with their unique profile against pain.

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