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Antidepressant Drugs and Pain

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1. Introduction

Physical pain is one of the most common somatic symptoms in patients that suffer depression and conversely, patients suffering from chronic pain of diverse origins are often depressed. Indeed, symptoms of physical pain in depressed patients are associated with a more severe prognosis of longer duration, greater functional impairment, a poorer clinical outcome and increased health-care costs. Moreover, the intensity of pain has been correlated with the severity of the symptoms of depression. While these data strongly suggest that depression is linked to altered pain perception, pain management has received little attention to date in the field of psychiatric research (Elman et al., 2011).

The monoaminergic system influences both mood and pain (Delgado, 2004), and since many antidepressants modify properties of monoamines, these compounds may be effective in managing chronic pain of diverse origins in non-depressed patients and to alleviate pain in depressed patients. There are abundant evidences in support of the analgesic properties of tricyclic antidepressants (TCAs), particularly amitriptyline, and another TCA, duloxetine, has been approved as an analgesic for diabetic neuropathic pain. By contrast, there is only limited data regarding the analgesic properties of selective serotonin reuptake inhibitors (SSRIs) (Saarto & Wiffen, 2007). In general, compounds with noradrenergic and serotonergic modes of action are more effective analgesics (Saarto & Wiffen, 2005), although the underlying mechanisms of action remain poorly understood, antidepressants appear to enhance endogenous analgesia and they are thought to increase the activity of the descending inhibitory bulbospinal pathway, which is compromised in chronic pain (Mico et al., 2006a).

While the utility of many antidepressant drugs in pain treatment is well established, it remains unclear whether antidepressants alleviate pain by acting on mood (emotional pain) or nociceptive transmission (sensorial pain). Indeed, in many cases, no correlation exists between the level of pain experienced by the patient and the effect of antidepressants on mood. Thus, in this chapter we will summarize our current knowledge relating to the use of

antidepressants in chronic pain conditions and in the treatment of pain as a somatic symptom of depression. We will review the pharmacological mechanisms and the neurobiological substrates underlying the analgesic properties of antidepressants, and discuss the varying analgesic effects of specific types of antidepressants.

2. Depression and pain: Linked diseases

Depression and pain are two reciprocally linked and highly prevalent conditions (Figure 1). Epidemiological studies in pain clinics indicate that major depressive disorder has a prevalence of 52%, ranging from 1.5-100% depending on the chronic pain condition considered, and the prevalence of pain in depressed patients ranges from 15-100% (Bair et al., 2003). Depression is defined as an affective disorder characterized by ill mood, feelings of worthlessness, diminished interest in pleasurable stimuli and impaired decision making abilities. Moreover, depression involves a somatic dimension that is characterized by weight change, fatigue, sleep disturbances, headaches, stomach aches and other painful symptoms (DSM-IVR, 2000), such as back pain, neck-shoulder pain and musculoskeletal pain (Leino & Magni, 1993). Depressed patients may also experience an heightened response to pain or in the associated suffering, and in a primary care setting, they frequently complaining of specific types of pain, including abdominal, joint and chest pain, and headaches (Kroenke et al., 1994; Mathew et al., 1981). Indeed, lower back pain is twice as likely to be reported by depressed versus non-depressed patients (Croft et al., 1995).

According to the IASP (*International Association for Study of Pain*), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, 1994). The experience of pain can also be significantly influenced by emotional and psychosocial factors. Accordingly, depression may exacerbate the response to painful stimuli (Berna et al., 2010).

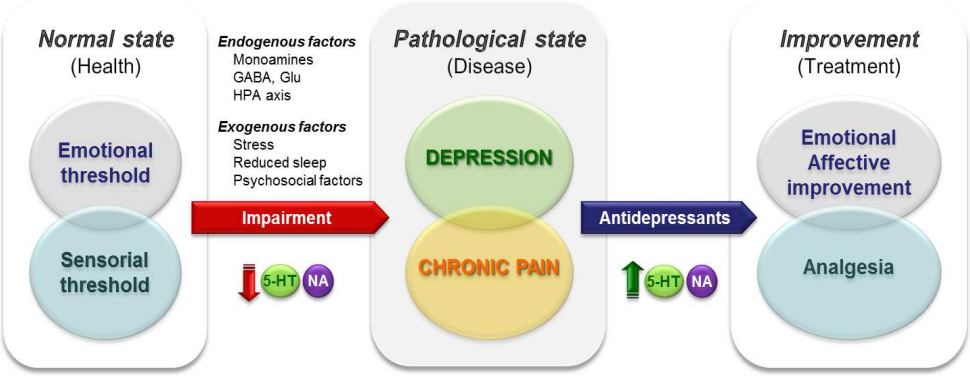

Fig. 1. Pain and depression. Pathological conditions of chronic pain and depression are associated with a decrease in the levels of both noradrenaline and serotonin. Treatment with some antidepressant drugs can improve both conditions.

3. Evidence of the analgesic effects of antidepressants

Currently, drugs that increase monoamine levels by inhibiting neurotransmitter reuptake represent the first line of treatment for depression, constituting a pharmacologically heterogeneous group known generically as "antidepressants". Typical antidepressant drugs are classified according to their mechanism of action (see Table 1) and they include the classical TCAs, SSRIs, noradrenaline reuptake inhibitors (NRIs) and mixed non-TCA antidepressants (SNRIs – serotonin and noradrenaline reuptake inhibitors). This group also includes dopamine and noradrenaline reuptake inhibitors (DNRIs), and reversible monoamine oxidase inhibitors (MAOIs) that inhibit both A and B subtypes of enzyme monoamine oxidase (MAO-A and MAO-B). The effects of atypical antidepressants include or rely exclusively on blocking of the α2-adrenoceptor and/or 5-HT2A receptors.

	Pharmacological action	**Observations**
Tricyclic antidepressants (TCAs)		
Desipramine Clomipramine Amitriptyline Nortriptyline Imipramine	Inhibitor of serotonin and noradrenaline reuptake Desipramine is essentially noradrenergic Clomipramine is principally serotonergic	Demethylated metabolites are associated with a more noradrenergic action The affinity for cholinergic, histaminergic and α_1-adrenergic receptors limits their use (side effects) Widely used in the treatment of pain
Selective serotonin reuptake inhibitors (SSRIs)		
Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Inhibitor of serotonin reuptake	Highly selective. Most commonly used in the treatment of depression. Not useful for pain treatment.
Noradrenaline reuptake inhibitors (non-tricyclic) *(NRIs)*		
Reboxetine	Inhibitor of noradrenaline reuptake	Low activity at histaminergic, cholinergic and α_1-adrenergic receptors. Some evidence of analgesic activity
Serotonin and noradrenaline reuptake inhibitors (non-tricyclic) *(SNRIs)*		
Venlafaxine Duloxetine Milnacipran	Inhibitor of serotonin and noradrenaline reuptake	No affinity for cholinergic, histaminergic or α_1-adrenergic receptors Widely used in the treatment of pain
Dopamine and noradrenaline reuptake inhibitors (DNRI)		
Bupropion	Inhibitor of dopamine and noradrenaline reuptake Minimal effect on serotonin reuptake	Highly selective. Currently used for smoking cessation treatment. Some studies have demonstrated efficacy in pain treatment
Inhibitors of monoamine oxidase (IMAOs)		
Phenelzine Tranylcyppromine	Irreversible inhibition of MAO-A and MAO-B	First generation drugs. Rarely used nowadays.
Moclobemide	Selective and reversible blockade of MAO-A	Less effective. Not currently used
Others		
Mianserin Mirtazapine	Noradrenergic receptor antagonists	Increase in noradrenergic transmission
Trazodone	Antagonist of postsynaptic 5-HT_2 receptors	Some inhibitory effects on serotonin reuptake
Tianeptine	Increases serotonin reuptake and dopamine release	

Table 1. Classification and general characteristics of antidepressants

3.1 Clinical studies

Several studies have demonstrated the intrinsic analgesic effects of antidepressants (McQuay et al., 1996; Onghena & Van Houdenhove, 1992; Smith et al., 1998). However, it remains unclear whether antidepressants are efficacious for the treatment of all types of pain or only for specific subtypes. Pain is a heterogeneous disorder that may have different origins: 1) nociceptive pain: caused by a lesion or potential tissue damage; 2) inflammatory: occurred as a consequence of an inflammatory process, 3) neuropathic pain: induced by an injury to the nervous system and finally, 4) pain that is not originated by a neurological disorder or peripheral tissue abnormality (irritable bowel syndrome, fibromyalgia and tension headache). The evidence currently available suggests that the antinociceptive effect of antidepressants is particularly relevant for the management of chronic pain, specifically neuropathic pain. Thus, antidepressants constitute the first line of pharmacological treatment of this disease, together with anticonvulsants such as gabapentin and pregabalin (Baidya et al., 2011; Moore et al., 2011). Neuropathic pain is a condition of chronic pain caused by injury to the nervous system. Currently, TCAs (amitriptyline, nortriptiline, imipramine and clomipramine) are the most common antidepressants used in the treatment of neuropathic pain processes associated with diabetes, cancer, viral infections and nerve compression. Among the TCAs, amitriptyline is considered the "gold standard" (Fishbain, 2003), with a demonstrated analgesic effect in several pain conditions, including headaches and fibromyalgia (Arnold et al., 2000; Descombes et al., 2001; Reisner, 2003). Other clinical studies have demonstrated also the efficacy of venlafaxine in several conditions, such as migraine, fibromyalgia and neuropathic pain, as well as cancer pain (Dwight et al., 1998; Tasmuth et al., 1998; Taylor & Rowbotham, 1996). Despite being a SNRI, at lower doses venlafaxine primarily acts on serotonergic transmission and it has no affinity for cholinergic or histaminergic receptors, providing an advantage over TCAs in terms of unwanted side effects. Following recent positive findings in controlled clinical studies, duloxetine has also been proposed as a suitable treatment for diabetic neuropathy (Goldstein et al., 2005; Leo & Barkin, 2003), while another SNRI with analgesic effects, milnacipran, has proved effective in the treatment of fibromyalgia (Leo & Brooks, 2006). SSRIs were successfully introduced in the 1980´s as effective treatments for depression, although in terms of chronic pain, these compounds have proved no more effective than traditional TCAs (McMahon, 2006). Moreover, some authors have proposed that SSRIs may enhance the process underlying acute pain (Dirksen R, 1998). A meta-analysis of antidepressant-induced analgesia by Onghena and colleagues found that selective NRIs were no more efficacious than dual-action antidepressants (Onghena & Van Houdenhove, 1992). However, based on the evidence described here, we can conclude that drugs that inhibit the reuptake of monoamines are likely to be effective in the treatment of chronic pain. In chronic pain it is known that there is a higher rate of action potential firing in nociceptors (Emery et al., 2011) that activate multiple pathophysiological mechanisms that lead to the different cluster of symptoms (spontaneous pain, hyperalgesia, allodynia…) in every pain condition. Evidences up-to-date are limited to the association of pain types with categories of drugs; for example, non-steroidal anti-inflammatory drugs (NSAIDS) with inflammatory pain or antidepressants and anticonvulsants with neuropathic pain. However, the distinction of different types of symptoms remains relevant for mechanism-based pain assessment and management. This makes difficult to identify the correlation of different pain symptoms to differently neurotransmission system (noradrenergic, sertonergic, opioid…).

In addition to their use in the treatment of chronic pain, antidepressants also alleviate physical symptoms (pain) associated with depression. This analgesic effect is typical of antidepressants that augment the levels of noradrenaline and serotonin. In general, TCAs demonstrated analgesic efficacy in a variety of pain conditions (*e.g.*, back pain, fibromyalgia and migraine) in patients with depression (Barbui et al., 2007; Hansen et al., 2005; McDermott et al., 2006; Mico et al., 2006b). In clinical studies, the SNRI venlafaxine was more efficacious in treating the physical symptoms of depression than SSRIs, suggesting that the emotional and physical symptoms of depression are modulated by distinct mechanisms (Nemeroff CN, 2003; Thase et al., 2001). Duloxetine also improves physical symptoms in depression (Detke et al., 2002a; 2002b) and thus, together these findings demonstrate that antidepressants that act on serotonergic and noradrenergic systems are useful to treat the physical symptoms of depression.

Many issues associated with the analgesic properties of antidepressants remain unclear. For example, are the antidepressant and analgesic effects of these compounds exerted at equivalent doses? It has been generally assumed that all antidepressants exert analgesic effects at doses lower than those at which antidepressant activity is induced, as demonstrated for TCAs (Lynch, 2001). However, more recent studies of the antidepressant/analgesic effects of non-TCA SNRIs (venlafaxine and duloxetine) do not support this hypothesis. While venlafaxine is effective in treating depression at doses of 75-225 mg/day (Golden & Nicholas, 2000), higher doses are required to relieve pain for review see (Briley, 2004; Sumpton & Moulin, 2001), although effective pain relief has been obtained with venlafaxine in the upper dose range of 150-225 mg/day (Rowbotham et al., 2004). In humans, venlafaxine inhibits preferentially serotonin uptake at 75 mg/kg, while doses of 150 mg/kg inhibit the uptake of both serotonin and noradrenaline (Roseboom & Kalin, 2000). These data are consistent with preclinical data suggesting that the contribution of both monoamines is required for the analgesic effect of venlafaxine (Berrocoso et al., 2009). By contrast, duloxetine inhibits the reuptake of serotonin and noradrenaline at similar doses, and exerts antidepressant and analgesic effect within the same dose range (Brannan et al., 2005; Goldstein et al., 2005). Thus, TCAs appear to provide effective pain relief at lower doses than those required for their antidepressant effects, while medium to high doses of SNRIs are necessary to produce analgesia (Sansone & Sansone, 2008).

3.2 Animal studies

The mechanisms by which antidepressants produce analgesic effects have been primarily studied in experimental animal models that reproduce the pathophysiological changes that occur in patients suffering pain (Yalcin et al., 2009b). While it is difficult to develop animal models that encompass all the processes associated with chronic pain, a variety of methodological approaches have been developed to model individual aspects of neuropathic pain, including chronic constriction injury of the sciatic nerve (Bennett & Xie, 1988) and induction of diabetic neuropathy through the administration of streptozotocin (Jakobsen & Lundbaek, 1976). These animal models permit the pain thresholds in response to different painful stimuli to be determined (mechanical, thermal, electrical, etc.) and using such approaches, it was demonstrated that diverse antidepressants reduce allodynia in a model of peripheral neuropathy, such as desipramine, venlafaxine, reboxetin and nortriptyline (Yalcin et al., 2009a; 2009b). Moreover, anti-allodynic effects of amitriptyline

and nortriptyline (TCAs) have been described in models of chronic but not acute pain (Benbouzid et al., 2008a), and fluoxetine (SSRI) was seen to be ineffective at relatively high doses. Hence, inhibition of serotonin reuptake appears to be insufficient to alleviate allodynia associated to neuropathy, further evidence of the analgesic effects of inhibiting noradrenaline reuptake (Benbouzid et al., 2008a).

Anti-depressant	Treatment (dose)*	Pain model#	Behavioural test	Effect	References
Amitriptyline	Acute (10 mg/kg i.p.)	Neuropathic	Tail flick	Analgesia	(Iyengar et al., 2004)
Imipramine	Acute (5 mg/kg i.p.)	Tonic	Acetic acid	Analgesia	(Aoki et al., 2006)
	Acute (25 mg/kg i.p.)	Tonic (carrageenan)	Paw oedema	Analgesia	(Abdel-Salam et al., 2004)
Fluoxetine	Acute (30 mg/kg i.p.)	Phasic	Tail flick	Analgesia	(Pedersen et al., 2005)
	Acute (30 mg/kg i.p.)	Tonic (formalin)	Second phase	Analgesia	(Pedersen et al., 2005)
	Acute (10 mg/kg i.p.)	Neuropathic	Von Frey	Analgesia	(Pedersen et al., 2005)
	Acute (20 mg/kg i.p.)	Tonic (carrageenan)	Paw oedema	Analgesia	(Abdel-Salam et al., 2004)
	Chronic (20 mg/kg i.p.)	Tonic (carrageenan)	Paw oedema	Analgesia	(Abdel-Salam et al., 2004)
Fluvoxamine	Chronic (10 mg/kg i.p.)	Neuropathic	Paw pressure	No analgesic effect	(Gutierrez et al., 2003)
	Acute (40 mg/kg i.p.)	Tonic	Acetic acid	Analgesia	(Aoki et al., 2006)
	Acute (0.1 M i.t.)	Neuropathic	von Frey	Analgesia	(Ikeda et al., 2009)
Reboxetine	Acute (30 mg/kg i.p.)	Phasic	Tail flick	Analgesia	(Pedersen et al., 2005)
	Acute (10 mg/kg i.p.)	Tonic (formalin)	Second phase	Analgesia	(Pedersen et al., 2005)
Paroxetine	Acute (0.1 M i.t.)	Neuropathic	Von Frey	Analgesia	(Ikeda et al., 2009)
Duloxetine	Acute (10 mg/kg i.p.)	Neuropathic	Place escape/ avoidance	Improvement in the emotional dimension of pain	(Pedersen & Blackburn-Munro, 2006)
	Acute (3 mg/kg i.p.)	Neuropathic	Tail flick	Analgesia	(Iyengar et al., 2004)
	Acute (10 mg/kg p.o.)	Neuropathic	von Frey	Analgesia	(Iyengar et al., 2004)
	Acute (10 mg/kg i.p.)	Phasic	Hot-plate	Analgesia	(Jones et al., 2005)
	Acute (30 mg/kg p.o.)	Tonic	Acetic acid	Analgesia	(Jones et al., 2005)
Venlafaxine	Acute (10 mg/kg i.p.)	Neuropathic	Tail flick	Analgesia	(Iyengar et al., 2004)
	Acute (100 mg/kg p.o.)	Neuropathic	von Frey	Analgesia	(Iyengar et al., 2004)
	Acute (30 mg/kg i.p.)	Tonic (formalin)	Second phase	Analgesia	(Pedersen et al., 2005)
Milnacipran	Acute (10 mg/kg i.p.)	Neuropathic	Tail flick	Analgesia	(Iyengar et al., 2004)
	Acute (200 mg/kg p.o.)	Neuropathic	von Frey	Analgesia	(Iyengar et al., 2004)
	Acute (5 mg/kg i.p.)	Tonic	Acetic acid	Analgesia	(Aoki et al., 2006)
	Acute (60 mg/kg i.p.)	Neuropathic	Paw pressure	Analgesia	(Barbui et al., 2007)
	Acute (0.1 M i.t.)	Neuropathic	von Frey	Analgesia	(Ikeda et al., 2009)

** The dose and route of administration is shown in parentheses (i.p., intraperitoneal; i.t., intrathecal; p.o., oral)*
 # Pain models are categorized as phasic (short-duration pain), tonic (long-duration pain) and neuropathic, according to (Le Bars et al., 2001).

Table 2. Analgesic effects of antidepressant drugs in animal models of pain

The role of the monoaminergic system in antidepressant-induced analgesia has been demonstrated in several studies. Inhibition of noradrenergic, serotonergic or dopaminergic tone significantly attenuates the analgesic effect of antidepressants. For example, the inhibition of tyrosine hydroxylase (an essential enzyme for noradrenaline synthesis) or tryptophan hydroxylase (an essential enzyme for serotonin synthesis) antagonizes the analgesic effect of antidepressants in a wide range of experimental models (Valverde et al., 1994). Monoamines act on multiple receptor subtypes in the nervous system, some of which mediate the analgesic effect of antidepressants, such as α-adrenoceptors (Ghelardini et al., 2000; Yokogawa et al., 2002) and β-adrenoceptors (Mico et al., 2006b), 5-HT_{1A}, 5-HT_2 and 5-HT_3 serotonin receptors (Bonnefont et al., 2005; Yokogawa et al., 2002), and D2 dopamine receptors (Gilbert & Franklin, 2001).

4. Analgesic mechanism of action

Although antidepressants have been used as pain-relieving drugs for over 40 years, the mechanism of action underlying their analgesic effects remains unknown. Although their primary effect on neural circuits is to increase the availability of noradrenaline and/or serotonin, direct and indirect effects of antidepressants on other systems have also been proposed, including opioid neurotransmission. Given the established links between chronic pain and depression, it is plausible that antidepressants may act on substrates common to both conditions.

4.1 The monoaminergic system

Several common biological processes are deregulated in depression and chronic pain, producing hypothalamic-pituitary adrenal axis dysfunction (Blackburn-Munro, 2004), increases in plasma pro-inflammatory cytokines (Omoigui, 2007; Raison et al., 2006), alterations in brain-derived neurotrophic factor (BDNF) expression (Duman & Monteggia, 2006; Geng et al., 2010) and opioid signalling (Gold et al., 1982; Spetea et al., 2002). Nonetheless, the monoaminergic system is the predominant biological substrate linking both conditions, as witnessed by the key role played by serotonin and noradrenaline in pain and depression (Gormsen et al., 2006; Robinson et al., 2009). These observations strongly suggest that pain transmission may be compromised in depression and vice versa.

Serotonin and noradrenaline neurotransmitters are primarily synthesized in the dorsal raphe nuclei and locus coeruleus, respectively. Ascending projections from these two brainstem nuclei (mainly to the hypothalamus, anterior cingulate cortex and amygdala) are involved in the regulation of anxiety, mood and emotion. Moreover, deterioration in mood appears to be associated with impaired transmission along ascending serotonergic and noradrenergic pathways (Figure 1). Descending projections from the raphe nuclei and locus coeruleus project to the spinal cord (descending pain pathway), where they exert inhibitory influences on pain threshold. Furthermore, projections from the nucleus raphe magnus, locus coeruleus and A5 (also a noradrenergic centre) control the release of serotonin and noradrenaline at the level of the spinal cord. As a general rule, when these monoamines augment in synaptic clefts within the spinal cord there is a decrease in the pain threshold (Figure 1). However, it should be noted that serotonin can both dampen and enhance the sensation of pain, depending on the receptor subtypes activated. Given the common noradrenergic and serotonergic pathways implicated in chronic pain and depression,

antidepressants are the most effective treatment to deal with chronic pain of diverse origins, with or without co-existing depression (Blier & Abbott, 2001; Campbell et al., 2003; Mico et al., 2006a). At the supraspinal level, these compounds increase noradrenaline and serotonin levels in the synaptic clefts while simultaneously enhancing the activity of the descending inhibitory bulbospinal pathways, thereby producing analgesia.

4.2 The opioid system

Some preclinical studies have demonstrated a functional relationship between endogenous opioid peptides and the analgesic effect of antidepressant drugs (Table 3). For example, the opioid antagonist naloxone or nor-binaltorphimine antagonize the analgesic effect of several TCAs and monoamine reuptake inhibitors in models of acute and chronic pain (Ardid & Guilbaud, 1992; Valverde et al., 1994). As opioid and monoaminergic systems appear to share common molecular mechanisms mediating nociception, opioid compounds are frequently co-administrated with antidepressants for pain relief. However, the validity of this therapeutic strategy for the treatment of mood disorders with comorbid pain remains unclear (Alba-Delgado et al., 2011; Berrocoso & Mico, 2009a; 2004; 2009; Rojas-Corrales et al., 2002; 2004). Moreover, the opioid doses required to produce antidepressant-like effects are higher than those required to produce analgesic effects, suggesting that these two processes are mediated by distinct mechanisms (Berrocoso & Mico, 2009a; Rodriguez-Munoz et al., 2011).

The influence of antidepressants on opioid signalling is region-specific. Indeed, the administration of antidepressants increases opioid receptor density in brain areas implicated in pain and depression (Ortega-Alvaro et al., 2004; Reisine & Soubrie, 1982). For example, chronic citalopram administration increases naloxone binding in cortical membranes (Antkiewicz-Michaluk et al., 1984), while imipramine and fluoxetine increase neuronal μ-opioid receptor expression in the prefrontal cortex, hippocampus and caudate putamen (de Gandarias et al., 1999; 1998). There is data revealing considerable variation in opioid receptor responses to antidepressant treatment depending on treatment duration, dose, the brain region analyzed and the antidepressant's mode of action. Importantly, opioids can also modify the action of antidepressants and a significant attenuation of the behavioural effects of two TCAs, clomipramine and desipramine, was observed in mice treated with the non-selective opioid antagonist naloxone (Devoize et al., 1984). This antagonistic effect was corroborated in subsequent studies, demonstrating a reduction in the antidepressant efficacy of tricyclic and non-tricyclic antidepressants in response to opioid pretreatment (Baamonde et al., 1992; Berrocoso et al., 2004; Besson et al., 1999; Tejedor-Real et al., 1995).

4.3 Other mechanisms involved

In addition to the monoaminergic and opioid systems, some antidepressants seem to exert their analgesic effect acting by other lesser-known mechanisms (see revision in Table 3). This is not surprising because other neurotransmission systems have been involved in the etiopathogenesis of pain and also in depression. Most evidences indicate the involvement of ionic channels (such as calcium, potassium and sodium) and neurotransmitter receptors (gamma-aminobutyric acid or GABA, N-methyl-D-aspartate, or NMDA and substance P) in the analgesic mechanism of action of antidepressants. It is interesting to note that among antidepressants, TCAs are those that act on multiple nociceptive targets both at central and

Mechanism of action	TCAs	SSRIs	NRIs	SNRIs	DNRIs	Other ADs	References
+ δ and μ-opioid receptors	Amitriptyline Mipramine Clomipramine Maprotiline Desmethylclo Imipramine Desipramine Nortriptyline Amoxapine	Paroxetine	Oxaprotiline Viloxazine	Venlafaxine	Nomifensine	Nefazodone Mirtazapine Mianserin	(Gray et al., 1998; Hamon et al., 1987; Marchand et al., 2003; Ortega-Alvaro et al., 2004; Schreiber et al., 1999; Schreiber et al., 2002; Valverde et al., 1994)
− Na^+ channel	Amitriptyline Imipramine Trimipramine Desipramine Doxepin	*Not known*	*Not known*	Venlafaxine	*Not known*	*Not known*	(Sudoh et al., 2003)
+ K^+ channel	Amitriptyline Clomipramine	Citalopram Fluoxetine	*Not known*	*Not known*	*Not known*	*Not known*	(Galeotti et al., 2001)
− Ca^{2+} channel	Amitriptyline Clomipramine Imipramine Trimipramine Desipramine Doxepin	Citalopram	Oxaprotiline	*Not known*	*Not known*	*Not known*	(Antkiewicz-Michaluk et al., 1991; Beauchamp et al., 1995; Lavoie et al., 1994)
+ A1-adenosine receptor	Amitriptyline	*Not known*	*Not known*	*Not known*	*Not known*	*Not known*	(Esser & Sawynok, 2000; Sawynok et al., 1999; Sawynok et al., 2008; Sawynok et al., 2005)
↑ Adenosine levels	Amitriptyline	*Not known*	*Not known*	*Not known*	*Not known*	*Not known*	
$GABA_B$ receptor ↑ function	Amitriptyline Desipramine	Fluoxetine	*Not known*	*Not known*	*Not known*	*Not known*	(McCarson et al., 2006; McCarson et al., 2005; Sands et al., 2004)
− NMDA receptor	Amitriptyline Desipramine Clomipramine	*Not known*	*Not known*	Milnacipran	*Not known*	*Not known*	(Cai & McCaslin, 1992; Eisenach & Gebhart, 1995; Mjellem et al., 1993; Skolnick et al., 1996; Su & Gebhart, 1998)
↓ Substance P synthesis	Imipramine Clomipramine	*Not known*	*Not known*	*Not known*	*Not known*	*Not known*	(Bianchi et al., 1995; Iwashita & Shimizu, 1992)

Abbreviations: ADs, antidepressants; DNRIs, dopamine and noradrenaline reuptake inhibitors; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; NRIs, noradrenaline reuptake inhibitors; SNRIs, serotonin and noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; +, activation; −, blockade; ↑, increase; ↓, decrease.

Table 3. Non-monoaminergic mechanisms implicated in the analgesic effect of antidepressants

peripheral levels (Table 3) and this may be the reason why TCAs seem to be more effective than other antidepressants with a more selective monoaminergic mechanism of action. For example, many actions have been described for amitriptyline: blocking NMDA receptors and sodium channels (Sudoh et al., 2003). Also, it decreases intracellular calcium levels in the dorsal horn (Cai & McCaslin, 1992), and increases adenosine levels and the activity of A1 receptor (Esser & Sawynok, 2000; Sawynok et al., 1999; Sawynok et al., 2008; Sawynok et al., 2005). Finally, it promotes $GABA_B$ receptor function (McCarson et al., 2005), among other actions. This may help to explain why amitriptyline is one of the most widely used antidepressants in the treatment of pain. However, it is important to bear in mind that many of these targets are closely related to monoaminergic system and that these actions could lead ultimately to the increased of noradrenaline, serotonin and dopamine levels in the synaptic cleft.

4.4 Lessons from knockout mice

Recent advances in the field of genomics have led to the creation of new preclinical models where mutations are targeted to specific genes. The use of genetically manipulated rodents, mainly mice, has contributed to a better understanding of the mechanisms underlying mood and pain disorders, and of the mechanism of action of antidepressants. Knockout (KO) phenotypes are characterized using behavioural tests to evaluate the basal nociceptive threshold following pain induction and in general, the sensorial threshold is not modified in transgenic animals, although some exceptions have been reported.

Knockout mice have been used to explore the relative contributions of serotonergic and noradrenergic pathways in antidepressant-mediated analgesia (Table 4). Using homologous recombination, a KO mouse was generated lacking the noradrenaline transporter (Xu et al., 2000), resulting in reduced noradrenaline reuptake. In the tail-flick test, these mice displayed a modest elevation in the pain threshold. Moreover, unlike wild-type mice, pre-treatment with desipramine did not enhance morphine analgesia in these mutants (Bohn et al., 2000), highlighting the importance of the noradrenaline transporter in desipramine-mediated analgesia.

The role of other noradrenergic targets in analgesia has also been studied in KO mice, including that of α- and β-adrenoceptors. The α-adrenergic receptors are pre- and postsynaptic autoreceptors that regulate neuronal activity (noradrenaline release, firing rate, etc.), and their activation also promotes antinociceptive, sedative and sympatholytic effects *in vivo*. Significantly, α_2-adrenoceptor agonists are widely used clinically to mimic these effects and the α_{2A} receptor subtype has been identified as the principal mediator of antinociception (Lakhlani et al., 1997). Indeed, amitriptyline analgesia is abolished in α_{2A}-adrenoceptor KO mice in the hot plate and tail-flick tests (Ozdogan et al., 2004), suggesting that α_{2A}-adrenoceptors play a significant role in mediating the acute analgesic effects of amitriptyline, although other neurotransmitter systems may also be involved. The expression of β-adrenoceptors in the descending noradrenergic inhibitory pathway (Nicholson et al., 2005) also suggests a role for these receptors in the analgesic effects of antidepressants and the β_2 subtype has been shown to fulfil a critical role in the antiallodynic effects of nortriptyline (Yalcin et al., 2009a), venlafaxine and desipramine (Yalcin et al., 2009b).

Target	Antidepressant	Behavioural test	Effects		References
			WT mice	KO mice	
Monoaminergic system					
α_{2A}-adrenoceptor	Amitriptyline	Tail-flick	Analgesia	No effect	(Ozdogan et al., 2004)
	Amitriptyline	Hot plate	Analgesia	No effect	(Ozdogan et al., 2004)
β_2-adrenoceptor	Desipramine	von Frey	Analgesia	No effect	(Yalcin et al., 2009b)
	Nortriptyline	von Frey	Analgesia	No effect	(Yalcin et al., 2009a)
	Venlafaxine	von Frey	Analgesia	No effect	(Yalcin et al., 2009b)
Noradrenaline transporter	Desipramine	Tail-Flick	Analgesia	No effect	(Bohn et al., 2000)
Lmx1b *(LIM homeodomain-containing transcription factor)*	Fluoxetine	Tail-Flick	Analgesia	No effect	(Zhao et al., 2007)
	Fluoxetine	Formalin (2º phase)	Analgesia	No effect	(Zhao et al., 2007)
	Fluoxetine	von Frey	Analgesia	No effect	(Zhao et al., 2007)
	Amitriptyline	Tail-Flick	Analgesia	Analgesia	(Zhao et al., 2007)
	Duloxetine	Tail-Flick	Analgesia	No effect	(Zhao et al., 2007)
	Duloxetine	Formalin (2º phase)	Analgesia	No effect	(Zhao et al., 2007)
	Duloxetine	von Frey	Analgesia	Analgesia	(Zhao et al., 2007)
RGS9-2 *(Regulator of G-protein signalling 9-2)*	Desipramine	von Frey	Analgesia	Analgesia	(Zachariou & Terzi, 2009)
	Desipramine	Hargreaves	Analgesia	Analgesia	(Zachariou & Terzi, 2009)
Opioid system					
μ-opioid receptor	Nortriptyline	von Frey	Analgesia	Analgesia	(Bohren et al., 2010)
δ-opioid receptor	Nortriptyline	von Frey	Analgesia	No effect	(Benbouzid et al., 2008b)
Other systems					
A1-adenosine receptor	Amitriptyline	Formalin (2º phase)	Analgesia	Analgesia	(Sawynok et al., 2008)
	Amitriptyline	Formalin (2º phase)	Analgesia	Analgesia	(Sawynok et al., 2008)

Abbreviations: KO, knockout; WT, wild-type.

Table 4. Analgesic response to antidepressant drugs in knockout and wild-type mice

While the majority of studies of the serotonergic action of antidepressants have focused specifically on antidepressant effects, antidepressant-induced analgesia has been studied in mice lacking Lmx1b (Zhao et al., 2007), a LIM homeodomain-containing transcription factor required for postmitotic differentiation of serotonergic neurons (Ding et al., 2003). These mice display dysfunctional central serotonergic neurotransmission and thus, they represent a novel tool to study the mode of action of antidepressants. Indeed, the analgesic effects of fluoxetine, amitriptyline and duloxetine on phasic and tonic pain (formalin and carrageenan tests) were abolished or greatly attenuated in transgenic mice (Zhao et al., 2007). This demonstrates the contribution of serotonergic neurotransmission to antidepressant-mediated analgesia, and provides important genetic evidence regarding the modulatory role of serotonin in inflammatory and acute pain.

While the contributions of noradrenaline and serotonin to pain and depression are well established, the role of other neurotransmitter systems, including the opioid system, remains unclear. Further studies are required to elucidate the neuroanatomical and molecular links between antidepressant action and opioid signalling. Indeed, several studies have suggested that this action may be centrally mediated, *e.g.*, via noradrenergic descending pathways. The generation of mice lacking μ- (Bohren et al., 2010) and δ-opioid receptors (Benbouzid et al., 2008b) has provided a novel approach to analyse the relationship between antidepressant activity and opioid signalling. Chronic treatment with the TCA nortriptyline induces antiallodynic effects in neuropathic wild-type and δ-opioid KO mice (Benbouzid et al., 2008b; Bohren et al., 2010), but not in μ-opioid deficient mice (Bohren et al., 2010), indicating that μ-opioid receptors are not required for the analgesic effects of nortriptyline in neuropathic pain. These results highlight the functional differences

between μ- and δ-opioid receptors in antidepressant-mediated analgesia. It was proposed that the analgesic effect of nortriptyline may involve signalling via the endogenous opioid system through the δ subtype (Benbouzid et al., 2008b). However, further studies will be necessary to determine whether a similar mechanism may also underlie the antidepressant effects of these compounds.

5. Conclusion

Depression and chronic pain are two multifaceted illnesses with a common and complex neurobiological basis. While several neurotransmitters have been implicated in the biological origins of both conditions, the monoaminergic system appears to be the principal pathway affected. Accordingly, the primary therapeutic approach involves the use of drugs that act on this system, normalizing monoamine levels. Antidepressants that act on noradrenergic and serotonergic systems are commonly used to treat both the emotional and somatic symptoms of depression, and they are effective as analgesics for the treatment of chronic forms of pain, such as neuropathic pain. However, further studies in the analgesic mechanism of action of antidepressants beyond the monoaminergic level might help to develop new therapeutic options and to improve the treatment and prognosis of patients.

6. Acknowledgments

This work was supported by grants from: the Fondo de Investigacion Sanitaria PI10/01221; MICINN (SAF 2009-08460); CIBERSAM G18; Junta de Andalucía, Consejería de Innovación, Ciencia y Empresa (CTS-510, CTS-7748 and CTS-4303); Catedra Externa del Dolor Grünenthal-Universidad de Cadiz; and FP7-PEOPLE-2010-RG (268377), as well as an FPU fellowship (AP2007-02397).

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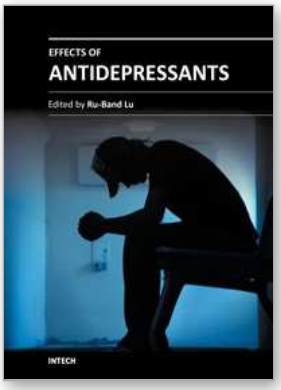

Effects of Antidepressants

Edited by Dr. Ru-Band Lu

ISBN 978-953-51-0663-0
Hard cover, 194 pages
Publisher InTech
Published online 29, June, 2012
Published in print edition June, 2012

Over the last fifty years, many studies of psychiatric medication have been carried out on the basis of psychopharmacology. At the beginning, researchers and clinicians found the unexpected effectiveness of some medications with therapeutic effects in anti-mood without knowing the reason. Next, researchers and clinicians started to explore the mechanism of neurotransmitters and started to gain an understanding of how mental illness can be. Antidepressants are one of the most investigated medications. Having greater knowledge of psychopharmacology could help us to gain more understanding of treatments. In total ten chapters on various aspects of antidepressants were integrated into this book to help beginners interested in this field to understand depression.

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