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Research report

Chronic administration of amitriptyline differentially alters neuropathic pain-related behaviour in the presence and absence of a depressive-like phenotype

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HIGHLIGHTS

- Amitriptyline attenuates nerve injury-induced thermal allodynia/hyperalgesia.
- In the OB rat, amitriptyline attenuates nerve injury-induced mechanical allodynia.
- Behavioural changes accompanied by alterations in inflammatory gene expression in prefrontal cortex.
- Differential effect of amitriptyline on neuropathic pain behaviour in presence or absence of depression.

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ABSTRACT

Chronic pain and depression share a complex, reciprocal relationship. Furthermore, in addition to treating depression, antidepressants such as amitriptyline are a first-line treatment for chronic pain conditions, indicating possible common neural substrates underlying both depression and pain. However, there is a paucity of studies examining the effect of antidepressant treatment on nociceptive and neuropathic pain responding in the presence of a depressive phenotype. The current study aimed to examine the effect of chronic amitriptyline administration on neuropathic pain-related behaviour and associated neuroinflammatory processes in the olfactory bulbectomised (OB) rat model of depression. Nociceptive responding to mechanical, innocuous cold or noxious heat stimuli in sham or OB rats was not altered by chronic amitriptyline administration. The induction of neuropathic pain following L5–L6 spinal nerve ligation (SNL) resulted in robust mechanical and cold allodynia and heat hyperalgesia in both sham and OB vehicle-treated animals. Chronic amitriptyline administration attenuated SNL-induced mechanical allodynia in both sham and OB rats at day 7 post-SNL, an effect which was enhanced and prolonged in OB rats. In comparison, chronic amitriptyline administration attenuated SNL-induced cold allodynia and heat hyperalgesia in sham, but not OB, rats. Evaluating the affective/motivational aspect of pain using the place escape avoidance paradigm revealed that OB-SNL rats exhibit reduced noxious avoidance behaviour when compared with sham counterparts, an effect not altered by chronic amitriptyline administration. Chronic amitriptyline administration prevented the increased expression of GFAP, IL-10 and CCL5, and enhanced the expression of TNFα, in the prefrontal cortex of OB-SNL rats. In conclusion, these data demonstrate that chronic amitriptyline differentially alters somatic nociceptive responding following peripheral nerve-injury, depending on stimulus modality and the presence or absence of a depressive-like phenotype, an effect which may involve modulation of neuroinflammatory processes.

Abbreviations: AMI, amitriptyline; CCL, chemokines; CC, motif ligand; CD11b, cluster of differentiation molecule 11b; GFAP, glial fibrillary acidic protein; IL, interleukin; OB, olfactory bulbectomy; SNL, spinal nerve ligation; TNFα, tumour necrosis factor alpha.

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1. Introduction

Depression is associated with an increased risk of developing chronic pain [1,2]. Over 60% of patients with major depressive disorder suffer from chronic pain [3,4], and this comorbidity increases the socioeconomic cost, with direct medical care costs over twice as high in depressed patients with pain compared to those without [5]. Thus, the combination of depression and pain is more disabling and costlier to patients and society than either alone, highlighting the need for adequate treatment options. Indeed, effective treatment of pain symptoms has been shown to result in higher remission rates in depressed patients [6,7]. It has been suggested that depression and chronic pain are caused and maintained by dysfunction of shared neurobiological processes, such as monoaminergic pathways. Further support for this arises from the efficacy of monoaminergic-based antidepressants in the treatment of depression and as a first-line treatment for chronic pain [7–10]. Amitriptyline (AMI) is a tricyclic antidepressant which inhibits the re-uptake of noradrenaline and serotonin and remains a gold-standard treatment for neuropathic pain [11].

Preclinical research has also provided evidence in support of a relationship between depression and chronic pain, with a number of rodent models of depression exhibiting altered nociceptive responding and vice versa (for review see [12]). For example, the well-characterised olfactory bulbectomised (OB) rodent model of depression has been shown to exhibit mechanical allodynia and enhanced inflammatory nociceptive responding [13,14], altered thermal nociceptive responding [13,15] and increased nociceptive responding to electrical stimulation [16]. Furthermore, recent studies from our group have demonstrated altered L5–L6 spinal nerve ligation (SNL)-induced neuropathic pain-related behaviour in the OB rat [17,18], indicating that a prior depressive phenotype alters the development and expression of neuropathic pain. Chronic administration of the selective-serotonin reuptake inhibitor fluoxetine [15] and the tricyclic antidepressant AMI [16] has been shown to attenuate enhanced nociceptive responding to thermal and electrical stimuli, respectively, in the OB rat. In addition, chronic AMI treatment is known to reverse OB-induced hyperactivity, passive avoidance deficits and anhedonia [19–22], indicating antidepressant-like activity in the OB model. AMI also attenuates thermal hyperalgesia in the spinal nerve ligation (SNL) model of neuropathic pain [23–26], indicating an analgesic effect on neuropathic pain behaviour. However, the effect of antidepressant treatment on the development and expression of neuropathic pain in the presence of a depressive-like phenotype has not yet been examined. Therefore, the aim of this study was to investigate the effect of chronic AMI administration, at a regimen that elicits antidepressant-like effects, on mechanical and thermal nociceptive responding in the OB model of depression and on the development and expression of neuropathic pain behaviour following SNL.

The place escape avoidance paradigm (PEAP) is a novel behavioural test based on the avoidance of a chamber associated with noxious stimulation and has been used to assess the affective/motivational aspects of pain in several preclinical animal models including SNL [27,28]. Affective pain behaviour associated with chronic neuropathic/inflammatory pain has been shown to be attenuated by analgesics, anti-inflammatory agents and anticonvulsants [28–30]. The effect of antidepressants on affective pain behaviour has revealed that the selective serotonin/noradrenaline reuptake inhibitor duloxetine, but not fluoxetine, reduced affective pain behaviour in the complete Freund's adjuvant model of inflammatory pain and chronic constriction injury model of neuropathic pain [30,31]. However, no study to date has investigated the effect of chronic antidepressant administration on affective pain responding following SNL or if affective pain responding in SNL animals is modified in the presence of a depressive phenotype. Thus, a further aim of this study was to evaluate the effect of chronic AMI administration on affective pain responding following SNL, and if this effect is altered in the OB rat.

In addition to modulation of monoaminergic neurotransmission, antidepressants are known to possess immunomodulatory properties [32–35]. AMI has been found to decrease levels of pro-inflammatory cytokines both *in vitro* and *in vivo* [36,37]. The tricyclic antidepressant desipramine attenuates stimulus-induced increases in plasma TNFα and IL-1β in OB rats [38], while imipramine normalises T-cell ratio [39]. In chronic pain models, AMI has been shown to inhibit inducible nitric oxide expression in the cerebellum and hippocampus [40], and attenuates astrocyte activation in the spinal cord [23]. Furthermore, in animal models of depression, the expression of pro-inflammatory cytokines is increased in brain regions responsible for processing emotion and pain, with concomitant inflammatory or neuropathic pain [41–44,18,45]. Recent research from our group has demonstrated that chronic administration of the microglial inhibitor minocycline attenuates SNL-induced mechanical allodynia earlier and more profoundly in OB rats compared with sham counterparts [17]. However, it is not known whether chronic AMI treatment alters neuroinflammatory processes in supraspinal regions differentially in sham and OB rats following SNL. Therefore, a further aim was to examine if AMI-induced changes in nociceptive responding following SNL in sham and OB rats are accompanied by alterations in the expression of inflammatory mediators in the prefrontal cortex, a key region responsible for the modulation of nociception and/or affect.

2. Materials and methods

2.1. Animal husbandry

Male Sprague-Dawley rats (180–220 g: Charles River, UK) were housed singly in plastic bottomed cages containing wood shavings as bedding, in a temperature-controlled room (20 ± 2 °C), relative humidity of 40–60%, with a 12:12 h light-dark cycle (lights on at 07:00 h). Rats were fed a standard laboratory diet of rat chow pellets; food and water were available *ad libitum*. The experimental protocol was carried out in accordance with the guidelines and approval of the Animal Care and Research Ethics Committee, National University of Ireland, Galway, under licence from the Irish Department of Health and Children and in compliance with the European Communities Council directive 86/609.

2.2. Drug administration

Animals were administered either amitriptyline (AMI; Amitriptyline hydrochloride (Sigma-Aldrich, Ireland; 10 mg/kg i.p.) or vehicle (sterile saline) once daily, at an injection volume of 1 ml/kg, beginning on the day of OB/sham surgery. The choice of dose was based on the antidepressant effects of chronic AMI in OB rats [20,22,46], and the anti-nociceptive effects following L5–L6 SNL [24,26]. Behavioural testing was conducted at least 15 h after administration of AMI or vehicle to avoid any potential confound associated with the acute effects of the drug.

2.3. Experimental design

Rats were tested in the open field (locomotor activity), von Frey (mechanical sensitivity) and acetone-drop (cold sensitivity) tests at baseline to ensure no differences between groups assigned to sham or OB surgery (see Fig. 1 for experimental timeline). Animals were then assigned to either Sham-Vehicle (Sham-Veh, $n = 12$), Sham-AMI ($n = 12$), olfactory bulbectomy-Veh (OB-Veh, $n = 13$) and OB-AMI ($n = 12$). AMI or vehicle was administered daily, beginning