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ScienceDirect
Neuropharmacology 51 (2006) 1172–1180
NEURO PHARMACOLOGY
www.elsevier.com/locate/neuropharm

Analgesic effects of serotonergic, noradrenergic or dual reuptake inhibitors in the carrageenan test in rats: Evidence for synergism between serotonergic and noradrenergic reuptake inhibition

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Received 12 March 2006; received in revised form 27 July 2006; accepted 3 August 2006

Abstract

The efficacy of antidepressant drugs with serotonergic, noradrenergic, or dual reuptake inhibition was evaluated in reversing carrageenan-induced thermal hyperalgesia and mechanical allodynia in rats. Duloxetine (1–30 mg/kg, i.p.), a balanced serotonergic–noradrenergic reuptake inhibitor (SNRI), was equiefficacious and more potent than the SNRI venlafaxine (3–100 mg/kg, i.p.) in reversing both thermal hyperalgesia and mechanical allodynia induced by carrageenan. In addition, the selective noradrenergic reuptake inhibitors (NRIs) thionisoxetine (0.03–10 mg/kg, i.p.) and desipramine (1–30 mg/kg, i.p.) also produced complete reversals of carrageenan-induced thermal hyperalgesia. However, only thionisoxetine exhibited a greater than 80% reversal of the carrageenan-induced mechanical allodynia. In contrast, the selective serotonergic reuptake inhibitors (SSRIs) paroxetine, sertraline, and fluoxetine (0.3–10 mg/kg i.p.) had little or no effect in the carrageenan model. In order to understand whether the observed enhanced effectiveness of the dual SNRIs was due to a possible synergism between serotonergic and noradrenergic reuptake inhibition, the effects of the NRI thionisoxetine alone and in combination with an inactive dose of the SSRI fluoxetine were determined. In the presence of fluoxetine, the potency of thionisoxetine in reversing carrageenan-induced hyperalgesia and allodynia was significantly increased by approximately 100-fold and brain concentrations of thionisoxetine were increased by 1.1- to 5-fold. The present data indicate fluoxetine pharmacodynamically potentiated the analgesic effects of thionisoxetine over and above a metabolic interaction between these two drugs. The present findings thus indicate that, in the carrageenan model, dual serotonergic–noradrenergic reuptake inhibition by dual SNRIs, or SSRI–NRI combinations, produces synergistic analgesic efficacy.

Keywords: Duloxetine; Noradrenergic reuptake inhibition; Serotonergic reuptake inhibition; Mixed serotonergic–noradrenergic reuptake inhibition; Carrageenan test; Persistent pain

1. Introduction

Antidepressant drugs with serotonergic and/or noradrenergic reuptake inhibition activity are frequently used for the treatment of persistent pain associated with various clinical conditions including diabetic neuropathy (e.g., Max, 1995; Sindrup and Jensen, 1999; Rowbotham et al., 2004), postherpetic neuralgia (Kishore-Kumar et al., 1990), back injury (e.g., Atkinson et al., 1999), and fibromyalgia (e.g. Goldenberg et al., 1996). However, in comparison, selective serotonergic reuptake inhibitors appear to have marginal efficacy in reducing pain symptoms (Sindrup et al., 1990; Max, 1995; Atkinson et al., 1999). While persistent pain arises from multiple etiologies, it is commonly characterized by the phenomenon of central sensitization, an altered responsiveness of dorsal horn neurons and expansion of their receptive fields to afferent stimulation (Devor and Wall, 1978; Woolf et al., 1994), resulting in hyperalgesia (an increased sensitivity to noxious stimuli) and/or allodynia

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0028-3908/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2006.08.005

(a nocifensive response to previously non-noxious stimuli) (Woolf and Doubell, 1994). Under normal conditions, descending serotonergic and noradrenergic inhibitory neuronal pathways, projecting from regions of the brainstem to primary afferent fiber terminals in spinal cord, dorsal horn neurons, and inhibitory interneurons within the dorsal horn of the spinal cord, provide a supraspinal control on the spinal transmission of nociceptive information (Fields and Basbuam, 1994; Jones, 1991; Millan, 2002). However, under conditions of inflammation or nerve injury, dysfunction of descending serotonergic and noradrenergic inhibitory pathways appears to contribute to the initiation and propagation of central sensitization and subsequent development of persistent pain (Fields and Basbaum, 1994; Traub, 1997; Millan et al., 2002). One possible mechanism of action of antidepressants in the treatment of persistent pain is the enhancement of serotonergic and noradrenergic descending inhibition by the blockade of serotonergic and/or noradrenergic reuptake. To date, however, the relative contribution of noradrenergic and serotonergic reuptake inhibition required for effective analgesia remains uncertain.

Duloxetine, a dual serotonergic–noradrenergic reuptake inhibitor (SNRI), originally developed for the treatment of major depression (Detke et al., 2002, 2004), has also been demonstrated to be clinically efficacious in alleviating painful symptoms of fibromyalgia (Arnold et al., 2004) and painful diabetic neuropathy (Goldstein et al., 2005). In addition, duloxetine has been shown to be efficacious in the prevention and/or reversal of pain in several preclinical models of inflammatory and neuropathic pain in rodents. Iyengar et al. (2004) demonstrated that duloxetine significantly attenuated late phase paw-licking behavior in the formalin model and also reversed mechanical allodynia behavior in the L5/L6 spinal nerve ligation model of neuropathic pain. Moreover, in the formalin model, inactive doses of the NRI thionisoxetine were efficacious when combined with an inactive dose of the SSRI paroxetine. Similarly, Bomholt et al. (2005) demonstrated that duloxetine attenuated flinching behavior in the late phase of the formalin model and attenuated thermal and mechanical hyperalgesia, but not mechanical allodynia, in the chronic constriction injury model. We (Jones et al., 2005) have previously demonstrated that duloxetine was efficacious in the acetic acid-induced writhing test and reversed carrageenan-induced thermal hyperalgesia and mechanical allodynia as well as capsaicin-induced mechanical allodynia. Duloxetine was efficacious in these models at doses (1–30 mg/kg) that produced little or no effect on either acute nociception or motor output (Iyengar et al., 2004; Bomholt et al., 2005; Jones et al., 2005). Duloxetine also has little or no affinity for other neurotransmitter receptors, including H1 histamine, α1-adrenergic and muscarinic receptors, or ion channels (Wong et al., 1988, 1993; Fuller et al., 1994; Bymaster et al., 2001) which might produce dose-limiting side effects, such as sedation, orthostatic hypotension, and cardiac conduction abnormalities, observed with the tricyclic antidepressants desipramine and amitriptyline (Max, 1995).

In order to further pharmacologically characterize the underlying mechanisms of action of duloxetine in the treatment of persistent pain, we evaluated the effects of antidepressant drugs with varying affinities for serotonin and/or noradrenaline transporters (see Table 1) in reversing persistent inflammatory pain as ascertained by carrageenan-induced thermal hyperalgesia and mechanical allodynia. To this end, dose–response curves were determined for the dual transporter inhibitor duloxetine in comparison with another dual transporter inhibitor venlafaxine, with preferential selectivity for the serotonin transporter, in reversing both carrageenan-induced thermal hyperalgesia and mechanical allodynia. For comparison, dose–response curves were determined for the selective noradrenergic reuptake inhibitors (NRIs) desipramine and thionisoxetine, as well as the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline in reversing both carrageenan-induced thermal hyperalgesia and mechanical allodynia. In addition, to ascertain whether the mechanisms of serotonergic and noradrenergic reuptake inhibition act synergistically, the effects of the selective NRI thionisoxetine administered alone or concomitantly with the SSRI fluoxetine were evaluated. We hypothesized that if these two mechanisms

Table 1
Affinities (K_i, nM) of the antidepressant drugs tested in the present study for the serotonergic and noradrenergic transporters and the H1 histamine, α1-adrenergic, α2-adrenergic, and muscarinic (nonselective) receptors in rat brain tissue

Antidepressant	Monoamine transporters (K_i, nM)			Receptors (K_i, nM)				Clinical efficacy
	5-HT	NE	Ratio NE/5-HT	H1	α1	α2	Muscarinic	
Thionisoxetine	44.1[a]	0.2[a]	0.005	>1000[a]	>1000[a]	>1000[a]	>1000[a]	NA
Desipramine	129 ± 7[b]	0.31 ± 0.01[b]	0.002	31 ± 1[b]	23 ± 1[b]	1379 ± 39[b]	37 ± 1[b]	Yes[e]/SE
Duloxetine	0.8 ± 0.04[c]	7.5 ± 0.3[c]	9.38	2300[d]	8300[d]	8600[c]	3000[d]	Yes[f]
Venlafaxine	19 ± 1.7[b]	1067 ± 29[b]	56.16	12909 ± 1075[b]	39921 ± 810[b]	>100000[b]	29966 ± 1464[b]	Yes[e]
Fluoxetine	2 ± 0.1[b]	473 ± 11[b]	236.5	933 ± 23[b]	1353 ± 17[b]	3090 ± 121[b]	512 ± 12[b]	None[e]
Paroxetine	0.05 ± 0.0003[b]	59 ± 0.7[b]	1180	13746 ± 404[b]	995 ± 35[b]	3915 ± 114[b]	42 ± 2[b]	None[e]
Sertraline	0.29 ± 0.01[b]	1597 ± 44[b]	5506	5042 ± 165[b]	36 ± 2[b]	477 ± 17[b]	232 ± 1[b]	None[e]

SE, dose-limiting side effects; NA, not available.
[a] Gehlert et al., 1995; personal communication.
[b] Owens et al., 1997.
[c] Bymaster et al., 2001.
[d] Wong et al., 1988, 1993.
[e] See Max, 1995; Sindrup and Jensen, 1999; and text.
[f] Arnold et al., 2004; Goldstein et al., 2005.