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Research report

Possible involvement of oxido-nitrosative stress induced neuro-inflammatory cascade and monoaminergic pathway: Underpinning the correlation between nociceptive and depressive behaviour in a rodent model

Vipin Arora, Kanwaljit Chopra*

Professor of Pharmacology, Pharmacology Research Laboratory, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh 160014, Panjab, India

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ABSTRACT

Background: Pain and depression are frequent co-morbid disorders. The prevalence rate of depression is several times higher in patients with chronic pain than in the general population but the mechanism underlying this association is unknown. A combination of interactions between neurotransmitters, neuropeptides, oxidative and nitrosative stress and cytokines are thought to take part in pathogenesis of pain as well as depression. Thus, the aim of the present study was two-fold, first to investigate the interplay between nociception and associated depression and second to investigate the protective potential of berberine against the reserpine-induced nociceptive and depressive behaviour and further to explore the role of oxidative–nitrosative stress mediated inflammatory cascade and apoptotic signalling pathway in this dyad.

Methods and results: Nociception and associated depression were induced by administration of reserpine (1 mg/kg subcutaneous daily) for three consecutive days. This behavioural deficit was integrated with decrease in the biogenic amine (dopamine, norepinephrine and serotonin) levels along with increased substance P concentration, oxidative–nitrosative stress, inflammatory cytokines, NF-κβ and caspase-3 levels in different brain regions (cortex and hippocampus) of the reserpinised rats.

Limitation: More studies are still warranted in similar rodent models of pain and depression, so, that the present findings can be further substantiated to establish the clinical effectiveness of berberine in a subset of patients suffering from pain as well as depression.

Conclusion: The findings from the current study suggested that reserpine-induced neurochemical alterations and dysregulation of oxidative–nitrosative stress induced inflammatory cascade underlies the co-morbidity of nociceptive behaviour and associated depression in rats.

1. Introduction

The prevalence rate of depression is several times higher in patients with chronic pain than in the general population (Arnow et al., 2006; Gureje et al., 2008; Henningsen and Lowe, 2006; Lee et al., 2009; Ohayon and Schatzberg, 2010). Moreover, patients with physical pain are more likely to develop depression (Kroenke, 2003; Ohayon and Schatzberg, 2003) vis a vis depression is likewise a powerful predictor of pain (Bahk et al., 2011; Greco et al., 2004; Leuchter et al., 2010). The co-existence of depression and chronic pain is associated with immense negative consequence such as increased severity, poor treatment response and an increase in the incidence of treatment-resistant depression (Leuchter et al., 2010; Williams et al., 2004). Although this intricate relationship between pain and depression has attracted increasing attention in all areas of research, but the mechanisms underlying the association of depression and pain are, however, not clear (Dersh et al., 2002; Kim et al., 2012). A combination of interactions between neurotransmitters (Goldenberg, 2010; Stahl and Briley, 2004), neuropeptides (Kramer et al., 1998; Werner and Covenas, 2010), oxidative and nitrosative stress (Arora et al., 2011; Maes et al., 2011) and cytokines (Dowlati et al., 2010; Wallace, 2006) are thought to take part in pathogenesis of pain and the depression.

It is theorized that the additive effect of enhancing neurotransmission in three monoamine systems (serotonin, norepinephrine, and dopamine) may lead to improved efficacy and quicker onset of antidepressant response along with the relief of painful symptoms associated with depression (Guiard et al., 2009). Furthermore, both

* Corresponding author. Tel.: +91 172 2534105; fax: +91 172 2541142.
E-mail address: dr_chopra_k@yahoo.com (K. Chopra).

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conditions involve increased plasma and cerebrospinal fluid substance P (SP) concentrations (Larson et al., 2000). There are studies which showed that SP is co-localised with serotonin, norepinephrine and dopamine within the same neuron in the mammalian central nervous system (Chan-Palay et al., 1978; Hahn and Bannon, 1998; Hokfelt et al., 1987; Pelletier et al., 1981). This makes it pronominal to investigate the role of SP along with the biogenic amines, particularly because empirical data suggests that SP and biogenic amines are involved in both the etiopathogenesis and treatment response of pain and depression. The other facet of association between pain and depression is the involvement of oxidative and nitrosative stress. Human studies have reported a number of oxidative disturbances in patients with major depression as suggested by the elevated lipid peroxidation products, with reduced levels of superoxide dismutase (Herken et al., 2007; Sarandol et al., 2007). Moreover, a significant positive correlation was found between oxidative stress index and the Hamilton depression rating scale (Yanik et al., 2004). Similarly higher serum levels of pentosidine and malondialdehyde (a marker of lipid peroxidation) along with reduced serum superoxide dismutase were found in patients with chronic pain compared with normal controls (Bagis et al., 2005). Cordero et al. (2009) also found higher levels of ROS in mononuclear cells from fibromyalgia patients again suggesting enhanced oxidative stress. It was suggested that NF-κβ activity is regulated by the intensity of intracellular oxidative and nitrosative stress (Schreck and Baeuerle, 1994; Sen and Packer, 1996). NF-κβ in turn controls the regulation of genes encoding proteins involved in immune and inflammatory responses (cytokines, chemokines, growth factors, immune receptors, cellular ligands, and adhesion molecules). Depressed patients and patients with pain disorders often display enhanced cytokine levels including interleukin-6 (IL-6), C-reactive protein, interleukin-1-beta (IL-1β), and tumor necrosis factor alpha (TNF-α) (Omoigui, 2007; Raison et al., 2006). Cytokines that are released in response to an activation of inflammatory pathways can enter the brain and they may cause alterations of the metabolism of serotonin and dopamine (Raison et al., 2006). Thus the constellation of these studies shows an interrelationship between oxidative and nitrosative stress, increased levels of cytokines and altered levels of biogenic amine.

Reserpine is a monoamine depletor that exerts a blockade on the vesicular monoamine transporter for neuronal transmission or storage, promoting dopamine-autoxidation and oxidative catabolism by monoamine oxidase may resulting in oxidative stress (Lohr et al., 2003). This dual action of reserpine (monoamine depletion and oxidative stress) makes it an ideal agent to address the pain and associated depression in animals (Oe et al., 2010).

Berberine, a plant derived isoquinoline quaternary alkaloid (5,6-dihydrodibenzoquinolizinium derivative), widely used in Ayurvedic and Chinese medicine, occurs in plants of Ranunculaceae, Berberidaceae, and Papaveraceae families. Berberine has had several reported bioactivities, including anti-inflammatory (Kupeli et al., 2002), antioxidative (Rackova et al., 2004) and monoamine oxidase enzyme inhibitory activity (Kong et al., 2001). Berberine has also shown an antidepressant-like effect in two animal models of depression (Peng et al., 2007). Thus, the aim of the present study was two-fold, first to investigate the interplay between nociception and associated depression and second to investigate the protective potential of berberine against the reserpine-induced biogenic amine depletion and oxidative–nitrosative stress mediated inflammatory cascade and apoptotic signalling pathway in rats.

2. Materials and methods

Adult male Wistar rats (200–220 g) bred in Central Animal House facility of Panjab University were used. The animals were housed under standard laboratory conditions, maintained on a 12:12 h light: dark cycle and had free access to food (Ashirwad Industries, Mohali, India) and water. Animals were acclimatized to laboratory conditions before the tests. All experiments were carried out between 09:00 and 17:00 h. The experimental protocols were approved by the Institutional Animal Ethics Committee of Panjab University and performed in accordance with the guidelines of Committee for Control and Supervision of Experimentation on Animals, Government of India on animal experimentation.

2.1. Drugs

Reserpine and berberine were purchased from Sigma (St. Louis, MO, USA). TNF-α, IL-1β and SP ELISA kit was purchased from R&D Systems (USA). While NF-κβ and caspase-3 ELISA kits were procured from Imegenex, San Diego, USA and Biovision, USA, respectively. All other chemicals used for biochemical estimations were of analytical grade.

2.2. Experimental design

2.2.1. Time-course measurements of thermal hyperalgesia, mechanical hyperalgesia, mechanical allodynia and immobility time (standardization of dose of reserpine)

Baseline tail withdrawal, muscle pressure and tactile response thresholds were measured in rats just before the first injection of reserpine. The rats were then divided into four groups, based on the dose of reserpine. Each group of rats received subcutaneously injection of reserpine at a dose of 0 (vehicle), 0.5, 1, or 2 mg/kg for three days ($n=5$ each group). The mechanical hyperalgesia and mechanical allodynia thresholds were again measured on 1–5, 7 and 10th day in reserpinised rats. All measurements were taken by a single person in a blind manner with regard to the dose of reserpine. After assessing the tail withdrawal, muscle pressure and tactile response thresholds in the reserpinised rats, the separate group was used to assess the immobility time in the reserpinised rats at the selected time point (5th day) to establish the correlation between pain and depression (Fig. 1).

2.2.2. Effect of berberine treatment on reserpine-induced decreases in pain thresholds and immobility time

Nociception and associated depression was induced by administration of reserpine (1 mg/kg subcutaneous daily) for three consecutive days. The animals were randomly divided into seven experimental groups. Group I comprised control animals ($n=5$); Group II animals ($n=5$) were administered reserpine (1 mg/kg; subcutaneously) for three consecutive days (i.e. day 1–3); Group III–V ($n=5$ each group) consisted of reserpinised rats receiving berberine (5, 10 and 20 mg/kg; ip) for 5 days; Group VI is per se group consisted of control animals ($n=5$) receiving berberine (20 mg/kg; ip) and Group VII consisted reserpinised rats ($n=5$) receiving the standard drug duloxetine (30 mg/kg; po). Dose of berberine was selected on the basis of previous studies stating CNS effects of berberine (Kulkarni and Dhir, 2007, 2008). Hyperalgesia (thermal and mechanical) and allodynia were assessed 48 h after the last reserpine injection. After behavioural assessment, rats were killed under deep anaesthesia and different brain regions were isolated and stored at −80 °C for biochemical, neurochemical and molecular estimations.

2.2.3. Thermal hyperalgesia (tail immersion test)

Rat's tail was immersed in a water bath maintained at 42 °C (a temperature that is normally innocuous in naive rats until tail withdrawal or signs of struggle were observed (cut-off time: 15 s). As this test involves handling of the animals, one day before the