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Full Length Article

Modulatory effect of cilostazol on tramadol-induced behavioral and neurochemical alterations in rats challenged across the forced swim despair test

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ABSTRACT

Pain-associated depression is encountered clinically in some cases such as cancer, chronic neuropathy, and after operations. Tramadol is an opioid analgesic drug that may modulate monoaminergic neurotransmission by inhibition of noradrenaline and serotonin reuptake that may contribute to its antidepressant-like effects. Clinically, tramadol is used either alone or in combination with other NSAIDs in the treatment of cases associated with pain and depression, e.g. low back pain, spinal cord injury, and post-operative pain management. However, tramadol monotherapy as an antidepressant is impeded by severe adverse effects including seizures and serotonin syndrome. Interestingly, phosphodiesterase-III inhibitors demonstrated novel promising antidepressant effects. Among which, cilostazol was reported to attenuate depression in post-stroke cases, geriatrics and patients undergoing carotid artery stenting. Therefore, this study was carried out to investigate the possible antidepressant-like effects of tramadol and/or cilostazol on the behavioral level in experimental animals, and to examine the neurochemical and biochemical effects of tramadol, cilostazol and their combination in rats, in order to explore the probable mechanisms of action underlying their effects. To achieve our target, male albino mice and rats were randomly allocated into five groups and administered either vehicle for control, fluoxetine (20 mg/kg, p.o.), tramadol HCl (20 mg/kg, p.o.), cilostazol (100 mg/kg, p.o.), or combination of both tramadol and cilostazol. At day 14, mice and rats were challenged in the tail suspension test and forced swim test, respectively. Rats were sacrificed and brains were isolated for determination of brain

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monoamines, MDA, NO, SOD, and TNF-α. The current results showed that concurrent administration of cilostazol to tramadol-treated animals modulated depression on the behavioral level, and showed ameliorative neurochemical and biochemical effects in rats exposed to FST.

1. Introduction

Pain-associated depression is encountered clinically in some cases such as cancer, chronic neuropathy, and after operations (Arbaiza and Vidal, 2007; Attal et al., 2009; Dogar and Khan, 2016). Moreover, patients with cardiovascular diseases such as myocardial infarction are at increased risk of developing depression. The latter is associated with an approximately two-fold increase in cardiac morbidity and mortality (Frasure-Smith et al., 2009; Lett et al., 2004). Forced swim despair test (FST) is an established experimental protocol to induce stress-related depression in laboratory rodents (Barros and Ferigolo, 1998). Stress has been regarded as the most important pathogenic factor in several neuropsychiatric disorders including depression due to its association with several biochemical, hormonal, and behavioral changes (García-Bueno et al., 2008).

Tramadol is a synthetic, centrally acting analgesic agent, which acts as an opioid agonist (Gibson, 1996). Tramadol may also affect monoaminergic systems by inhibiting the reuptake of noradrenaline and serotonin in a mechanism similar to that of antidepressant drugs (Bamigbade et al., 1997). Moreover, it was previously demonstrated that drugs that affect the opioidergic system might show antidepressant effects (Perlikowska et al., 2014). Experimentally, tramadol has shown promising antidepressant effects (Rojas-Corrales et al., 1998). Clinically, tramadol is used either alone or in combination with other NSAIDs in the treatment of cases associated with pain and depression, e.g. low back pain, spinal cord injury, and post-operative pain management (Dogar and Khan, 2016; Tetsunaga et al., 2015). However, tramadol monotherapy as an antidepressant or in combination with other traditional antidepressant drugs resulted in severe adverse effects such as seizures and serotonin syndrome (Boyd, 2005; Sansone and Sansone, 2009). Moreover, long-term use of tramadol developed psychological and physical dependence similar to that of other opiates (Ripamonti et al., 2004).

Cilostazol, on the other hand, is a selective phosphodiesterase-III inhibitor that is therapeutically implicated in the treatment of intermittent claudication. It suppresses platelet aggregation and causes direct arterial vasodilation (Cariski and Lindmayer, 2002). On the experimental level, cilostazol has shown neuroprotective and memory enhancement effects (Yanai et al., 2014; Yoneyama et al., 2015). Interestingly, some clinical studies have shown promising effects of cilostazol in the treatment of geriatric and post-stroke depression cases (Baba et al., 2007; Nishimura et al., 2007). In addition, cilostazol alleviated pre-procedural depression in patients undergoing carotid artery stenting (Tsutsumi et al., 2013). However, up to our knowledge, the effect of cilostazol on brain monoamines balance and depression-induced biochemical alterations has not been studied before.

Therefore, the current study was carried out to investigate the possible antidepressant-like effects of tramadol and/or cilostazol on the behavioral level in experimental animals and to explore the underlying neurochemical and biochemical influences.

2. Materials and methods

2.1. *Animals*

Adult male Swiss albino mice (20–25g) and Wistar albino rats (180–200 g) were used in this study. They were housed in plastic cages under standardized conditions (23 ± 2 °C, 12 h light/ 12 h dark cycle) and were allowed free access to water and standard chow pellets. Animals were left to acclimatize for one week before the experiment. Experiments were performed during the light phase of the cycle, and all procedures were approved by the Ethics Committee of the National Research Centre and in accordance with the international recommendations of the Canadian Council on Animal Care Guidelines (1984) for the proper care and use of laboratory animals.

2.2. *Chemicals*

Fluoxetine was obtained from the Egyptian International Pharmaceutical Industry Co. (EIPICO), Egypt. Tramadol HCl was a gift from October Pharma, Egypt. Cilostazol was obtained from Otsuka Pharmaceutical Co., Japan. All other chemicals were of analytical grade.

2.3. *Experimental design*

Rats or mice were randomly distributed into five groups with 12 animals each. Animals of the control group were daily administered the drug vehicle (7% Tween 80 in normal saline) by oral gavage. Fluoxetine, tramadol, and cilostazol groups were administered fluoxetine (20 mg/kg/day, p.o.), tramadol HCl (20 mg/kg/day, p.o.), and cilostazol (100 mg/kg/day, p.o.), respectively (Ghorpade et al., 2011; Jesse et al., 2008; Yanai et al., 2014). Rats or mice of the last group were treated daily with both tramadol and cilostazol. Treatments were continued for 14 successive days. At day 13, rats were exposed to FST pretest, while on day 14, rats were challenged across the forced swim test (FST) and mice were exposed to tail suspension test (TST), then all animals were sacrificed after 60 min by decapitation. Brains were rapidly isolated on ice and immediately stored at –80 °C until biochemical assays were performed.