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Anti-pruritic activity of pioglitazone on serotonin-induced scratching in mice: Possible involvement of PPAR-gamma receptor and nitric oxide

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ABSTRACT

Pioglitazone is a member of peroxisome proliferator-activated receptor gamma (PPARγ) agonists, particularly used in management of type II diabetes. However it also has effects in some dermatological disorders. The current study was designed to investigate the effects of oral administration of pioglitazone and the association of nitric oxide, in serotonin-induced scratching in mice. In order to produce the scratching activity, serotonin (141 nm/site) was administered intradermally in the nape of the neck. Pioglitazone in concentrations of 10, 20, 40 and 80 mg/kg, was peroral administered (p.o) as a single dose, 4 h before the serotonin injection. PPAR-γ antagonist, GW9662 (2 mg/kg, i.p); a non-specific nitric oxide synthase (NOS) inhibitor, NG-nitro-L-arginine methyl ester (L-NAME; 1 mg/kg, i.p); or a nitric oxide precursor, L-arginine (100 mg/kg, i.p.); adminstrated 15 min before pioglitazone were analyzed for anti-scratching activity. Results obtained showed that pioglitazone (40 and 80 mg/kg, p.o) reduced the scratching in a dose-dependent manner. GW9662 inverted the anti-scratching effect of pioglitazone (80 mg/kg). Acute dose of L-NAME (1 mg/kg, i.p) also prevented the anti-scratching property of pioglitazone (80 mg/kg, p.o); although L-arginine was used in sub-effective dose (100 mg/kg, i.p), however it potentiated the anti-scratching behavior when co-injected with pioglitazone (20 mg/kg, p.o). The results indicate that acute pioglitazone has an anti-scratching effect on serotonin-induced scratching in mice. It is concluded that anti-scratching outcome of acute pioglitazone is initiated via activation of PPAR-γ receptor and to some extent by the NO pathway.

1. Introduction

Pruritus (itch) is an unpleasant cutaneous sensation usually coupled by instant craving to scratch. It may be either due to primary skin diseases, or a dermatological manifestation of some underlying systemic disease (Stander et al., 2007). Pruritus may also be observed during inflammatory process, metabolic diseases, malignancies, infectious process, psychiatric disorders, drug use and stress (Steinhoff et al., 2006).

Peroxisome proliferator activated receptors (PPARs) are the ligand-stimulated transcription factors which have been classified as α, δ/ β and γ (Berger and Moller, 2002; Chinetti et al., 2000). Following activation, PPARs regulate widespread biological processes, many of which are crucial for the skin e.g. lipid storage and lipocyte differentiation (Boyd, 2007; Friedmann et al., 2005).

However some prior studies have shown that Thiazolidinediones (TZDs) as a potent exogenous PPARγ agonists (Bell-Parikh et al., 2003; Berger et al., 2005) with these own constellation of pharmacological properties are effective in patients with dermatological disorders such as; lipodystrophy, melanoma, necrobiosis lipoidica, hirsutism, angiosarcoma and other soft-tissue sarcomas (Boyd, 2007). Various clinical studies reported the beneficial effects of PPAR-γ agonists on pruritus in a variety of dermatological disorders (Ellis et al., 2000; Pershadsingh et al., 1998; Sepmeyer et al., 2007). But due to lack of strong experimental evidence, further investigation is needed to elucidate the role of PPAR-γ agonists in pruritus.

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