Possible Involvement of Nitric Oxide Pathway in Anti - Scratching Activity of Metformin on Chloroquine - Induced Scratching in Mice

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ABSTRACT

Chloroquine (CQ), a 4-aminoquinoline drug, has long been used in the treatment and prevention of malaria. However its side effect generalized pruritus contributes to treatment failures, and consequently results in the development of chloroquine resistant strains of Plasmodium falciparum. It was proposed that the administration of CQ correlated with increase in nitric oxide (NO) production. Metformin is among the first-line treatments for management of the type 2 diabetes and avoiding its vascular problems .It was showed that metformin has a modulatory effect on NO production and also in itch .The current study was designed to investigate the effects of intraperitoneal (i.p.) administration of metformin and the association of nitric oxide, in chloroquine (CQ)-induced scratching in mice. Scratching behaviors were recorded by a camera after intradermal (i.d.) injection of CQ (200 and 400 µg/site). CQ was administrated at doses of 200 µg/site and 400 µg/site. Metformin in concentrations of 5 10, 100 and 200 mg/kg, was administered (i.p.) as a single dose, 4 h before the CQ injection .A non-specific nitric oxide synthase (NOS) inhibitor, NG-nitro-L-arginine methyl ester (L-NAME; 1 and 10 mg/kg, i.p); or a nitric oxide precursor, L-arginine (10 and 100 mg/kg, i.p.); administrated 30 min before CQ-injection. Also a neural NOS inhibitor, 7-nitroinidazole (7NI; 1 and 10 nmol/site, i.d.) simultaneously administrated with 400 µg/site of CQ. For evaluation the role of NO in anti-scratching effect of metformin we administrated L-NAME at dose of 1 mg/kg (i.p.) 30 min before CQ injection or 7-NI at dose of 1 nmol/site (i.d.) simultaneously with CQ in metformin-treated (5mg/kg, i.p.) mice. Also l-arginine at dose of (10 mg/kg, i.p.) was administrated 30 min before CQ injection in metformin-treated (200 mg/kg, i.p.).The results obtained show that CQ elicited scratching at dose of 400 µg/site. Metformin (100 and 200 mg/kg, i.p.) reduced the

scratching in a dose-dependent manner. Injection of L-NAME or 7-NI enhanced the anti-scratching effect of metformin significantly. On the other hand, administration of L-arginine as a precursor of NO significantly inhibited this effect of metformin. The results indicate that acute metformin has an anti-scratching effect on CQ-induced scratching in mice. It is concluded that anti-scratching outcome of acute metformin is initiated via inhibition of the NO pathway.

Keywords: Scratching, Chloroquine, Nitric Oxide, Metformin, Mice