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PHARMACOLOGICAL EFFECTS OF NOVEL QUINOLINEDIONE COMPOUNDS ON INHIBITION OF DRUG-INDUCED RELAXATION OF RAT AORTA AND THEIR PUTATIVE ACTION MECHANISM

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Two 6-(fluorinated-phenylamino)-5,8-quinolinedione derivatives, OQ21 and OQ1, were newly synthesized as potent inhibitors of endothelial-dependent vasorelaxation. The purpose of the present study was to investigate the effect of OQ21 and OQ1 on different types of vasorelaxation and to pursue their action mechanisms. For acetylcholine both compounds, at a low concentration (0.1 μM), reduced the maximal response with increase of EC_{50} values. Especially OQ21 showed a more potent and efficacious inhibitory effect on acetylcholine-induced relaxation of rat aorta than that of LY83583 (6-anilino-5,8-quinolinedione). Relatively high concnetration (1 μM) of OQ21 and OQ1 inhibited the sodium nitroprusside- induced relaxation of endothelium-denuded ring, producing rightward shifts of the curve for sodium nitoprusside without altering the maximal response. They also prevented acetylcholine and sodium nitroprusside-induced elevations of cyclic GMP. In addition, OQ21 and OQ1 (1 μM) significantly decreased (52-72%) the sensitivity of L-arginine-induced relaxation of precontracted endothelium-denuded aortic rings from lipopolysaccaride-treated (20 mg/kg, i.p.) rats. The inhibitory effect of OQ21 on endothelium-dependent vasodilation was enhanced by N^G-nitro-L-arginine which inhibits nitric oxide synthase (NOS) by binding oxygenase domain of the enzyme, but not by diphenylendiodonium which inhibits NOS by binding to reductase domain of the enzyme. Treatment of platelets with OQ21 or OQ1 showed a significant induction of oxygen consumption which was prevented by adding superoxide dismutase and catalase, whereas it showed lacks of depletion of glutathione (GSH) and protein thiols contrary to the significant depletion by menadione. This result suggests that superoxide generation might be involved in action mechanism for OQ21, but arylation would not. Present results indicate that OQ21 potently inhibit endothelial NOS by possibly interacting to reductase domain of the enzyme which leads to induce superoxide formation. The new quinone compounds, OQ21 and OQ1, inhibit not only endothelium-dependent vasorelaxation but also endothelium- independent relaxation induced by exogenous NO generated from a nitrovasodilator via the reduction of cyclic GMP. They also reduced L-arginine-induced vasorelaxation in endotoxin-treated rats, indicating their possession of inhibitory effect on inducible NOS.