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PPARα-dependent and independent signaling process in clofibrate-mediated increased in nitric oxide

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Clofibrate (CF), a prototype peroxisome proliferator activated receptor α (PPARα) ligand has been shown to increase Nitric Oxide (NO) production in the kidney. It is not clear how induction of PPARα transcriptionally regulates Nitric Oxide Synthase (NOS) activity or whether it is a PPARα independent process. In this study we examined the involvement of different signaling pathways in clofibrate-mediated increase in NO production using PPARα Knockout (KO) mice. Real time NO production was determined in renal Proximal Tubular (PT) suspensions isolated from KO and Wild Type (WT) mice challenged with CF (2 αM) using NO specific fluorescence dye DAF-FM2 in the presence of PKC or PKA inhibitors. WT and KO mice were also treated with CF (250 mg/kg; i.p, 7 days) and whole kidney homogenate was used for protein expression. Basal NO production in the PT was significantly lower in PPARα KO mice (21±2%). CF enhanced NO production in both WT (88±12%) and KO (86±6%) mice that was abolished by L-NAME (3αM). PKA 14-22 (20 αM), a PKA inhibitor, reduced CF-mediated NO production (WT: 56±5%; KO: 46±2%). Similarly, chelerythrine (3 αM), a PKC inhibitor, reduced NO production (WT: 47±4%; KO: 45±2%). CF increased eNOS and iNOS mRNA and iNOS protein expression in the KO but not in WT mice and did not affect PKC or PKA protein expression. These data suggest that CF increased NO production by inducing iNOS gene via a PPARα-independent mechanism. We suggest that PKC/PKA signaling pathways are equally required for CF-mediated enhanced acute NO production irrespective of PPARα.

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