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Role of Adrenoceptor Signaling in PPARα Regulation

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SUMMARY

PPARα holds a fundamental role in lipid homeostasis by directly regulating genes involved in fatty acid uptake, β- and ω-oxidation. It is worthy of note that PPARα agonists are effective in raising HDL-cholesterol and reducing triglycerides, properties that prevent atherosclerosis and reduce the risk for cardiovascular diseases. This study investigated the role of adrenoceptor signaling in PPARα regulation using wild type and humanized PPARα mice treated with either phenylephrine hydrochloride (2 mg/kg i.p., α_1-agonist) or isoprenaline hydrochloride (2 mg/kg, i.p., β1/2-agonist). Dexmedetomidine hydrochloride (5 μg/kg, s.c.) was used for α2-adrenergic receptor stimulation. The data of this study showed that adrenergic receptors (ARs), major components of the stress system and targets of various drugs, used in the treatment of cardiovascular diseases hold key roles in PPARα regulation. In particular, stimulation of α1-ARs with phenylephrine and beta-ARs with isoprenaline was followed by a significant up-regulation of PPARα and target genes, including ACOX, ACOT-1, ACOT-4, cyp4α10 and cyp4α14 that regulate the metabolism of fatty acids. *In vitro* studies using primary hepatocyte cultures treated with AR-agonists confirmed the involvement of hepatic AR-signaling in PPARα regulation. Overall, the data of this study set the basis of a better understanding the complex physiopathological states related to lipid disturbances and potentially introduce innovative therapeutic approaches.