Anotace v anglickém jazyce:

Thesis abstract:

Background and aims: Both obesity and metabolic syndrome form severe health problems in the whole world. Nevertheless the armament of pharmacotherapy for both diseases remains unsatisfactory. We aimed our work to main organs in risk of the mentioned diseases –liver and visceral fat using hepatocytes and visceral adipocytes as model. We detected 3 main metabolic and signalization activities- glycogenolysis, Nitric oxide (NO) production and transcription of inducible NO synthase (iNOS) in hepatocytes, lipolysis, NO production and iNOS transcription rate in adipocytes. We directed our interest to combination of peroxisome proliferation activator receptor γ (PPARγ) agonist, antagonist and β_3 adrenergic agonist in the culture of epididymal rat adipocytes in the first part of our work. While in the second part we investigated the influence of β and α adrenergic mimetics, adrenergic blockers in the culture of rat high glycogen content hepatocytes.

Methods: NO production was detected under the active agents treatments by detection of NO oxidative products NO2 and NO3 in media. Glycogenolysis was measured as free glucose rise released by hepatocytes into the media. NOS transcription level was extrapolated after comparative polymerase chain reaction with reverse transcription and either after quantitative real time RT-PCR. Lipolysis was calculated after free glycerol released to media in adipocyte culture.

Results: Troglitazone as PPARγ agonist attenuated partially lipolysis triggered by β_3 agonist BRL-37344 and blocked the triggered NO synthesis in rat isolated adipocytes. Addition of PPARγ antagonist SR-202 brought no blocking effect on troglitazone activity. That fact offered an alternative hypothesis of nonPPARγ effect of troglitazone to us. The blockade of troglitazone action on β_3 adrenergic triggered lipolysis and NO production could be seen not earlier than after addition of AMPK (adenosine monophosphate protein kinase) blocker- Compound C. The level of iNOS detected by RT-PCR imitated the NO level measured in adipocyte culture media. Both Epinephrine and Phenylephrine caused increase in rate of glycogenolysis and NO production in the culture of glycogen rich hepatocytes but the effect could be blocked by prazocin – α adrenergic blocker only despite no blockade detected after - propranolol - β adrenergic blocker . Upward trend of glycogenolysis could be seen even after SNAP as NO donor while downward trend was detected after L-NAME or aminoguanidine- known NOS blockers. Similar effect to adrerergicaly stimulated glycogenolysis and NO production could be seen after stimulation of glycogenolysis and NO prodution by glucagon.

Conclusion: The supposed non PPARγ dependent and AMPK dependent effect of troglitazone on lipolysis and NO production in visceral adipocytes ascertained by us could help in invention of more selective compounds from the same group of glitazones without common adverse effect on weight gain in patients. The detected α adrenergic mechanism of catecholamine induced glycogenolysis could help to prolong atiglycogenolytic effect of several newly invented glucagon receptor blockers by effective adrenergic blockade. The investigation of NO signaling effect in both adipocytes and hepatocytes could help to clarify oxidative/reductive signalization and alternatively help in finding out vasodilatation effect of newly invented drugs for treatment obesity and metabolic syndrome.