RAXOFELAST, A NOVEL DUAL VITAMIN E-LIKE ANTIOXIDANT, INHIBITS ACTIVATION OF NUCLEAR FACTOR-KAPPAB AND REDUCES CERULEIN-INDUCED ACUTE PANCREATITIS

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Reactive oxygen radicals, nitric oxide, cytokines (IL-1, IL-6, TNF-a) and adhesion molecules have been implicated in cerulein-induced pancreatitis[1]. Furthermore oxidative stress has been shown to activate the transcription factor nuclear factor kappaB (NF-kB), a cytoplasmatic messenger able to turn on several inflammatory genes[2]. We investigated whether lipid peroxidation inhibition might reduce NF-kB activation and the inflammatory response in cerulein-induced pancreatitis.
Male Sprague-Dawley rats (230-250 g body weight) received administration of cerulein (80 µg/kg/sc in four injections at hourly intervals). A control group received four s.c. injections of 0.9% saline at hourly intervals. All these rats were sacrificed 2h after the last injection.
Raxofelast administration, an inhibitor of lipid peroxidation[3] (20 mg/kg/ip administrated with cerulein) significantly reduced malonildialdehyde (MDA) levels, an index of lipid peroxidation (CER+DMSO = 3.075±0.54 µmol/g; CER+IRFI = 0.693±0.18 µmol/g; $p<0.001$), decreased myeloperoxidase (MPO) activity (CER+DMSO = 22.2±0.54 mU/g; CER+IRFI = 9.07±2.056 mU/g; $p<0.01$), increased glutathione levels (GSH) (CER+DMSO = 5.21±1.79 µmol/g; CER+IRFI = 15.71±4.14 µmol/g; $p<0.001$) and reduced acinar cell damage studied by the means of serum levels of both amilase (CER+DMSO = 4063±707.9 U/L; CER+IRFI = 1198±214.4 U/L; $p<0.001$) and lipase (CER+DMSO = 1654±530 U/L; CER+IRFI = 386±218.2 U/L; $p<0.001$) .Furthermore, treatment with Raxofelast significantly reduced NF-kB activation and the TNF-a m-RNA levels and tissue content of mature protein.
Our data demonstrated that lipid peroxidation plays a pivotal role to trigger inflammatory cascade and raxofelast could be considered a potential therapy to prevent the severe damage in acute pancreatitis.

References

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