

# Novel peripheral role of Nurr-1/GDNF/AKT trajectory in carvedilol and/or morin hydrate hepatoprotective effect in a model of hepatic ischemia/ reperfusion

Hanan Salah ,Nermein F El Sayed, Dalaal M Abdallah, Azza S Awad, Kawkab A Ahmed

## Abstract

Although the central role of Nurr-1/GDNF has been reviewed amply, scarce data are available on their peripheral impact. Carvedilol and morin hydrate have previously conferred their hepatic anti-fibrotic action.

**Aim:** Thus, our aim was to unveil the potential hepatoprotective role of carvedilol (CR) and/or morin hydrate (MH) using a hepatic 70% partial warm ischemia/reperfusion (I/R) rat model.

**Main method:** Rats were allocated into sham-operated, hepatic I/R, and I/R preceded by oral administration of CR (10 and 30 mg/kg; CR10/CR30), MH (30 mg/kg), or CR10 + MH for one week.

**Key findings:** On the molecular level, pretreatment with CR and/or MH increased the hepatic contents of Nurr-1, GDNF, and the protein expression of active/p-AKT. On the other hand, they inactivated GSK3 $\beta$  and NF- $\kappa$ B to increase the antioxidant enzymes (GPx, SOD, CAT). All regimens also enhanced the autophagy/lysosomal function and boosted the protein expression of beclin-1, LC3II, and TFEB.

Moreover, their antiapoptotic effect was signified by increasing the anti-apoptotic molecule Bcl2 and inhibiting Bax, Bax/Bcl2 ratio, and caspase-3, effects that were confirmed by the TUNEL assay. These improvements were reflected on liver function, as they decreased serum aminotransferases and liver structural alterations induced by I/R. Despite its mild impact, CR10 showed marked improvements when combined with MH; this synergistic interaction overrides the effect of either regimen alone.

**Significance:** In conclusion, CR, MH, and especially the combination regimen, conferred hepatoprotection against I/R via activating the Nurr-1/GDNF/AKT trajectory to induce autophagy/lysosomal biogenesis, inhibit GSK3 $\beta$  /NF- $\kappa$ B hub and apoptosis, and amend redox balance.

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