Signaling mechanisms of water soluble curcumin derivative in diabetic cardiovascular complications



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Diabetic Cardiomyopathy

***CARDIOMYOCYTE HYPERTROPHY** with subsequent apoptosis and focal myocardial fibrosis are structural hallmarks of diabetic cardiomyopathy and functionally manifest as defective cardiac contractility.*

Diabetic Cardiomyopathy

- ***Oxidative stress***
- **DM may lead to myocardial hypertrophy in association with an up-regulation of vasoactive factors such as endothelin-1 and activation of redox-sensitive transcription factors such as NF-κB and activating protein-1**

Diabetic Cardiomyopathy

Transcription factors are regulated by transcriptional co-activators, especially those containing histone acetyltransferase (HAT) activity

p300 is the best known of such proteins.

P300 and MEF2

p300 plays an important role in regulating myocyte enhancer factor 2 (MEF2)

P300 and MEF2

- ***MEF2 (MEF2A and MEF2C) are important transcription factors in myocyte hypertrophy and is involved in mediating the hypertrophic action of glucose on cardiomyocytes***
- **MEF2 controls the expression of many fetal cardiac genes.**

P300 and MEF2

- **The normal adult heart has no MEF2-dependent gene expression .**
- **However, MEF2 gene expression is activated in cardiac hypertrophy.**
- **Blockade of MEF2-dependent gene expression completely inhibits cardiac hypertrophy caused by a variety of prohypertrophic stimuli**

P300 and MEF2

Association of MEF2 with HATs, like p300, leading to the transcription of effector genes.

P300 and Curcumin

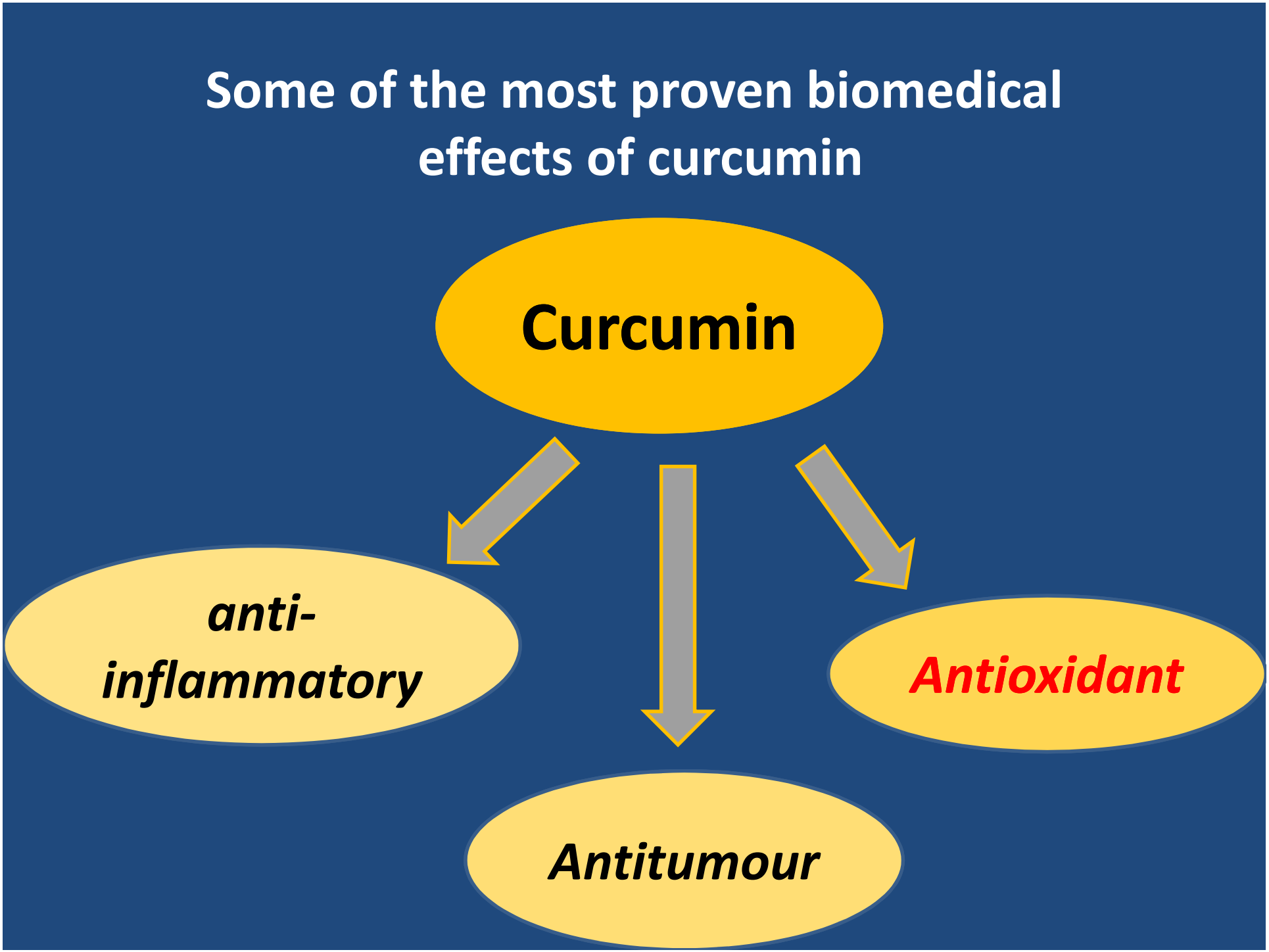
Curcumin has been reported to be an inhibitor of p300-HAT therefore; it may possess an effect in the prevention of cardiac hypertrophy and heart failure.

Curcumin

- **Diferuloylmethane.**
- **It is a nutraceutical widely used in ayurvedic medicine**



Some of the most proven biomedical effects of curcumin



Curcumin

Can protect against oxidative stress and induce heme oxygenase-1 (HO-1) expression, which exerts cytoprotective effects in mouse pancreatic beta-cells *(Pugazhenthi et al., 2007).*

Curcumin and DM

- **Curcumin exhibits therapeutic actions in DM**
- ***Abdel Aziz et al., 2010* reported that insulin secretion, HO-1 gene expression and HO activity were *significantly increased* when rat isolated islets of Langerhans were incubated with curcumin**

Curcumin and DM

- **This increase in insulin secretion was inhibited with stannous mesoporphyrin (SnMP), a HO-1 inhibitor .**

- **This suggests that the action of curcumin on insulin secretion may be, in part, mediated through increased HO-1 gene expression**

- However, the systemic bioavailability of orally administered curcumin is relatively low in human.
- Oral administration of 500 mg/kg B.Wt. showed that curcumin was present in plasma at levels near its detection limit of 1.5 µg/ml.

Several water-soluble curcumin derivatives were prepared to achieve clinically efficient systemic bioavailability however, most of them were made through bonds involving the curcumin natural functional groups

Our novel curcumin derivative (NCD) was developed through covalent modification of the curcumin molecule on sites remote from its natural functional groups *(Rezq et al., 2010).*

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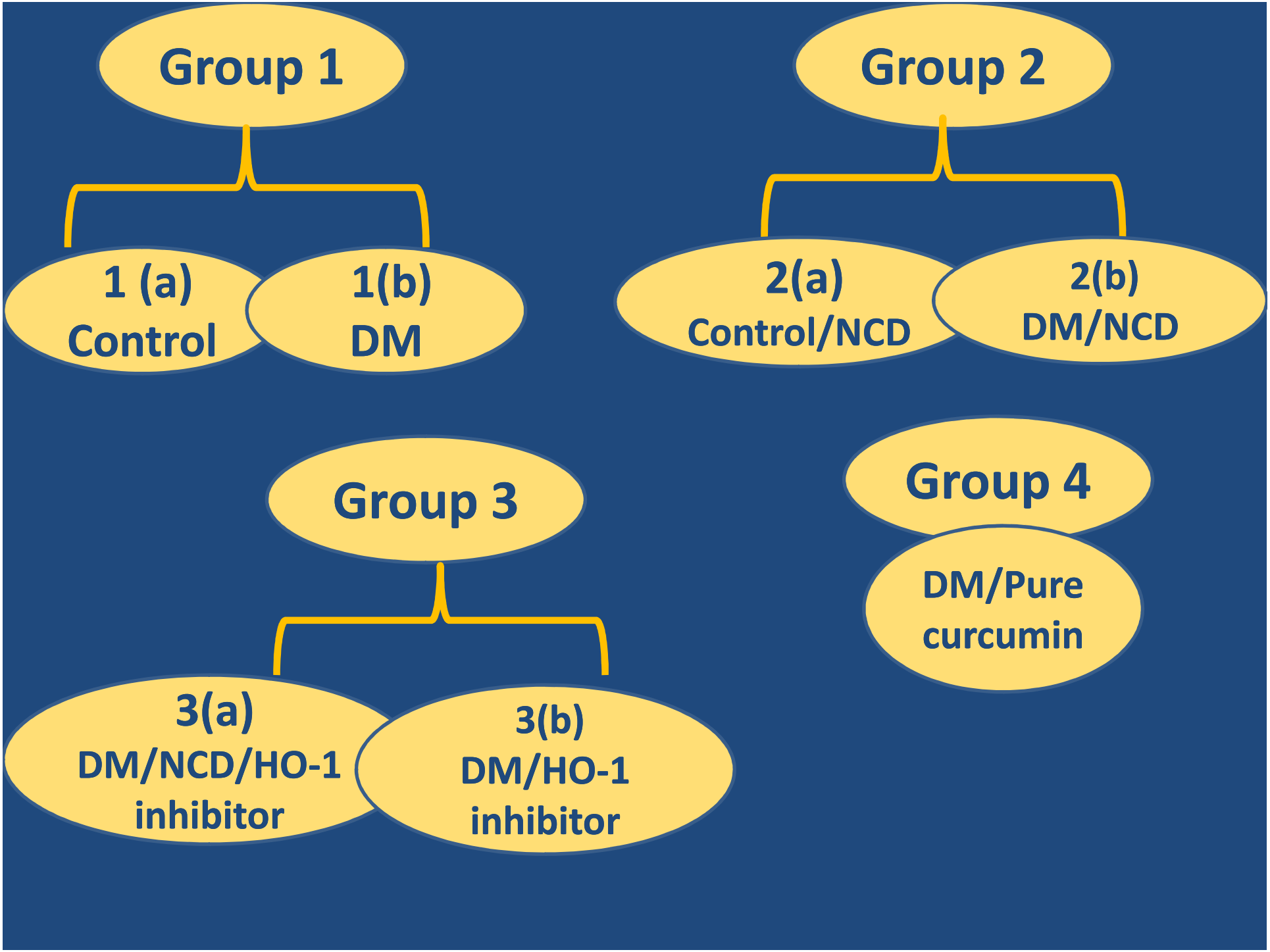
Indian National Phase Patent Pending.

Aim of the Work

Comparative evaluation of the effect of natural curcumin and the NCD (3% curcumin content) on signaling mechanisms involved in Diabetic Cardiomyopathy and whether their action is mediated via inducible HO-1.

Materials and Methods

- **One hundred forty inbred colony (Curl: HEL1) female rats were included in this study.**
- **They were divided equally into the following groups (20 rats/ group):**


Group 1
1 (a)
Control
1(b)
DM
Group 2
2(a)
Control/NCD
2(b)
DM/NCD
Group 3
3(a)
DM/NCD/HO-1
inhibitor
3(b)
DM/HO-1
inhibitor
Group 4
DM/Pure
curcumin

Materials and Methods

Six animals from each group were used to study some cardiac physiologic parameters such as:

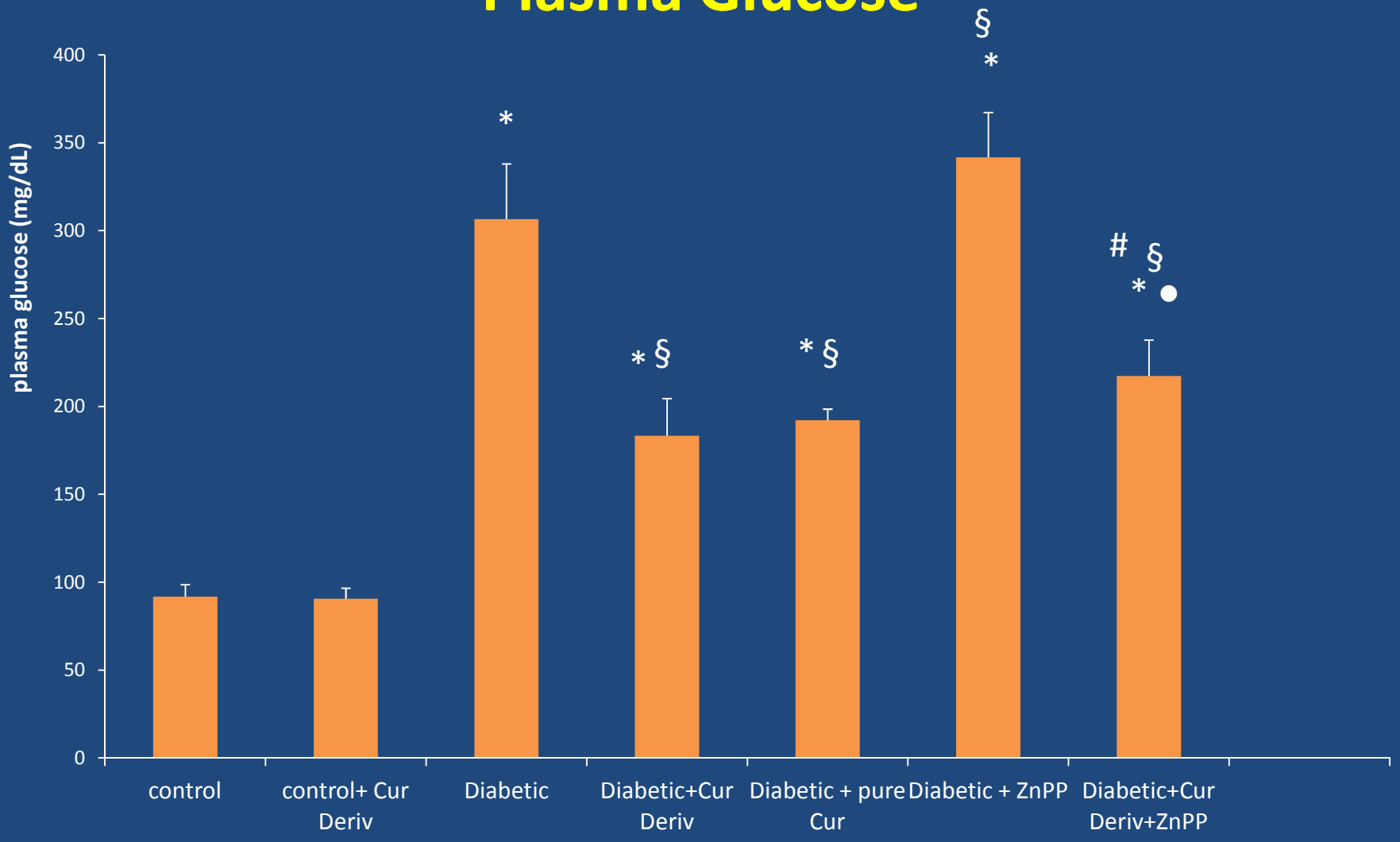
- *LT ventricular developed pressure*
- *LT ventricular delta pressure/ delta time (contractility index).*
- *Systolic blood pressure.*
- *Heart rate.*

The following biochemical parameters were assessed :

- *Blood glucose*
- *Glycated Hb.(Hb A_{1c})*
- *Plasma Insulin level*
- *HO-1 enzymatic activity and gene expression in cardiac and pancreatic tissues.*
- *Gene expression of p300 and molecular markers of cardiac hypertrophy: ANP, MEF2A, and MEF2C*

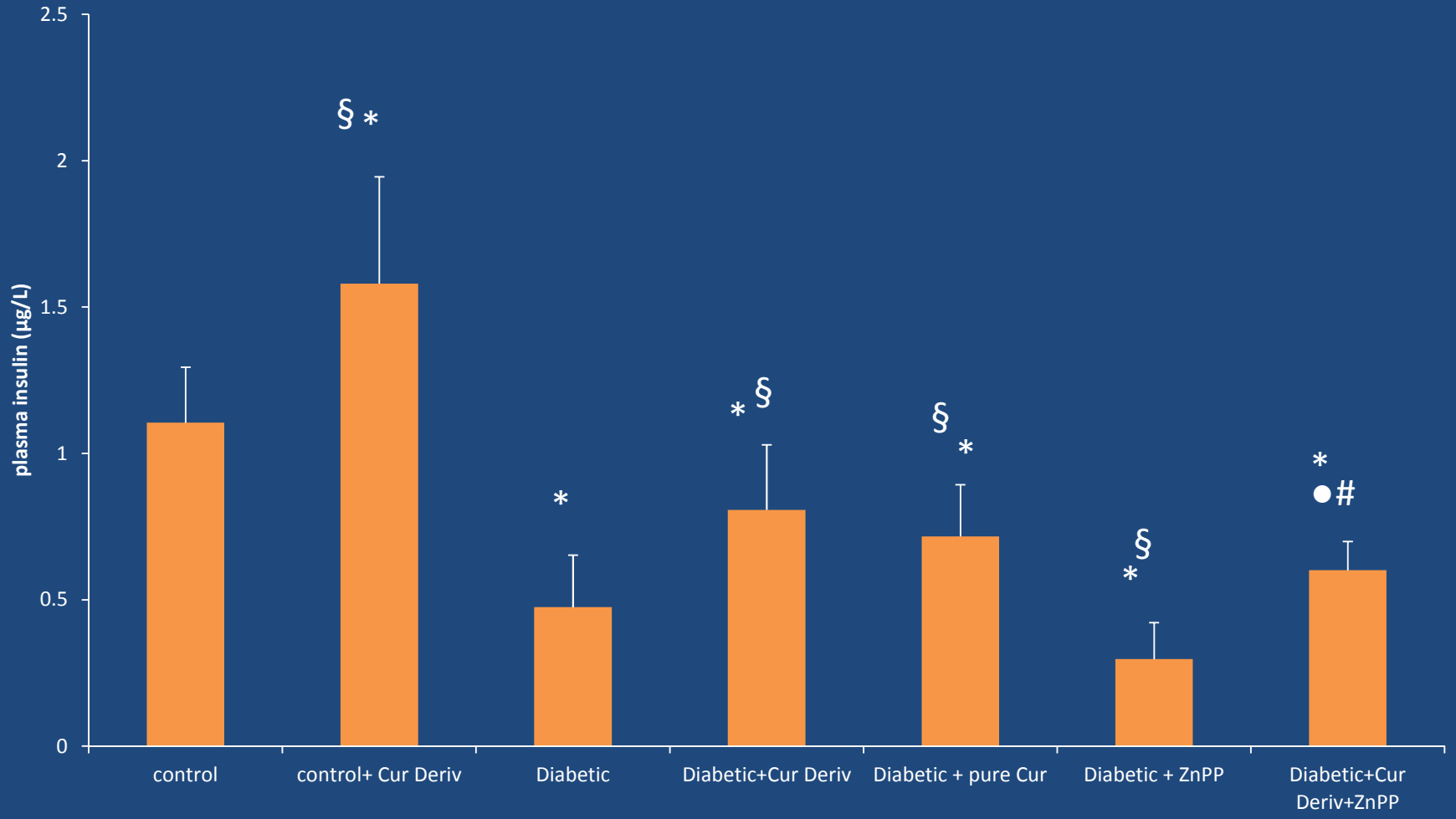
Results

Plasma Glucose



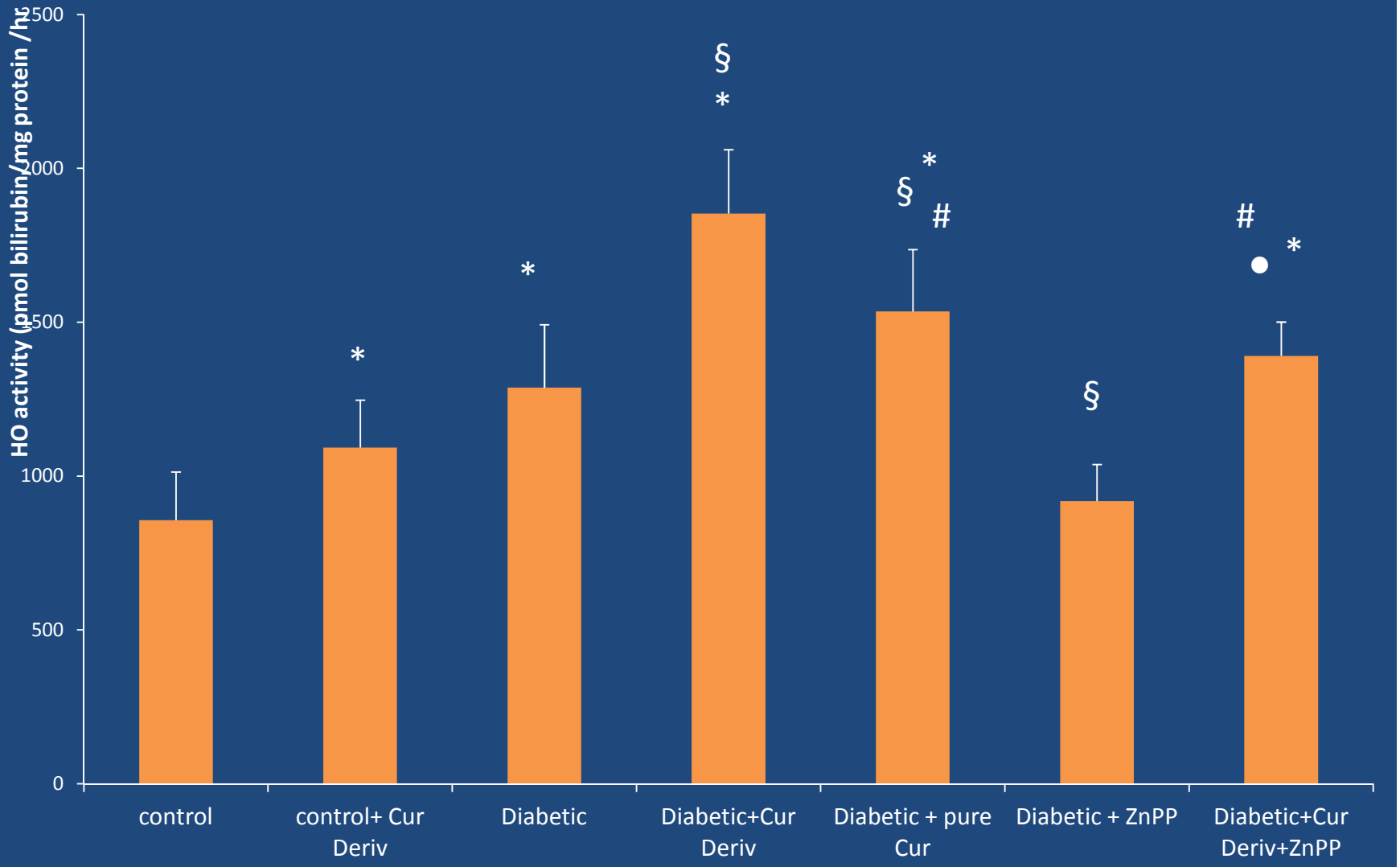
*Values differ significantly from control
§ Values differ significantly from diabetic
# Values differ significantly from diabetic +curcumin derivative
● Values differ significantly from diabetic + inhibitor

Plasma insulin



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HO-activity in pancreas



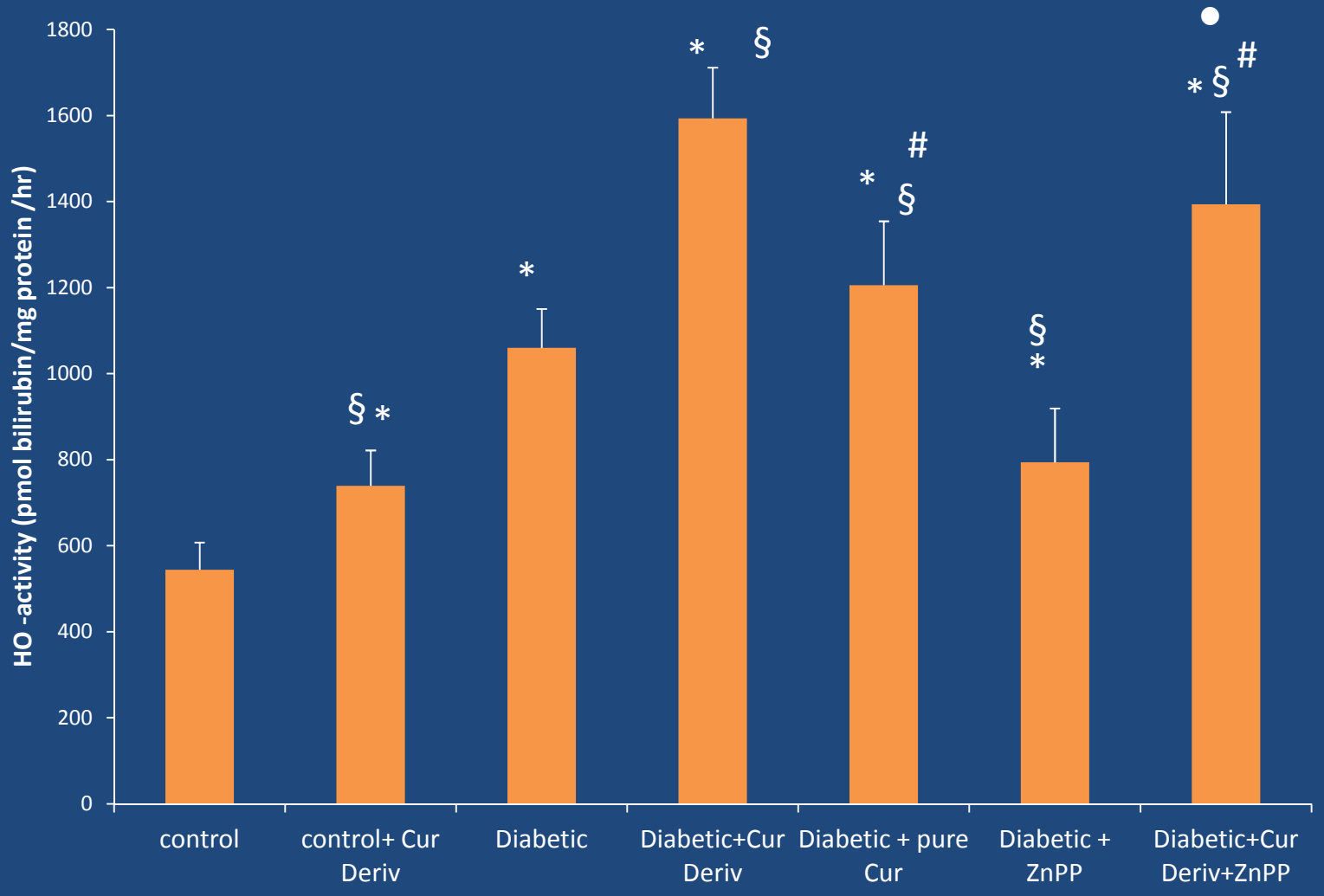
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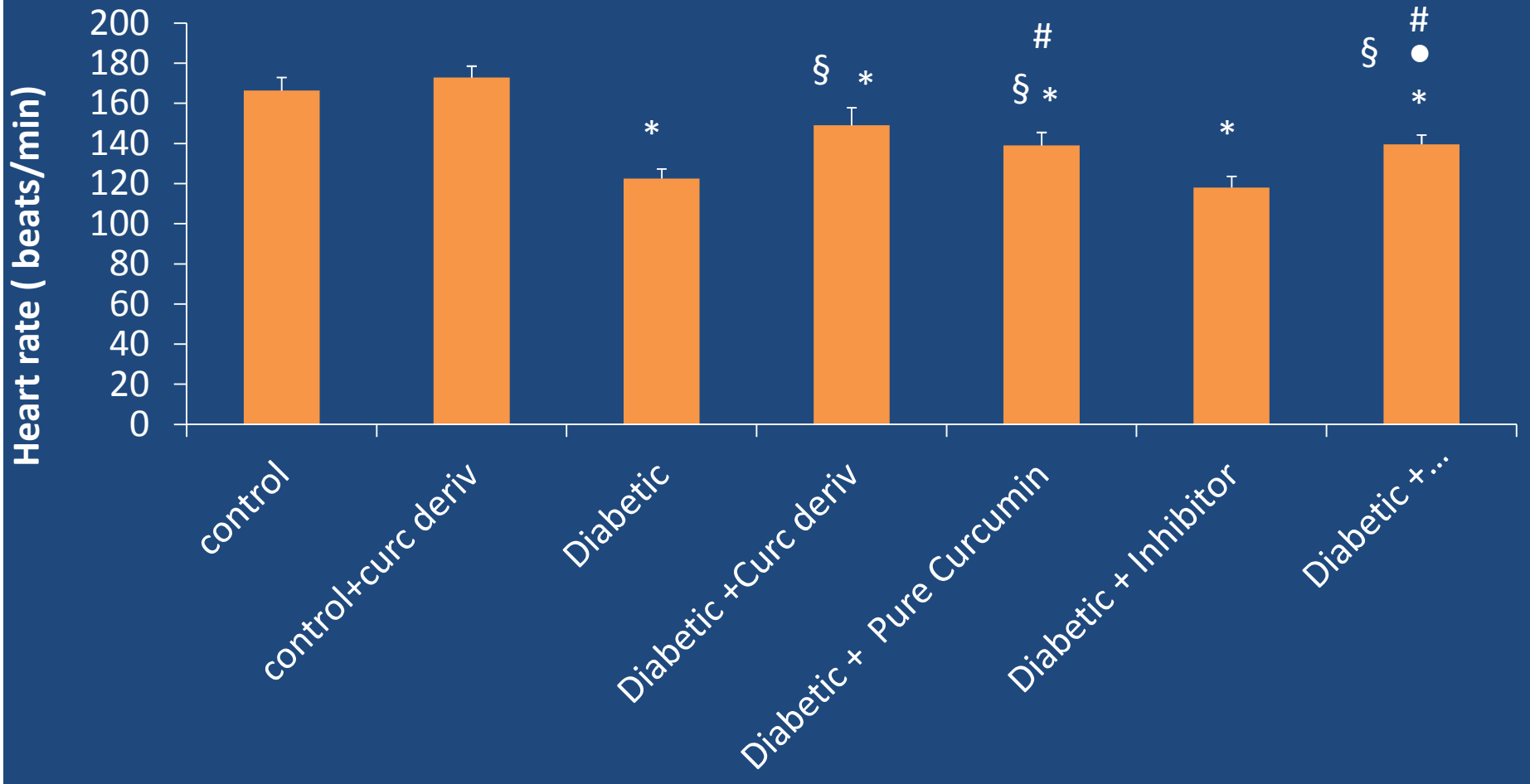
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HO-activity in heart



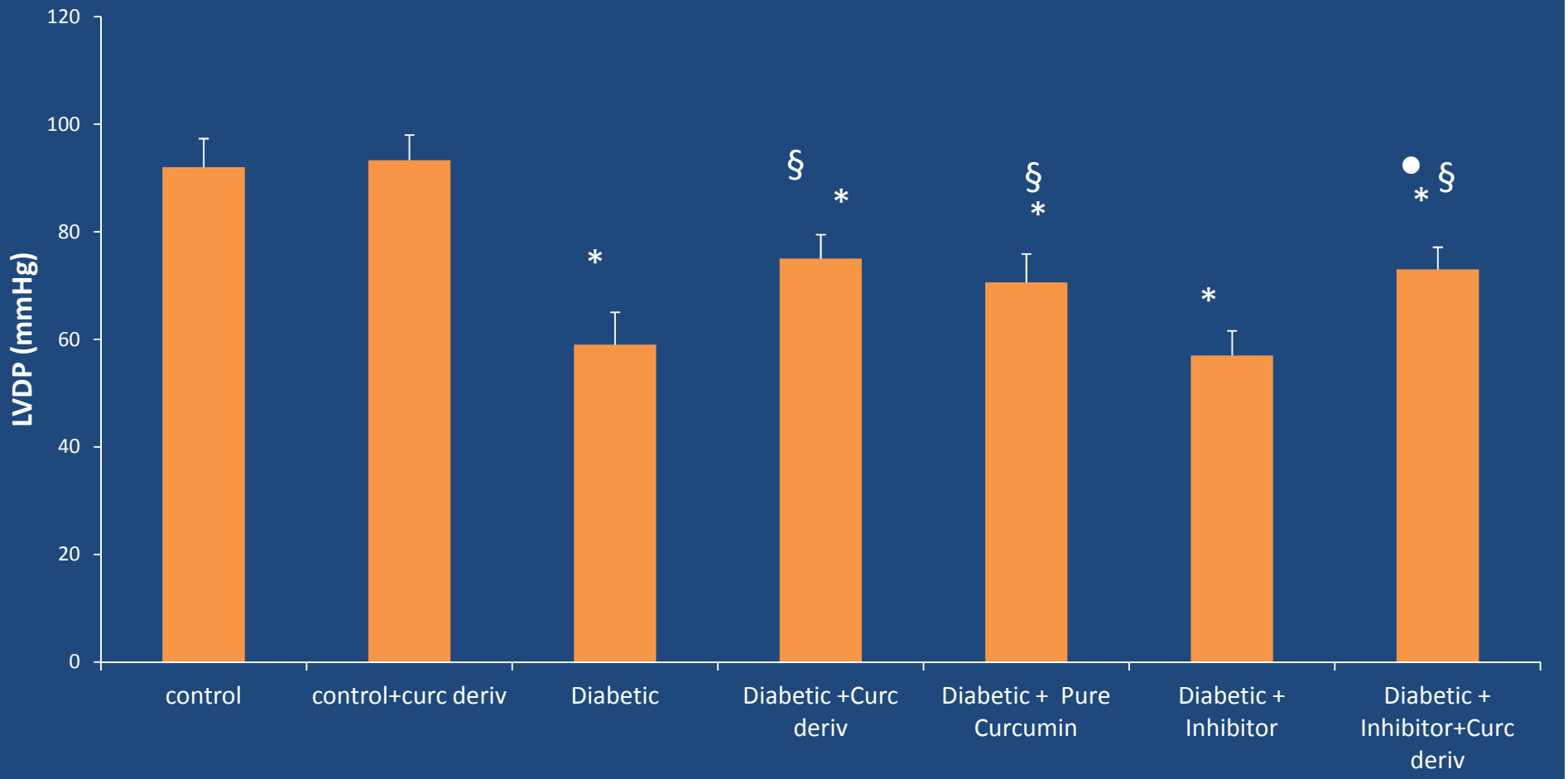
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Heart Rate



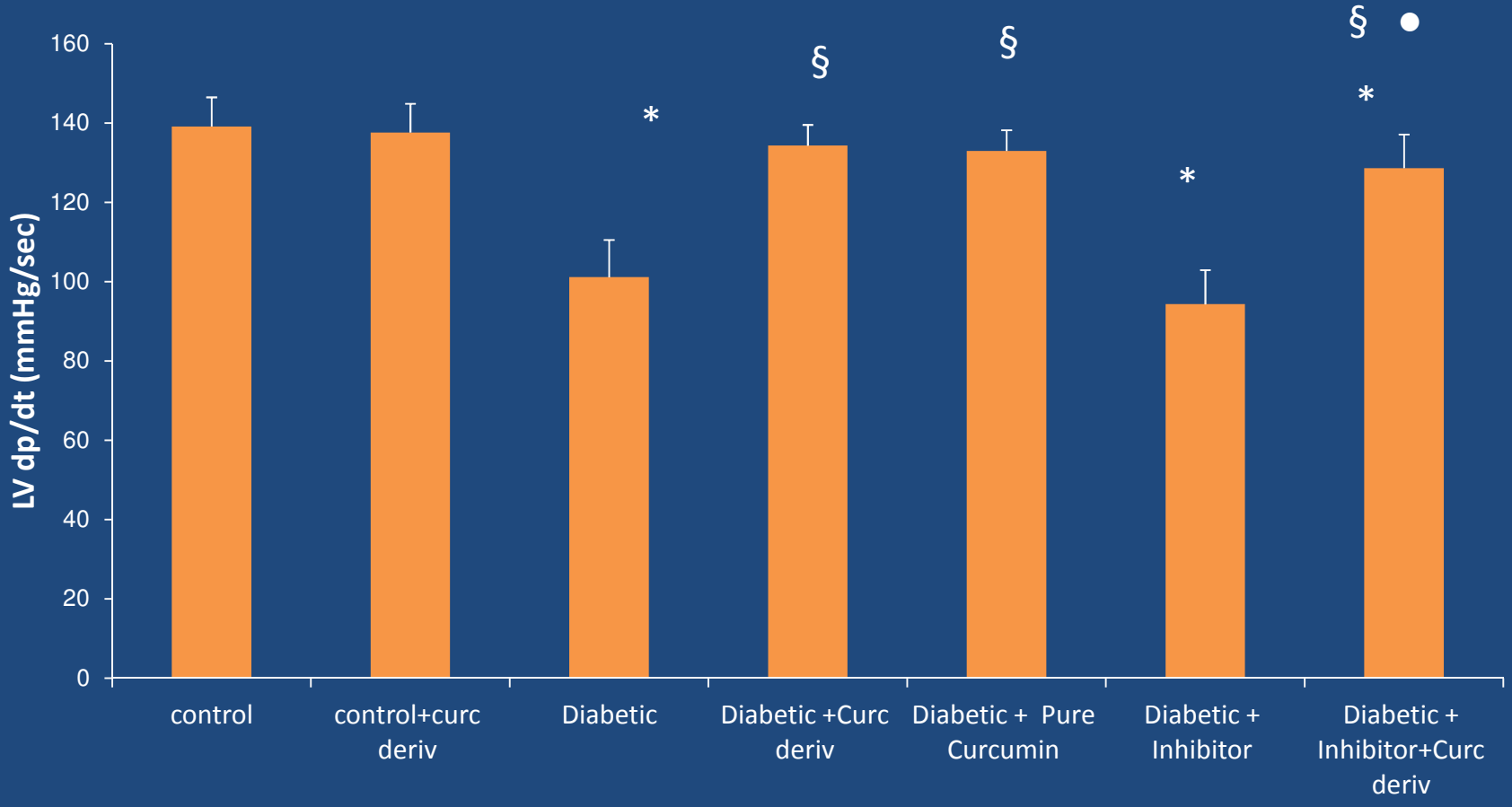
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LVDP



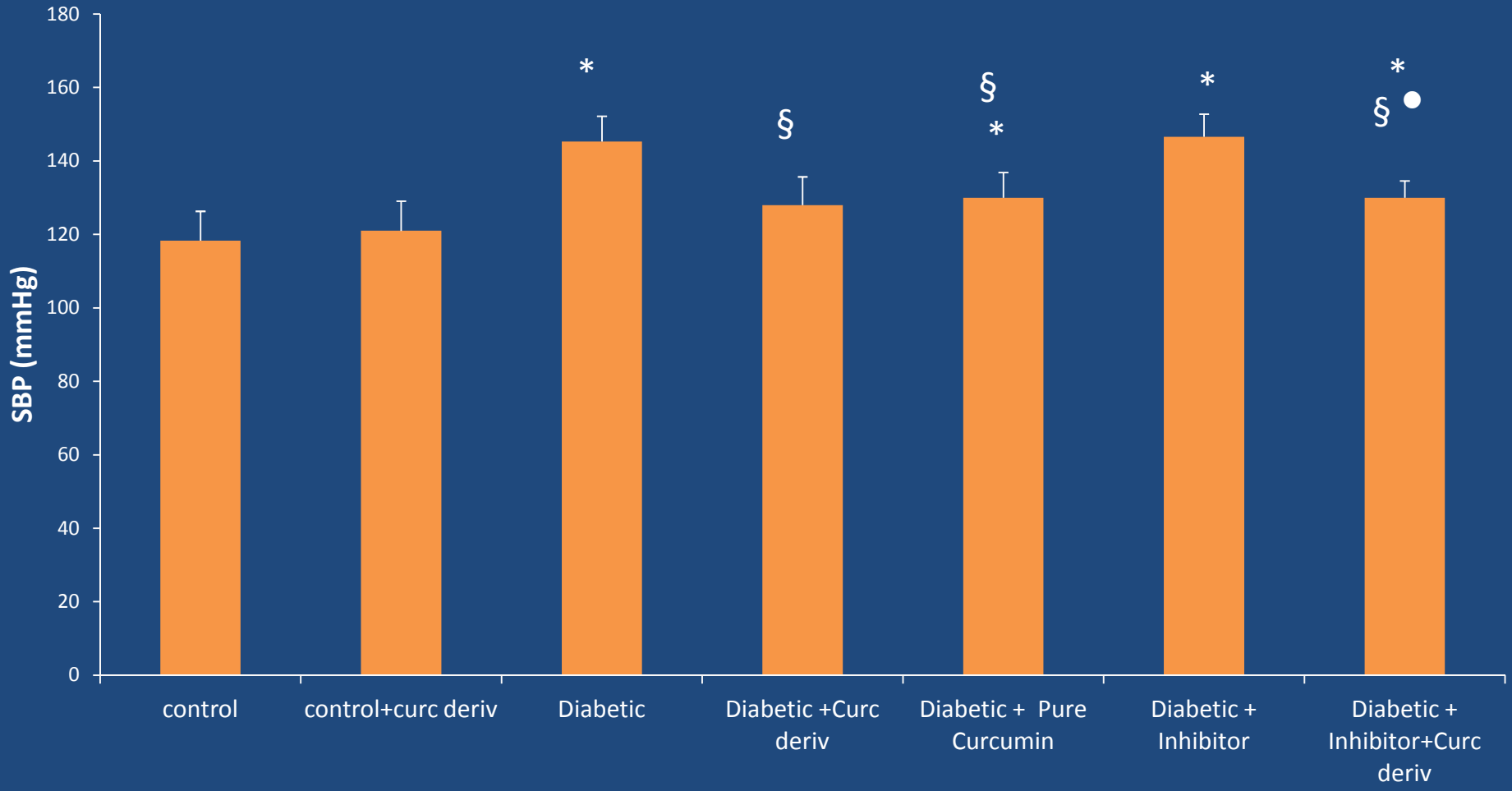
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LV dp/dt



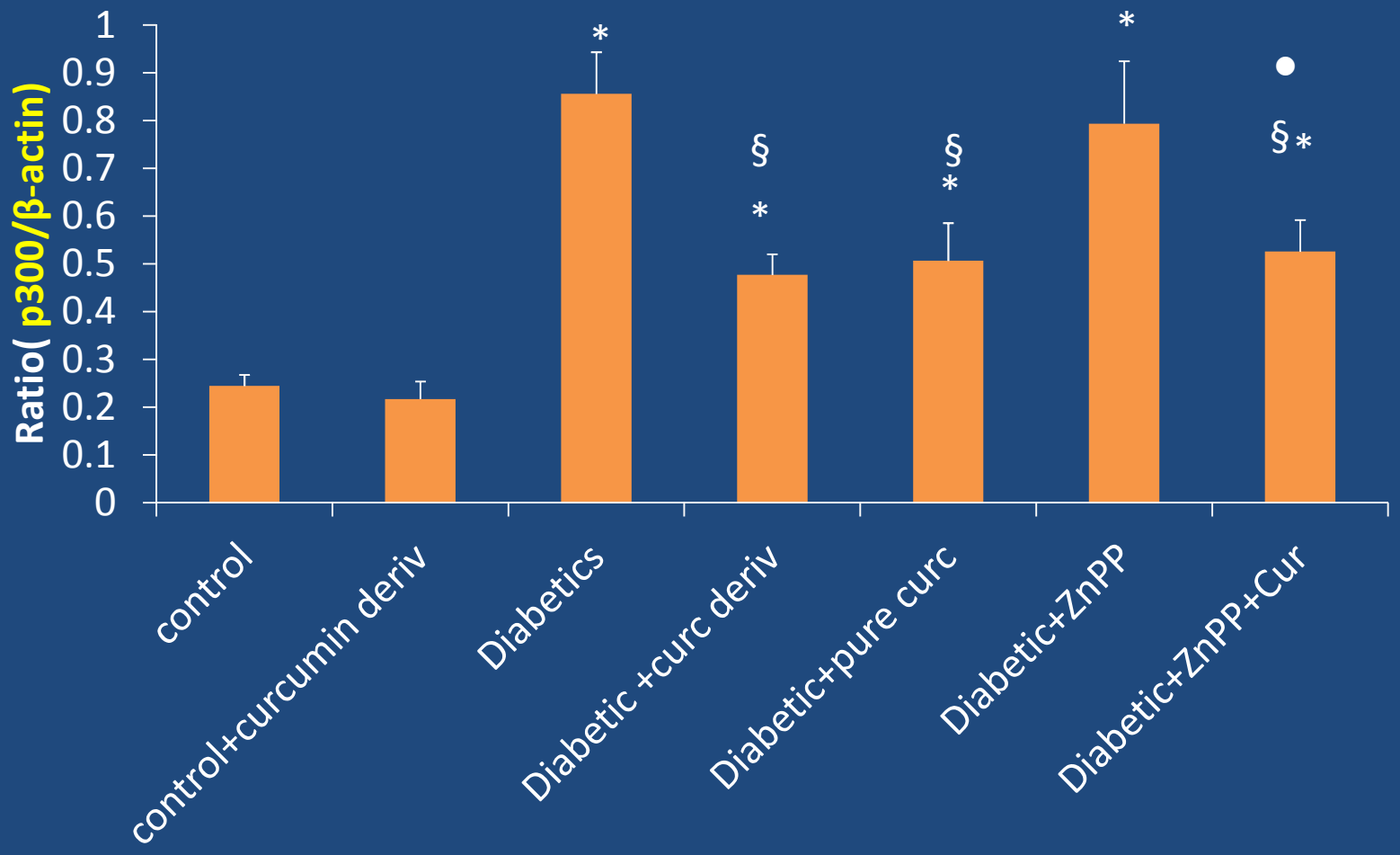
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SBP



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p300 gene expression in heart



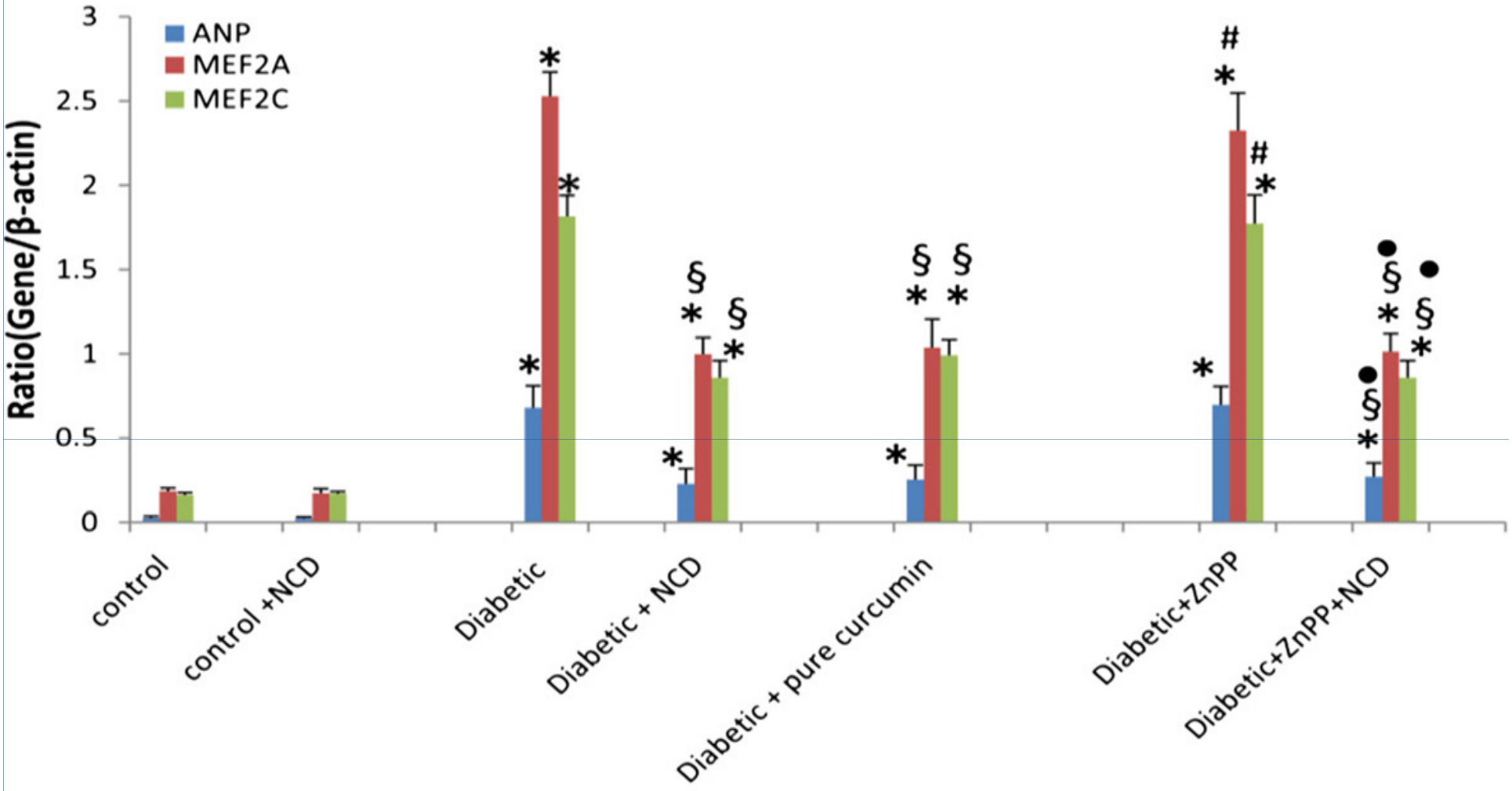
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Gene expression of molecular markers of cardiac hypertrophy



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Conclusion

- ***NCD and curcumin had the ability to decrease plasma glucose, GHb and increased plasma insulin levels significantly in diabetic rats***

- ***These actions may be partially mediated by induction of heme oxygenase-1 gene .***

Conclusion

The HO-1 activity and gene expression were significantly increased in diabetic heart and pancreas.

Conclusion

Both compounds improved LV function; HR, systolic pressure, LVDPand LV delta pressure/delta time (contractility index).

Conclusion

- **DM up-regulated expression of cardiomyopathy markers *(ANP,MEF2A and MEF2C)* and p300.**

- **However, NCD and curcumin *(p300 blockers*) prevented DM-induced upregulation of these parameters and improved left ventricular function.**
- ***Curcumin's action on cardiomyopathy is not mediated through HO-1.***

Conclusion

- **There was no significant difference between administration of NCD and pure curcumin.**

- **However, the effect of NCD by its small dose (20 mg/Kg/day orally for 45 days) taking into consideration that NCD has only a 3.0% curcumin content, gave the same results as pure curcumin (20 mg/Kg/day orally for 45 days).**

Conclusion

Thus, NCD was absorbed at a higher rate than pure curcumin and still retains the essential potencies of natural curcumin.

Recommendations

- ***Management of DM without the traditional drug side effects is still a challenge to the medical community***

- ***There is an increasing demand by the different communities to use the natural products with anti-diabetic activity instead of insulin and oral hypoglycemic drugs which possess undesirable side effects***


Thank You