

# Chronic treatment with H<sub>2</sub>S donor, GYY4137, Mitigates Aging-Induced Functional Abnormalities In The Isolated Strips of Rat Corpus Cavernosum



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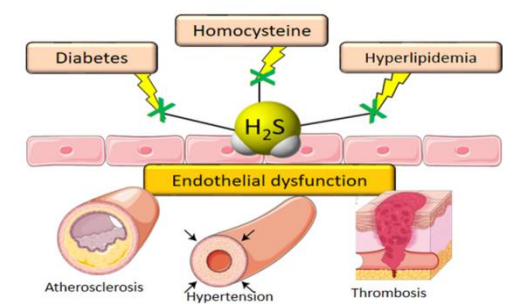
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## Introduction:

The role of hydrogen sulfide (H<sub>2</sub>S) in regulating vascular homeostasis has been proven by many studies. H<sub>2</sub>S has been shown to act as a vasodilator and may possess a hyperpolarizing effect. It has been reported that H<sub>2</sub>S is involved in several physiological effects in the body and may be linked to different pathological conditions such as diabetes, hypertension and atherosclerosis [1-3]. GYY4137 is a slow-release H<sub>2</sub>S donor which has been shown in our previous studies to be effective in preventing or reducing erectile dysfunction (ED) induced by diabetes [2, 3].



Cited from Valentina et al., 2021 [1]

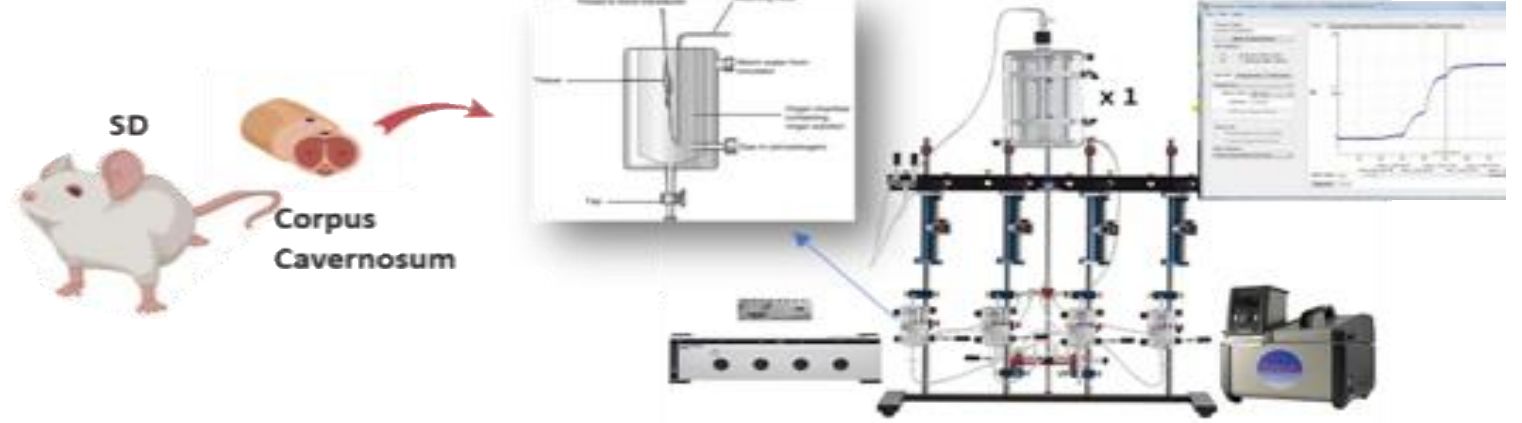
## Objectives:

The aim of this study was to investigate the protective effect of the H<sub>2</sub>S donor GYY4137, on the abnormal function of the corpus cavernosum associated with erectile dysfunction in an aged murine model.

## Methods:

Male Sprague Dawley (SD) rats were used in this study. All experimental procedures were carried out in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (NIH Publication number 85–23, Revised 1985) as approved by the Animal Welfare and Ethics Committees of Kuwait University. Animals were divided into three groups (n = 8/group): Group 1 are control animals (10 weeks old); Group 2 are older (aged) animals (20 months old). Group 3 are older (aged) rats + GYY4137 (50 mg/kg). The doses of the drugs and route and duration of administration were chosen based on previous in vivo studies [2]. The animal's body weights were re-measured before sacrificing the animals. Following sacrifice, the corpus cavernosum (CC) was isolated immediately from the three animal groups and mounted in organ bath to examine the reactivity by measurement of changes in isometric tension to vasoactive agonists (phenylephrine (PE), carbachol and sodium nitroprusside (SNP)) using computerized automatic organ bath LSI. Ascending concentrations of PE (10<sup>-9</sup> - 10<sup>-5</sup> M) were applied to establish a cumulative concentration response curve using CC strips isolated from the various animal groups included in the study. In another group of experiments, relaxant responses induced by carbachol, or SNP were tested in the CC strips isolated from the different groups. The CC tissues were first pre-contracted with PE (10<sup>-7</sup> M), and then the relaxant effects to carbachol or SNP (10<sup>-9</sup> - 10<sup>-4</sup> M) were examined. The relaxant responses are expressed as percentage reduction of tension that was induced by pre-contraction with PE [2, 3].

### Laboratory Organ Bath Setup



## Results:

Chronic treatment with GYY4137 had no significant effect on the body weight of aged-treated rats compared to the aged non-treated group (table-1). Blood glucose levels were not significantly different among the three groups. The results showed that CC strips from aged rats produced a significant increase in the contractile response to PE compared to the control young rats (P < 0.05). Treatment with GYY4137 50 mg/kg resulted in reduced contractility to PE in the aged CC compared to aged-non treated rats (P < 0.05) (Fig. 1). In addition, the relaxant response to carbachol was significantly attenuated in CC from aged animals compared to controls (P < 0.05). GYY4137-treated aged CC showed a significant improvement in the relaxant response to carbachol, compared to the aged non-treated CC (P < 0.05) (Fig. 2). The relaxant responses to SNP were not significantly different in the three animal groups (Fig. 3).

### Results: Figure 2. Carbachol-Induced Vasodilator Responses

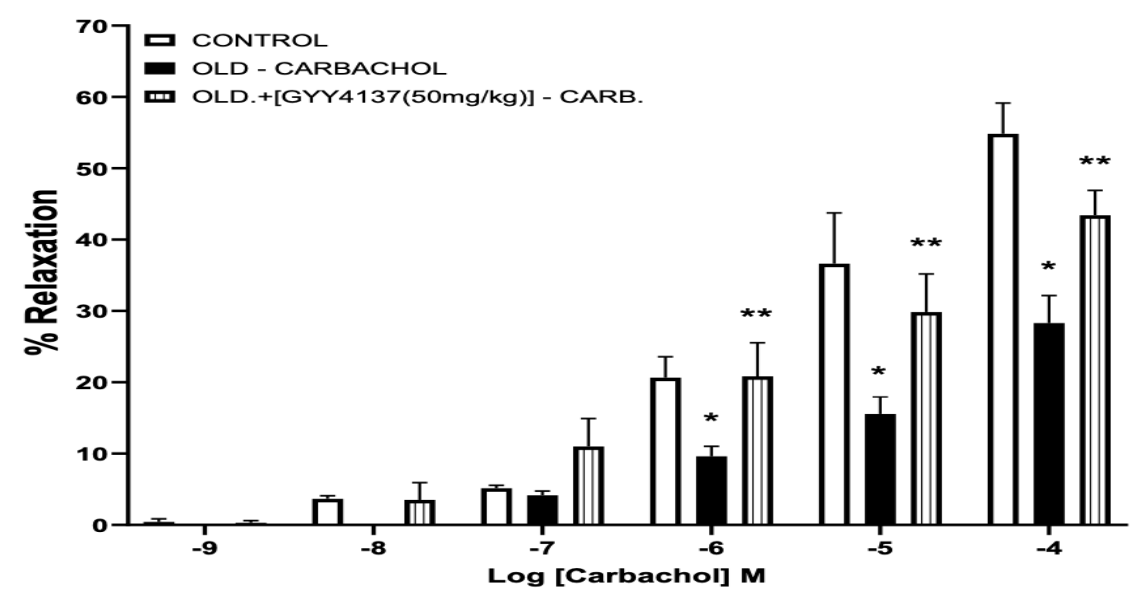


Figure 2: Carbachol-induced relaxation (expressed as %) in the corpus cavernosum segments from control, old, and old-GYY4137-treated rats (Mean ± SEM, n = 8). (\*) indicates significantly different mean values as compared to control, (\*\*) indicates significantly different mean values as compared to old rats, P < 0.05.

### Results: Figure 3. SNP-Induced Vasodilator Responses

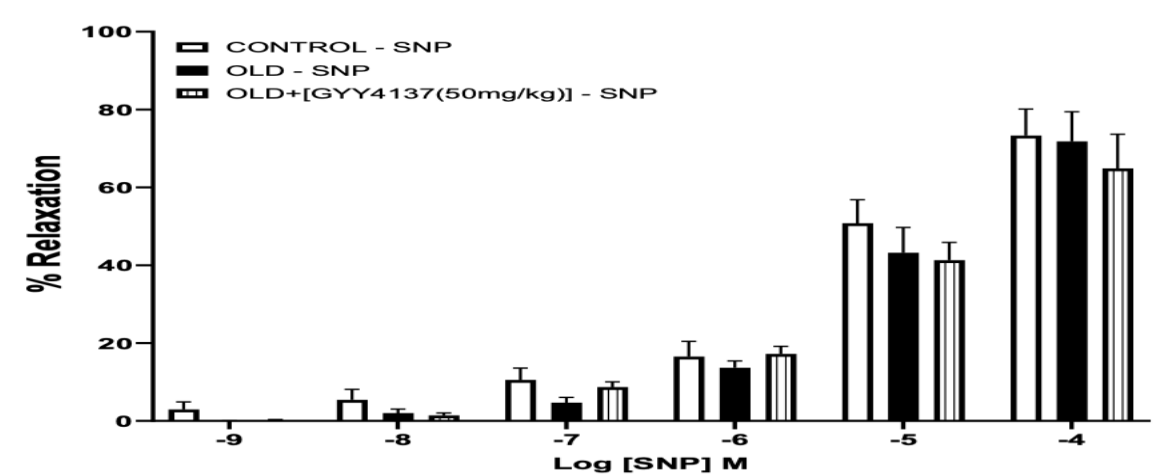


Figure 3: S N P -induced % relaxation in the corpus cavernosum segments from control, old, and old-GYY4137-treated rats (Mean ± SEM, n = 8).

Table (1):

Animal Groups	Treatment	No. of Animals	Initial body weight (g)	Final body weight at day of sacrifice (g)	Initial glucose level (mg/dl)	Final glucose level at day of sacrifice (mg/dl)
Control SD rats	Vehicle (Saline)	8	274	275	91	94
Aged SD rats (20 months)	Vehicle (Saline)	8	715	762	118	120
Aged SD rats + GYY4137	GYY4137 (50mg/kg body weight) (daily i.p.)	8	730	692*	108	130

Table 1 : Effect of GYY4137on body weight and blood glucose levels in control, old and old-treated rats with GYY4137 (50mg/kg body weight). Values are presented as mean ± SE; n = 8 . (\*) indicates significantly different mean values as compared to aged rats' initial body weight before treatment, P < 0.05.

### Results: Figure 1. PE-Induced Vasoconstrictor Responses

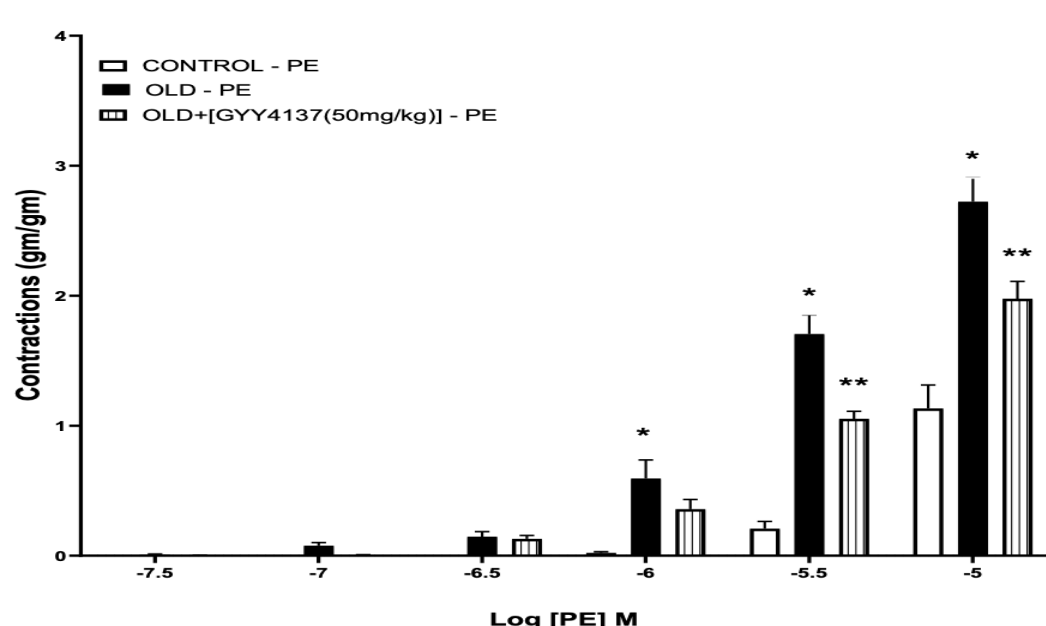


Figure 1: PE-induced vasoconstriction in the corpus cavernosum segments from control, old, and old-GYY4137-treated rats (Mean ± SEM, n = 8). (\*) indicates significantly different mean values as compared to control, (\*\*) indicates significantly different mean values as compared to old rats, P < 0.05.

## Conclusion:

Findings from this study suggest a promising role of the H<sub>2</sub>S donor GYY4137 as a potential novel approach in preventing erectile dysfunction associated with aging. Future studies are needed to investigate the signaling pathways involved in mediating the protective effects of H<sub>2</sub>S.

## References:

- Valentina C , Alma M, Era G, Simone B, Lara T, Vincenzo C. Role of hydrogen sulfide in endothelial dysfunction: Pathophysiology and therapeutic approaches. Journal of Advanced Research 27 (2021) 99–113.
- Qabazard B, Yousif M, Mousa A, Phillips OA. GYY4137 attenuates functional impairment of corpus cavernosum and reduces fibrosis in rats with STZ-induced diabetes by inhibiting the TGF-β1/ Smad/CTGF pathway. Biomedicine & Pharmacotherapy. 2021; 138: 111486.
- Al-Shahwan H, Qabazard B, Moussa A, Chandrasekhar B, Santhosh K, Yousif MHM. Hydrogen sulfide donor GYY4137 attenuates vascular complications in mesenteric bed of streptozotocin-induced diabetic rats. European Journal of Pharmacology. Volume 933, 2022, 175265.

## Acknowledgment:

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