

ABSTRACT NATURAL HISTORY OF ERECTILE DYSFUNCTION IN THE SPONTANEOUSLY HYPERTENSIVE RAT: A LONGITUDINAL IN VIVO STUDY

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ABSTRACT

Introduction and Objectives: Men with hypertension have a significantly higher prevalence of erectile dysfunction (ED) than the general population. We have previously demonstrated that ED occurs in the 12-week old SHR. The aim of this study was to evaluate the progressive development of ED in a well-established model of genetic hypertension, the SHR and compare it to its normotensive age-matched counterpart, the WKY.

Methods: We have studied erectile responses elicited by various electrical stimulations of the cavernous nerve and expressed as the frequency-dependent increase in intracavernosal pressure (ICP), normalized by the mean arterial pressure (MAP) in SHR and WKY of ages ranging from the pre-hypertensive to the well-established hypertensive state (6, 12 and 24 weeks of age, n=12).

Results: In both anaesthetized (xylazine, 10mg/kg and ketamine, 90mg/kg) WKY and SHR, MAP increased significantly between 6 and 12 weeks of age while it was unchanged between 12 and 24 weeks of age. MAP was significantly higher in SHR compared to WKY starting at 12 weeks of age (96.4 ± 4.3 vs 112.7 ± 3.7 mmHg, p<0.05). Erectile responses in WKY at 6, 12 and 24 weeks of age did not vary greatly (responses to 10 Hz-6V of 66.2 ± 2.2 %, 67.0 ± 3.0 % and 66.4 ± 1.9 %, respectively, NS). Strikingly, however, the magnitude of the erectile responses was drastically reduced in SHR compared to WKY rats at all time points and for each frequency except 1 Hz (responses to 10 Hz-6V of 31.8 ± 3.4 %, 33.9 ± 3.3 %, 34.0 ± 3.3 %, at 6, 12 and 24 weeks of age respectively, p<0.001). Interestingly, erectile responses in the SHR remained identically impaired between 6 (pre-hypertensive state) and 24-weeks of age (well-established hypertension).

Conclusions: The magnitude of erectile responses is considerably reduced in SHR before hypertension is well-established and remains so with time thereafter. This seems to indicate that the onset of erectile dysfunction is detectable prior to the onset of hypertension. If shown in humans, this could be of utmost interest since it could confer the valuable property for ED to be an early warning sign/sentinel for hypertension.

BACKGROUND

➤ Epidemiology of ED: The Key Role of Hypertension

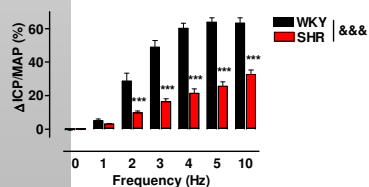
- The prevalence of ED in men with hypertension is significantly higher than in the general population (15% vs 9.6 %)

Feldman et al., J Urol, 151:54-61 (1994)
Jensen et al., Am J Hypertens, 12:271-275 (1999)

- ED is a symptom occurring in 8-10 % of untreated hypertensive patients

Lewis et al., 1st International Consultation on Erectile Dysfunction, WHO (2000)

➤ In vivo Erectile Dysfunction in 12-weeks old SHR



&&& p<0.0001 Two-Way ANOVA
***p<0.001 Bonferroni's complementary analysis

Behr-Roussel et al., Am J Physiol, 2003

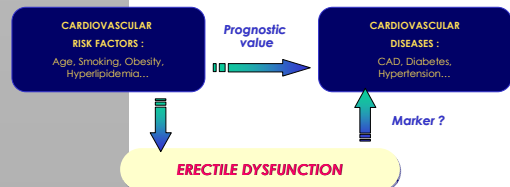
➤ Erectile dysfunction may be a marker of underlying undiagnosed cardiovascular disease

Lewis et al., Urol Clin North Am 2001;28:209-216

DeBusk et al., Am J Cardiol 2000;86:62F-68F

Lewis et al., 1st International Consultation on Erectile Dysfunction, WHO (2000)

Solomon et al., Heart 2003;89:251-253



OBJECTIVES

To study the erectile responses from SHR and their normotensive counterparts, WKY *in vivo*

- at 6 weeks of age : pre-hypertensive state
- at 12 weeks of age
- at 24 weeks of age : well-established hypertension

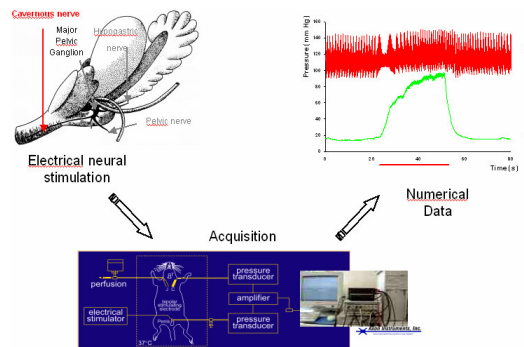
in order to evaluate the progressive development of ED in a well-established model of genetic hypertension

METHODS

In vivo evaluation of erectile function

- Spontaneously Hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats
 - 6-weeks old (n=12)
 - 12-weeks old (n=12)
 - 24-weeks old (n=12)
- Evaluation of erectile function by simultaneous monitoring of the arterial pressure and intracavernosal pressure (ICP) following electrical stimulation of the cavernous nerve *in vivo* (0-10 Hz) under ketamine (90 mg/kg) and xylazine (10 mg/kg) anaesthesia

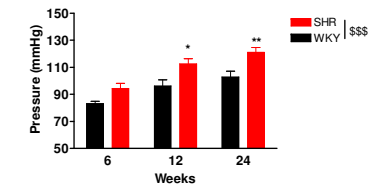
Results are expressed as the increase in ICP elicited by electrical stimulation of cavernous nerve, normalized by the mean arterial pressure (MAP) of the animal



This work was supported by a research grant from NOVARTIS

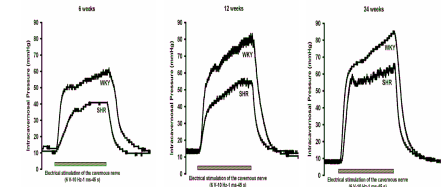
RESULTS

Evolution of mean arterial pressure in anaesthetized WKY and SHR with time



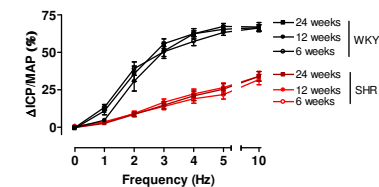
\$\$\$p<0.001 Two-Way ANOVA
*p<0.05, **p<0.01 versus age-matched WKY, Bonferroni's complementary analysis

Representative tracings of original recording of intracavernosal pressure when stimulating the cavernous nerve (6 V, 10 Hz, 1 ms, 45 s) in SHR and age-matched WKY rats



Mean arterial pressures in anaesthetized SHR and WKY at rest were
94 ± 4 versus 83 ± 2 mmHg at 6 weeks of age,
113 ± 4 versus 96 ± 4 mmHg at 12 weeks of age
121 ± 4 versus 96 ± 4 mmHg at 24 weeks of age

Effect of cavernous nerve stimulation at increasing stimulation frequencies on the ICP rise of anaesthetized rats



Erectile dysfunction in the SHR whatever the age

CONCLUSION

- Despite the fact that the magnitude of an erectile response is directly driven by the magnitude of the arterial blood pressure, erectile responses elicited by cavernous nerve stimulation are already impaired in the pre-hypertensive SHR
- The onset of ED is detectable prior to the onset of hypertension in the SHR, without further deterioration with time
- If confirmed in humans, this finding could be of utmost interest since it could confer the valuable property for ED to be an early warning sign/sentinel for hypertension as it has been postulated for cardiovascular conditions in general.

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