

MEETING ABSTRACT

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Cardiac soluble guanylate cyclase protects against the cardiac dysfunction induced by chronic doxorubicin treatment in mice

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Background

The use of doxorubicin (DOX), a potent chemotherapeutic agent, is limited by cardiotoxicity, leading to congestive heart failure in up to 5% of DOX-treated patients. Dysfunctional cyclic guanosine 3', 5'-monophosphate (cGMP) signaling has been implicated in various cardiovascular diseases, including cardiotoxicity associated with DOX administration. We tested the hypothesis that cGMP generated by soluble guanylate cyclase (sGC), the target for clinically available pharmacological agents that enhance cGMP levels (e.g. riociguat), protects against DOX-induced cardiomyopathy.

Methods and results

Nitric oxide (NO)-stimulated sGC enzyme activity was lower in myocardial tissue extracts from wild-type (WT) mice exposed to DOX (20 mg/kg, IP, 24h), than from vehicle-treated WT mice (20.4±2.1 vs. 25.7±1.4 pmol cGMP/mg protein/min, respectively, n=10 for both, $P<0.05$). To investigate whether decreased cardiac cGMP synthesis by sGC contributes to DOX-induced cardiotoxicity, we studied mice with a cardiomyocyte-specific deficiency in the $\alpha 1$ -subunit of sGC (sGC $\alpha 1^{-/-}$), obtained using a Cre-lox conditional knockout strategy. At baseline, left ventricular (LV) dimensions and function, assessed via transthoracic echocardiography (TTE), were similar in sGC $\alpha 1^{-/-}$ and WT mice. After 12 weeks DOX (2 mg/kg/week, IP), TTE and invasive hemodynamic

measurements revealed greater LV dysfunction and dilatation in sGC $\alpha 1^{-/-}$ than in WT mice (Table 1).

In a second mouse model, myocardial sGC activity was reduced by cardiomyocyte-specific expression of a dominant-negative sGC $\alpha 1$ mutant (DNsGC $\alpha 1^{tg/+}$) in an inducible manner (Tet-Off). Withdrawing tetracycline from the diet resulted in a ~50% reduction of cardiac sGC activity (18.6±2.6 vs. 32.0±5.4 pmol cGMP/mg protein/min in 8 DNsGC $\alpha 1^{tg/+}$ and 8 WT mice, respectively, $P<0.05$). At baseline, LV dimensions and function were similar in DNsGC $\alpha 1^{tg/+}$ and WT mice. Chronic DOX treatment resulted in greater LV systolic dysfunction and dilatation in DNsGC $\alpha 1^{tg/+}$ than in WT mice after 8 and 12 weeks (TTE, data not shown). Importantly, LV dysfunction observed in DNsGC $\alpha 1^{tg/+}$ exposed to DOX for 12 weeks could be attenuated by re-adding tetracycline to the diet [thereby suppressing expression of the dominant negative sGC $\alpha 1$ mutant and de-repressing endogenous sGC activity] after 8 weeks of DOX administration: fractional shortening improved significantly in DNsGC $\alpha 1^{tg/+}$ mice by 16 weeks (28±1% at 8 weeks vs. 35±1% at 16 weeks, n=17 and 20, respectively, $P<0.05$).

Conclusions

Reduced myocardial sGC activity results in increased LV dysfunction and dilatation in DOX-treated mice. Pharmacological stimulation of sGC may represent a promising therapeutic approach to tackle DOX-associated cardiotoxicity.

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Table 1. DOX-induced LV dysfunction and remodeling after 12 weeks chronic treatment is greater in sGC α 1^{-/-} than WT mice

<i>Echocardiography</i>	WT + saline (n=7)	sGC α 1 ^{-/-} + saline (n=6)	WT + DOX (n=12)	sGC α 1 ^{-/-} + DOX (n=11)
LVID _S (mm)	1.3±0.1	1.3±0.0	1.7±0.1†	2.0±0.1+*
LVID _D (mm)	3.0±0.0	3.0±0.0	3.2±0.1†	3.3±0.0†
FS (%)	57±1	57±1	48±2†	40±1†*
HR (bpm)	531±13	505±18	428±17†	426±18†
<i>Hemodynamic measurements</i>	WT + saline (n=6)	sGC α 1 ^{-/-} + saline (n=5)	WT + DOX (n=12)	sGC α 1 ^{-/-} + DOX (n=9)
ESV (μl)	19±1	19±1	26±3†	37±3†*
EDV (μl)	43±2	41±2	51±2†	58±2†*
EF (%)	60±2	58±3	55±4	42±3†*
dP/dt _{max} (mmHg/s)	13,499±1,433	11,995±601	13,503±678	10,386±875*
dP/dt _{min} (mmHg/s)	-12,053±1,809	-11,420±950	-13,531±846	-10,943±940¶
Tau (ms)	5.1±0.1	4.9±0.2	5.6±0.2†	6.3±0.3†¶
PRSW	83±9	84±6	70±9	49±7†¶
Ees (mmHg/μl)	6.3±1.2	7.3±1.4	4.0±0.8†	2.3±0.3†¶
EDPVR (mmHg/μl)	0.21±0.03	0.18±0.02	0.16±0.02	0.19±0.02
HR (bpm)	576±8	614±12	528±9†	530±14†*

LVID_S indicates left ventricular internal diameter at end-systole; LVID_D, left ventricular internal diameter at end-diastole; FS, fractional shortening; HR, heart rate; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction; dP/dt_{max} and dP/dt_{min}, maximum and minimum of the first derivative of LV pressure over time; Tau, time constant for isovolumic relaxation; PRSW, pre-load recruitable stroke work; Ees, end-systolic elastance; and EDPVR, end-diastolic pressure volume relationship. Values are presented as mean±SEM.

† P<0.05 vs. saline,

* P<0.05 vs. WT + DOX, and

¶ P≤0.10 vs. WT + DOX.

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