Effects of doxorubicin and mitoxantrone in the brain of differently aged mice: an *in vivo* chemobrain study

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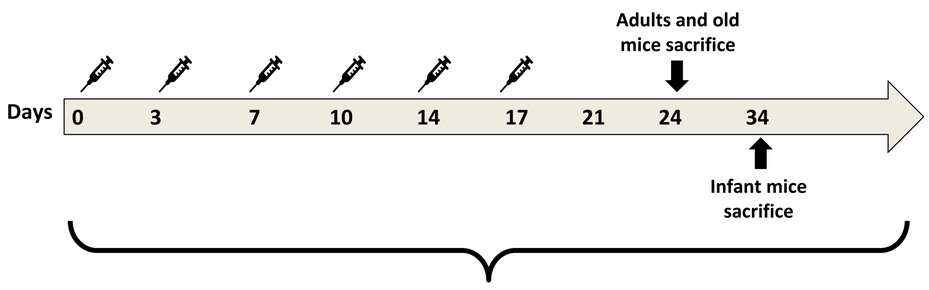
Introduction

Despite its success in cancer-treatment, **chemotherapy** targets healthy tissues, which leads to toxicity and long-term health problems (1). The term "**chemobrain**" is used to summon the cognitive deficit effects of chemotherapy in the long term (2). **Chemobrain affects 17% to 34% of chemotherapy-treated patients** (2). **Doxorubicin (DOX)** and **mitoxantrone (MTX)** are two widely used chemotherapeutic agents with a broad spectrum of activity against neoplastic cells (3). Therefore, this work aimed to evaluate the effects towards the brain of clinically relevant doses of DOX and MTX in male CD-1 mice of different ages (infant, adult, old), and to understand if these pathways are involved in DOX and MTX-induced chemobrain.

Experimental Protocol

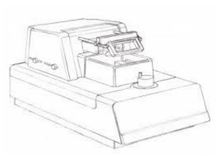
	Age	Average weight (g)	Total cumulative dose of DOX	Total cumulative dose of MTX
Infant	4 weeks	23	18 mg/kg	6 mg/kg
Adult	3 months	47		
Old	18-20 months	63	9 mg/kg	



Animal weight, **food** and **water** consumption as well as **animal well-being** were **monitorized** throughout the experiment.

Adult left-brain hemisphere was fixated in 4% paraformaldehyde.

Determination of the total glutathione levels (**GSHt**), reduced glutathione (**GSH**), oxidized glutathione (**GSSG**) and **ATP** levels.



Sectioned in the vibratome

Sections are being used for immunofluorescent detection of **phosphorylated Tau, glial fibrillary acidic protein, BAX and p53 proteins** in the **hippocampal formation.**

Results

	Juvenile		Adult		Old	
Treatment	**DOX**	**MTX**	**DOX**	**MTX**	**DOX**	**MTX**
Average body weight	***Decreased**	No changes	***Decreased**	No changes	No changes	No changes
GSH total	No changes	No changes	***Decreased**	No changes	No changes	No changes
GSH			No changes			
GSSG			***Decreased**			
GSH/GSSG			***Decreased**			
ATP	***Increased**	No changes	No changes	No changes	Not quantified	

*Comparing to the respective control group.

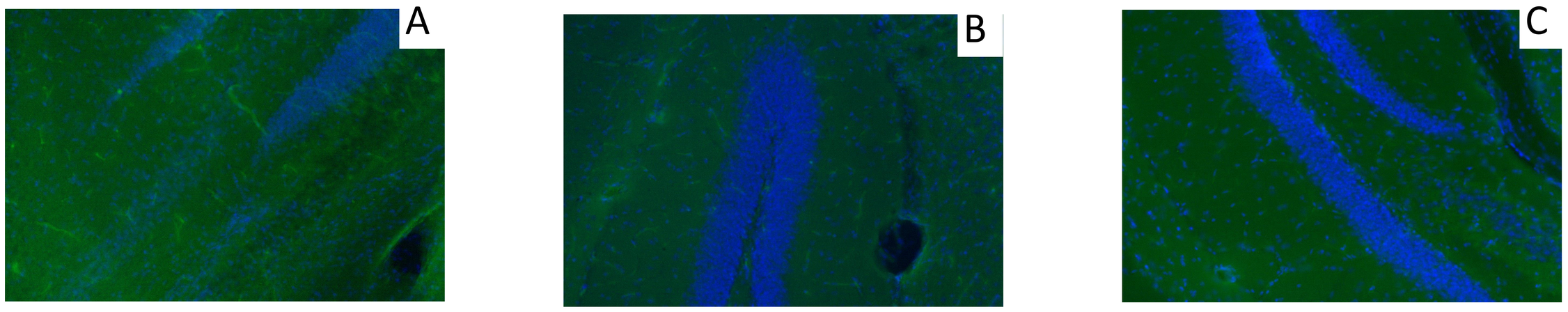


Figure 1: Fluorescence microscopy images of the dentate gyrus stained with Alexa Fluor 488 (green, phosphorylated tau) and the cell nuclei stained with DAPI (blue) in DOX 18 mg/kg treated mice (A to C).

Discussion and conclusions

Considering the measurements of the glutathione levels as a marker of oxidative stress, **only the adult mice treated with DOX had significant alterations namely lower levels of GSHt and GSH and a decrease in the GSH/GSSG ratio. The administration of DOX also increased the ATP levels in the infant mice.** The MTX-treatment did not affect the measured parameters in any groups tested. **The presented data suggests that DOX causes redox impairment and could be a possible cause of chemobrain in the adult brain.** On the other hand, MTX was shown not to influence the GSH levels and cause less distress in this dose to the animals.

References:

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Acknowledgements
ARM and VMC acknowledge Fundação da Ciência e Tecnologia (FCT) for their grants (SFRH/BD/129359/2017 and SFRH/BPD/110001/2015, respectively). VMC's Grant was funded by national funds through FCT – Fundação para a Ciência e a Tecnologia, I.P., under the Norma Transitória – DL57/2016/CP1334/CT0006. This work was supported by FEDER funds through the Operational Programme for Competitiveness Factors – COMPETE and by national funds by the Fundação para a Ciência e Tecnologia (FCT) within the project "PTDC/DTP-FTO/1489/2014 – POCI-01-0145-FEDER-016537".