Methamphetamine exposure during pregnancy at pharmacological doses produces neurodevelopmental effects in rat offspring

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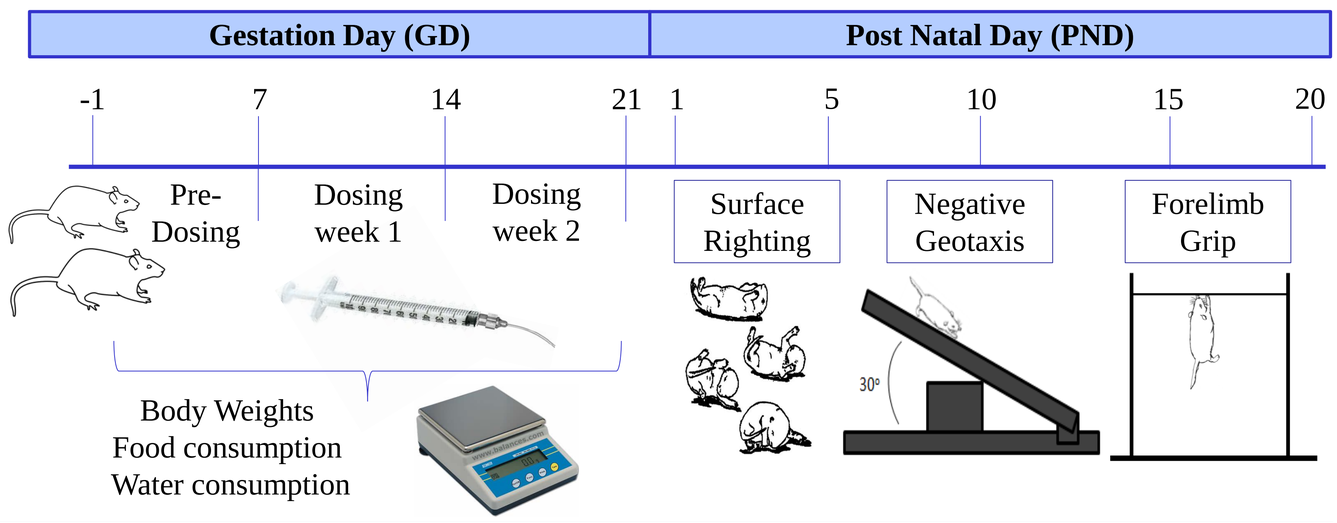
Introduction

In recent years methamphetamine (MA) has become more popular as a drug of abuse. Of particular concern is the popularity of MA among women of childbearing age and hence MA abuse in pregnant women is becoming an increasingly prevalent issue [1]. In order to enhance our knowledge of the risks associated with such exposure, animal models can play a valuable role. Despite its widespread use, studies examining MA effects on the developing offspring are limited. Thus, the aim of this study was to determine if *in utero* MA exposure in rats at pharmacological doses can have a negative impact on neonatal neurodevelopment and behaviour.

Methods

Animals	Environment	Drug Treatment	Statistical Analysis
40 Female & 12 Male Sprague-Dawley rats	Food & water ad libitum	MA 0.625, 1.25 or 2.5 mg/kg	Normality and homogeneity of variance (p>0.05)
Males group housed Females housed singly	Temperature: 22±2ºC Humidity: 34-61%	Control: Distilled water 1ml/kg	Significance level p<0.05
Plastic bottom cages, sawdust bedding and nesting materials	12-hour light/dark cycle (lights on 08:00 – 20.00)	Oral Gavage at 14:00h daily GD7-GD21	Parametric tests: Two-Way ANOVA *Post hoc* SNK Non-Parametric tests: Kruskal-Wallis test



Major Findings

MA has no effect on maternal daily body weight

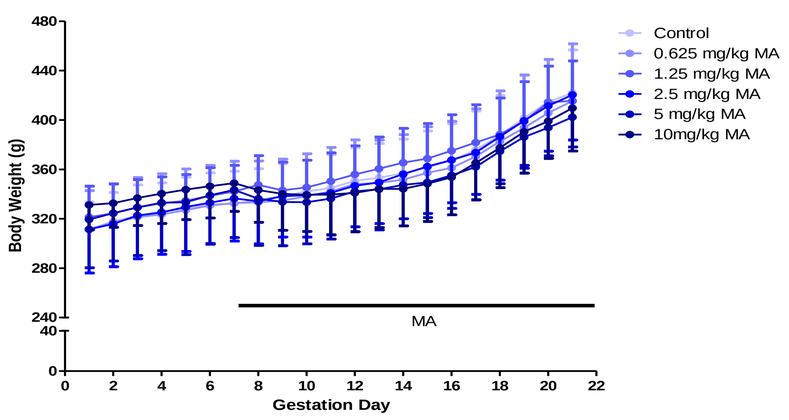


Fig 1: Data expressed as Mean ± SD; n=5-10 dams/group

MA reduces total body weight gain over the first dosing period

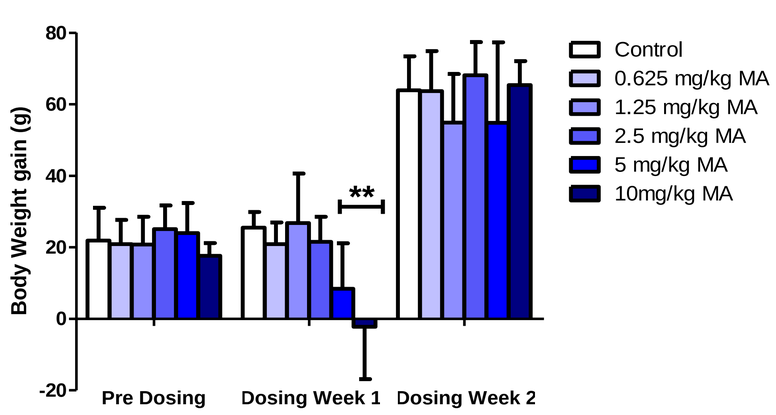


Fig 2: Data expressed as Mean ± SD ; n=5-10 dams/group
**p<0.01 vs. Control

MA reduces total food consumption over the first dosing period

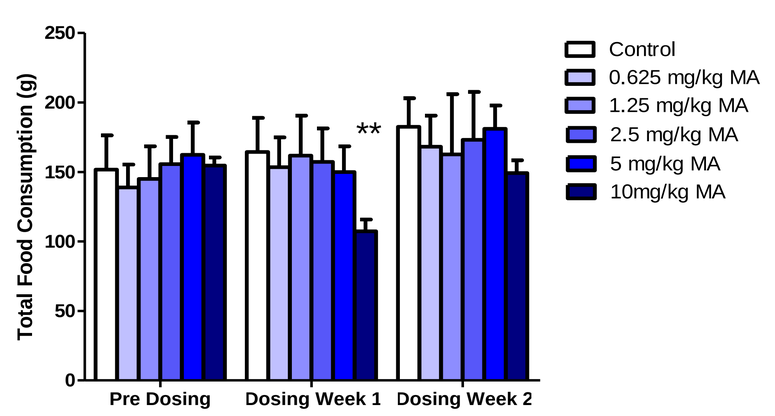


Fig 3: Data expressed as Mean ± SD; n=5-10 dams/group
**p<0.01 vs. Control

MA increases the % of neonatal deaths and maternal deaths

Group	Dose mg/kg Control	0.625	1.25	2.5	5	10
% Mothers Died	0	0	0	0	16.7	37.5
% Pups stillborn	0.0	0.0	0.0	0.0	1.3	4.2
% Pups found dead	2.9	0.7	1.9	7.1	8.6	17.6
% Pups eaten	0.4	0.9	0.4	0.9	6.1	21.1
% Total Deaths	3.3	1.6	2.3	8.0	16.0	42.9

Table 1: Data expressed as percentages, n=5-10 litters/dams per group.

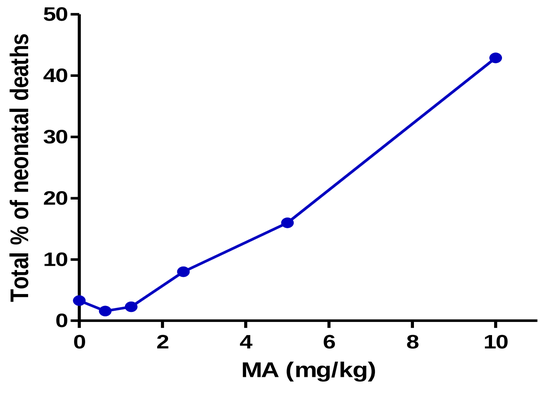


Fig 4: Data expressed as total % of pups that died n=53-146 pups/group.

MA delays development of ano-genital distance in males (PND 3)

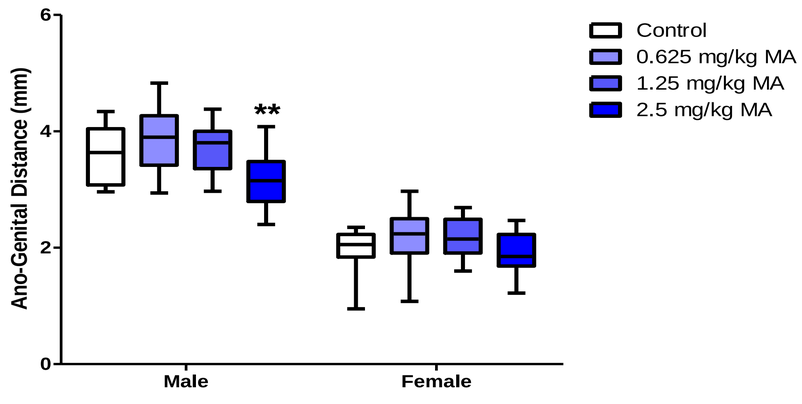


Fig 4: Data expressed as Median ± IQ Range; n=16-20 pups/group; **p<0.01 vs. Control

MA delays surface righting in males and females (PND 3)

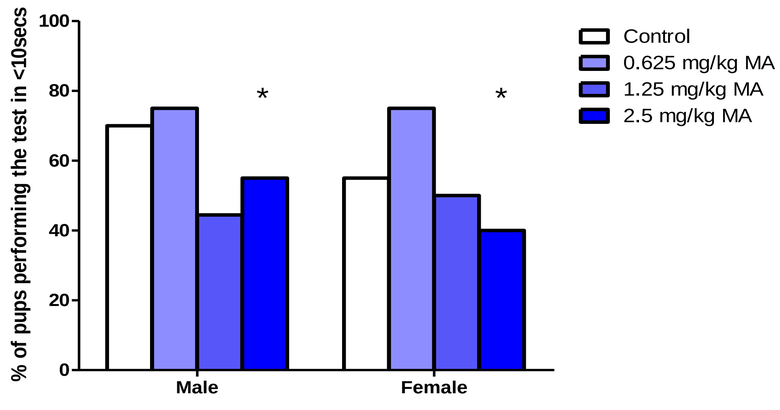


Fig 5: Data expressed as percentage of pups; n=16-20 pups/group; *p<0.05 vs. Control

MA reduces body length in males and females (PND 7)

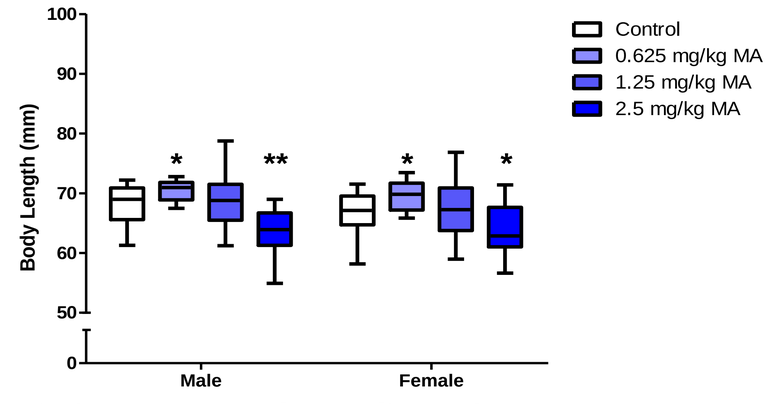


Fig 6: Data expressed as Median ± IQ Range; n=16-20 pups/group; **p<0.01 vs. Control, *p<0.05 vs. Control

Conclusions

The incidences of maternal deaths, stillborns, filial death and filial cannibalism increased with the increasing dose of MA . Exposure to the 2.5 mg/kg MA dose resulted in a significant reduction in ano-genital distance in males, and in both sexes resulted in delayed fur appearance and eye opening, impairments in surface righting reflex and a reduction in body length. This demonstrates that by using pharmacologically relevant doses and route of administration, MA can have a profound dose-related effect on maternal and neonatal outcome. If extrapolated to the clinical scenario this will give cause for concern regarding the risks associated with this drug of abuse at relatively low doses.

References

1. National Advisory Committee on Drugs (NACD) & Public Health Information and Research Branch (PHIRB) 2008, Ballsbridge, Dublin 4 & Stormont, Belfast.

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