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Neurotoxic effects of valproic acid in Wistar rats: transgenerational alterations after exposure of the first generation

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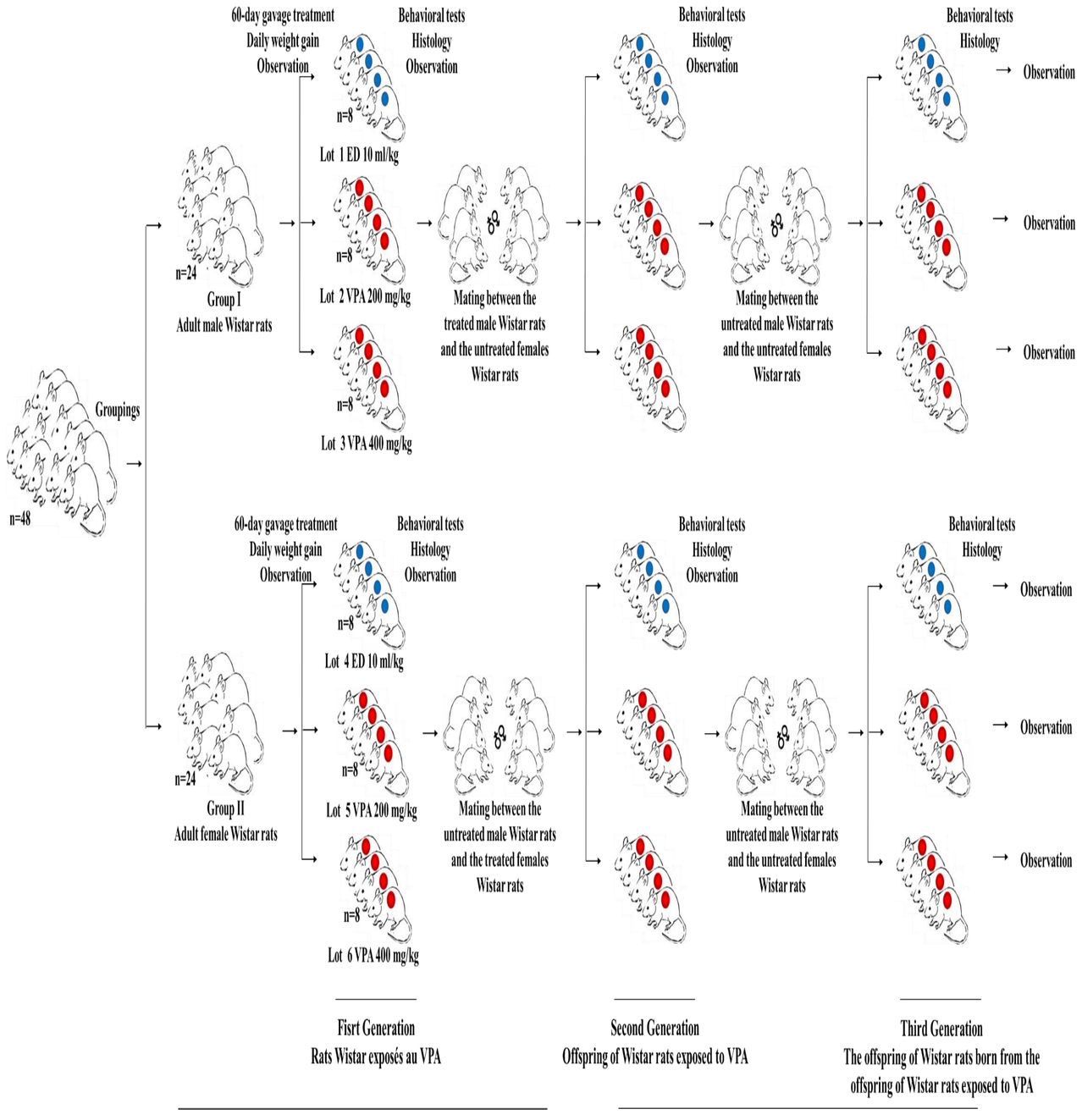
INTRODUCTION & AIM

Valproic acid (VPA) is a broad-spectrum anticonvulsant that is particularly effective against epilepsy, acting by increasing GABA (cerebral inhibitor) activity and blocking sodium channels. Despite its therapeutic benefits, VPA presents significant risks. This study aimed to evaluate the neurotoxic effects of VPA in Wistar rats.

METHOD

Forty-eight male and female Wistar rats were divided into six groups: (1 and 4) a control group, (2 and 5) a VPA 200 mg/kg group, and (3 and 6) a VPA 400 mg/kg group. The products were administered daily by gavage for 60 days. Wistar rats weighing between 100 and 300 g exposed to VPA and their offspring constituted our study population. Daily observations were made for three generations of Wistar rats. Behavioral, biochemical, cerebral histological, and reproductive parameters were evaluated, as well as 8-OH-dG dosage by PCR on one genetic region.



The rats were divided into two groups of males and females. These groups were subdivided into six batches. Batches 1 and 4 were the control batches for the two different groups. Batches 2, 3, 5, and 6 were the batches exposed to VPA. They were treated for sixty days by gavage. They were also observed, weighed daily, and subjected to behavioral tests. These Wistar rats constituted the first generation.

The second generation was born of Wistar rats exposed to VPA. By mating the rats born to Wistar rats exposed to VPA, a third generation was obtained. The second and third generations were not treated. Both generations were observed, weighed daily and subjected to behavioral tests.

Fig 1. Protocol expérimental

RESULTS & DISCUSSION

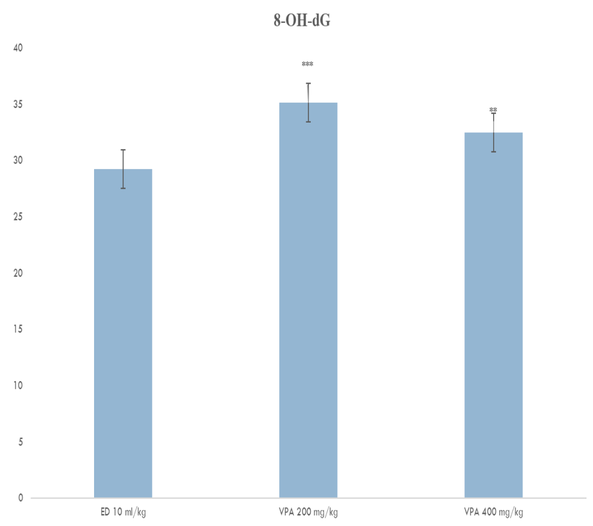


Fig 2. First-generation oxidative DNA damage

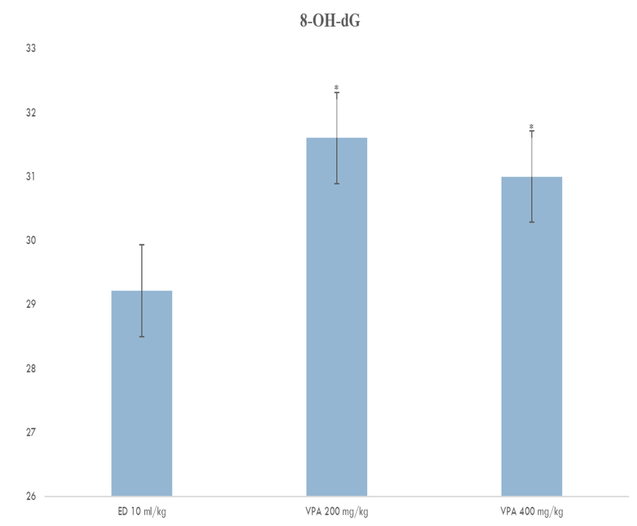


Fig 3. Second-generation oxidative DNA damage

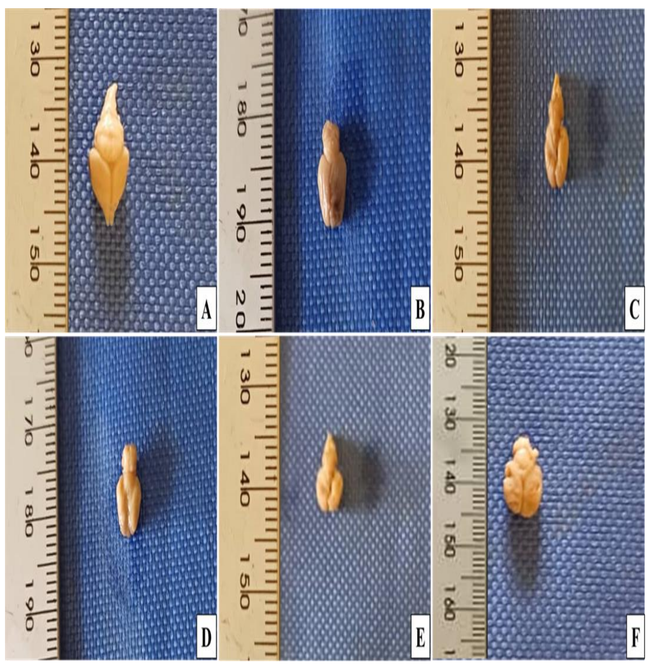


Fig 4. Photographs of size and shape abnormalities (B, C, D, E, and F) and a normal brain (A) from the second generation

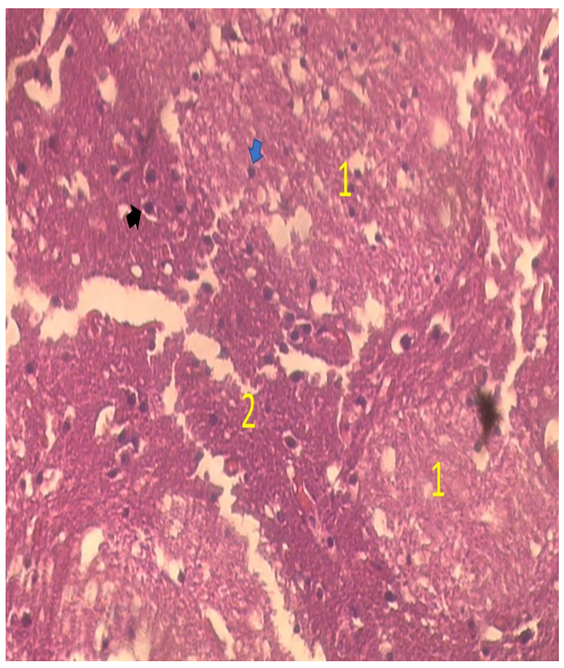


Fig 5. Onthese HE-stained histological sections, foci ofcerebral parenchyma necrosis (1) are observed withthe presence of a few glial cells (blue arrow). Between these foci of necrosis, we observe areas ofnormal parenchyma (2) with oligodendroglial-type glial cells (black arrow).

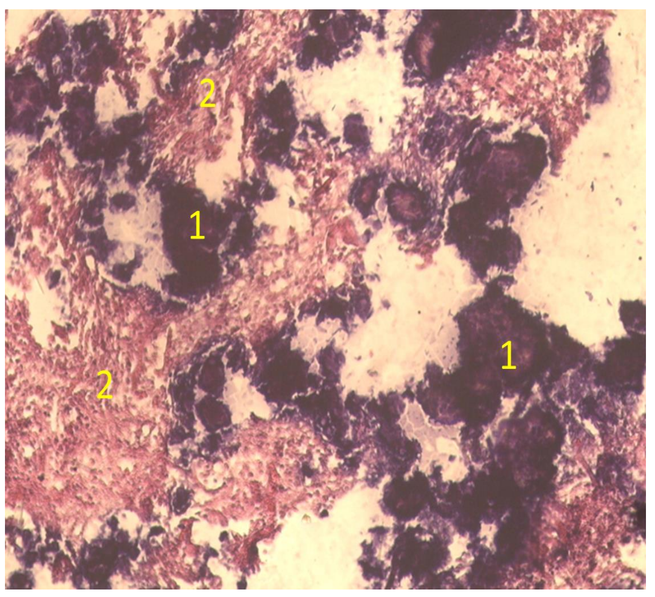


Fig 6. HE-stained histological sections show multiple calcifications (1) and bands of fibrosis (2)

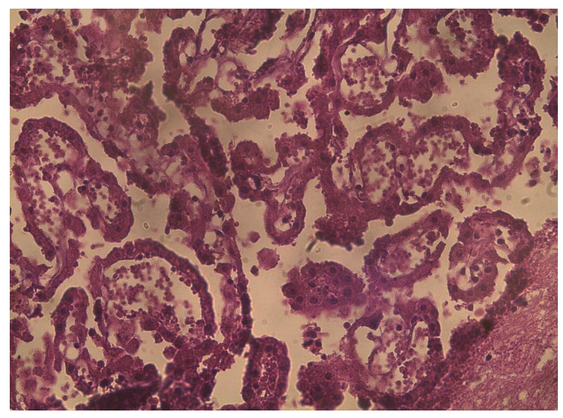


Fig 7. Microphotograph showing a tumor lesion with cerebellar papillary architecture (HE x 40)

CONCLUSION / FUTURE WORK

The abnormalities observed in the three generations of Wistar rats during our study reflect VPA-induced neurotoxicity at the doses studied after the exposure of the first generation. Our future work will consist of consolidating a neurotoxicity model based on APV.

REFERENCES

Landry Martial Miguel, Archange Emmanuel Mboungou Malonga et al. Early neurodevelopmental anomalies in young rats from adult female treated with valproic acid. International Journal of Pharmacology and Toxicology, 9 (2) (2021) 75-83