LIBERTY UNIVERSITY

The Study of the Effect of Post-natal Day 26 Methotrexate Chemotherapy on Cognition

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Purpose and Rationale

- A previous study done in mice with methotrexate showed that it had detrimental effects in the microglial cells, astrocytes, and the oligodendrocytes. Evidence has shown similar damaging cognitive effects in adolescent patients diagnosed with ALL that received methotrexate.
- This study will determine whether similar cognitive effects exist in Sprague Dawley rats after methotrexate.
- The novel object recognition task proposed in this experiment is used to measure memory. Tests will be done for two months and possibly three months to determine how long cognitive effects last.
- The choice procedure is used to measure impulsivity, and this procedure has not been previously tested following methotrexate. It is important to determine if changes in choice also last for a long period of time.

Background

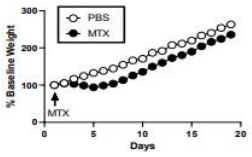

Figure 1. Effects of methotrexate on body weight. On day one, male rats received either phosphate-buffered saline (PBS, N = 4) or methotrexate (MTX, N = 4). Shown is the mean body weight as a percentage of day one.

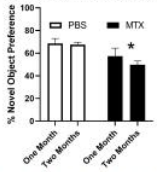

Figure 2. Effects of methotrexate on the novel object recognition task. Male rats received either phosphate-buffered saline (PBS, N = 4) or methotrexate (MTX, N = 4). The novel object recognition task was done one and two months after treatment. Shown is the mean ± SEM. *Significant main effect of treatment, $F(1, 6) = 11.93$, $p < .05$.

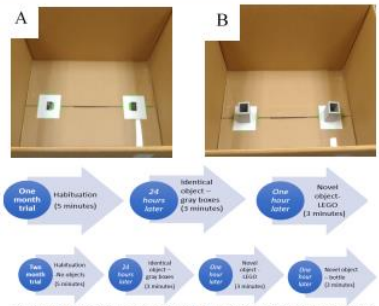

Figure 3. Novel object recognition task methods. (A) shows the box during the habituation period. (B) through (D) show the similar and novel objects used at one and two months. The diagram shows the trial progression for one month (top) and two months (bottom). If possible, three months will be tested with a similar design as two months.

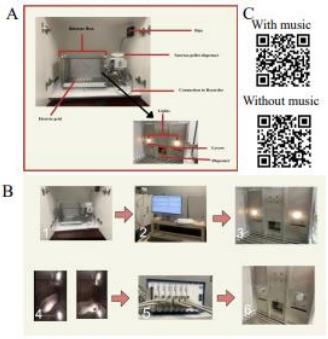

Figure 4. Choice procedure apparatus and procedure flow chart. (A) shows the operant conditioning chamber. (B) shows the progression of the program. **(1)** The rat is placed inside the operant chamber to begin the evaluation. **(2)** The program is turned on. **(3)** Following an intertrial period, the lights inside the box will turn on and the two levers appear on either side of the dispenser. **(4)** To reinforce the behavior targeted, rats receive either 1 sucrose pellet immediately (left lever) or 4 pellets after a series of delays (right lever). **(5)** The data is counted on a recorder connected to each box. The number of presses for either lever and the number of pellets received are recorded for our data. **(6)** After pellets are dispensed, the rats reenter the intertrial period. (C) shows QR codes to watch the procedure. (This figure was produced by Melida Molina, a former student in the lab.)

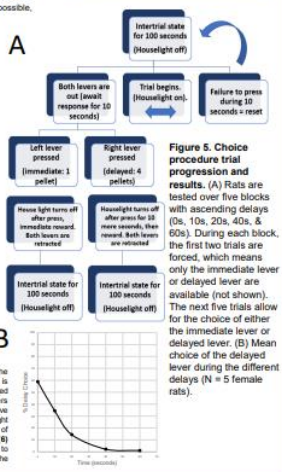

Figure 5. Choice procedure trial progression and results. (A) Rats are tested over five blocks with ascending delays (0s, 10s, 20s, 40s, & 60s). During each block, the first two trials are forced, which means only the immediate lever or delayed lever are available (not shown). The next five trials allow for the choice of either the immediate lever or delayed lever. (B) Mean choice of the delayed lever during the different delays (N = 5 female rats).

Goals and Expected Results

- Demonstrate the effect of methotrexate on memory as well as choice.
- Determine sex differences by testing male (n=6) and female (n=6) Sprague Dawley rats that receive either vehicle (PBS) or one injection of 250 mg/kg of methotrexate.
- Record and monitor female and male responses to the novel object recognition task up to the third month.
- Measure responses in the choice procedure four times a week for three months.
- It is expected that methotrexate will affect both male and female rats in both memory and choice.

Future Work

Success in understanding the effects of this drug will enable better treatment plans and overall long-term better quality of life for cancer patients. This is incredibly significant because the common age group administered this drug treatment ranges from two to five years old. The young age of these patients demands further studies concerning the vulnerability of the developing brain to the toxicity of methotrexate. Understanding the effect of methotrexate on the microglia, astrocytes, and oligodendrocytes will allow scientists and doctors in the future to compensate effectively for the toxicity of methotrexate on neural function via therapy or drug treatment.

Acknowledgments

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References

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