Refining Drug Delivery: Behavioral and Pharmacokinetic Validation of MDA in Mice

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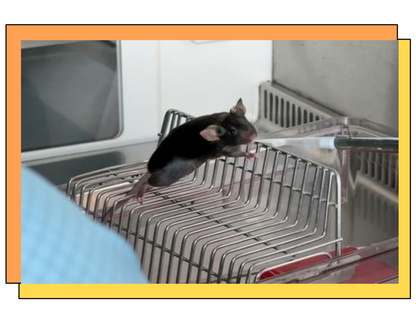
Introduction

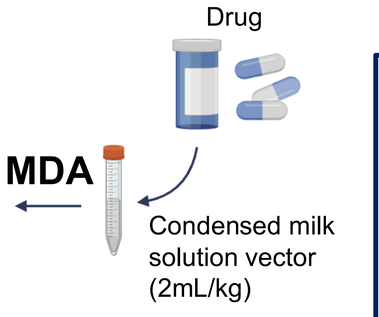
Precise and low-stress drug delivery is essential for reliable outcomes in neuroscientific research, especially in **behavioral & pharmacological** studies.

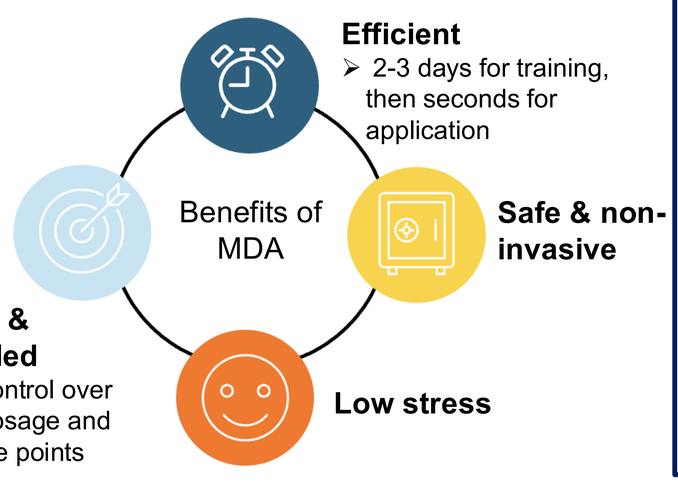
This project aims to validate the micropipette-guided drug administration (MDA) method in mice across behavioral and pharmacokinetic paradigms.

Primary objectives

- **Assess** effects of acute and chronic MDA treatment on performance in reward-driven behavioral tests.
- **Compare** MDA and subcutaneous injection for carprofen delivery in a pharmacological model.







MDA Oral Drug Administration

Micropipette-guided **D**rug **A**dministration (MDA) is a stress-reducing oral delivery method in mice that enables precise dosing without restraint.

The mice learn to drink the drug, formulated in a palatable solution, over 2-3 training days (**Fig. 1**).

Day 1: Mice are restrained and introduced to the milk solution via pipette.

Day 2: Mice are loosely restrained by the tail base and fed the milk.

Day 3: Mice voluntarily drink the milk solution without restraint.

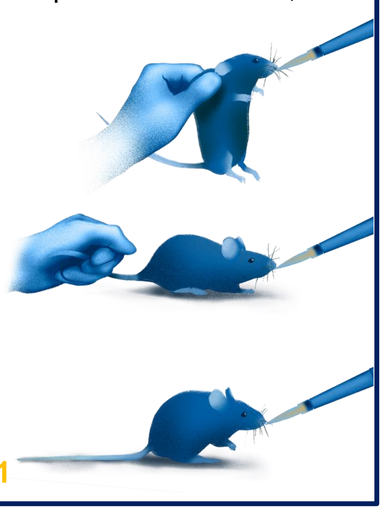


Fig. 1

METHODS

1 Behavioral Assessment

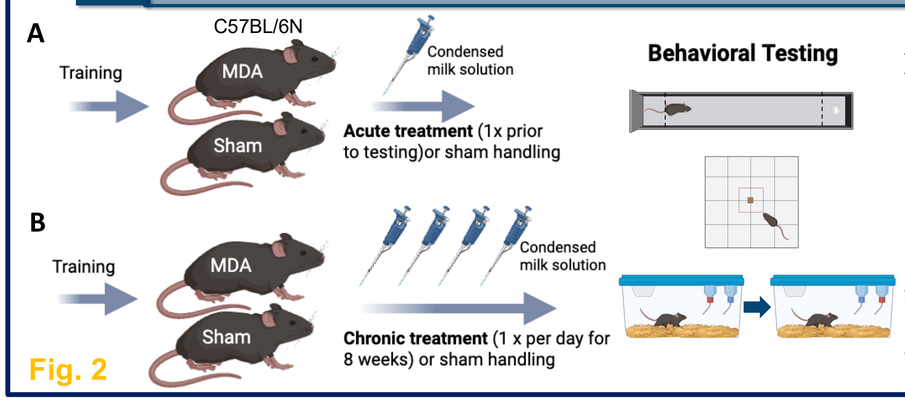


Fig. 2

Adult mice were treated with either **acute** (a) or **chronic** (b) MDA (**2mL/kg**) using a condensed milk solution or received sham handling. Reward-related behaviors were then assessed using a series of behavioral tests.

2 Pharmacokinetic Study

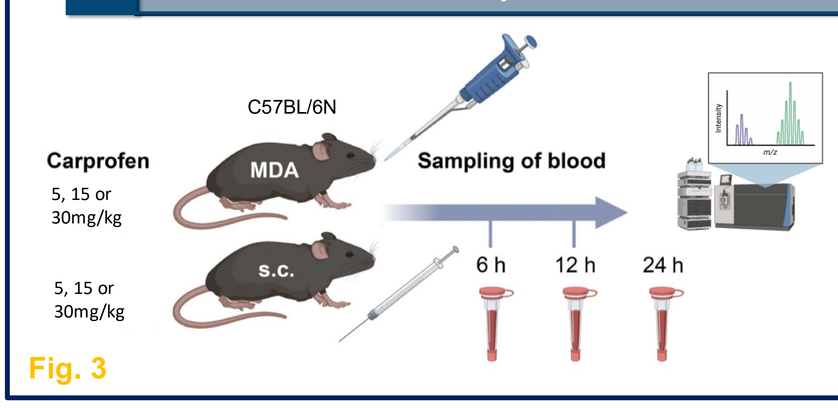


Fig. 3

Mice received **carprofen**(5, 15 or 30mg/kg) via **MDA or subcutaneous injection**. Plasma levels were measured by LC-MS to evaluate the suitability of MDA for systemic drug delivery.

RESULTS & CONCLUSIONS

1 MDA Has Minimal Impact on Reward-Driven Behaviors

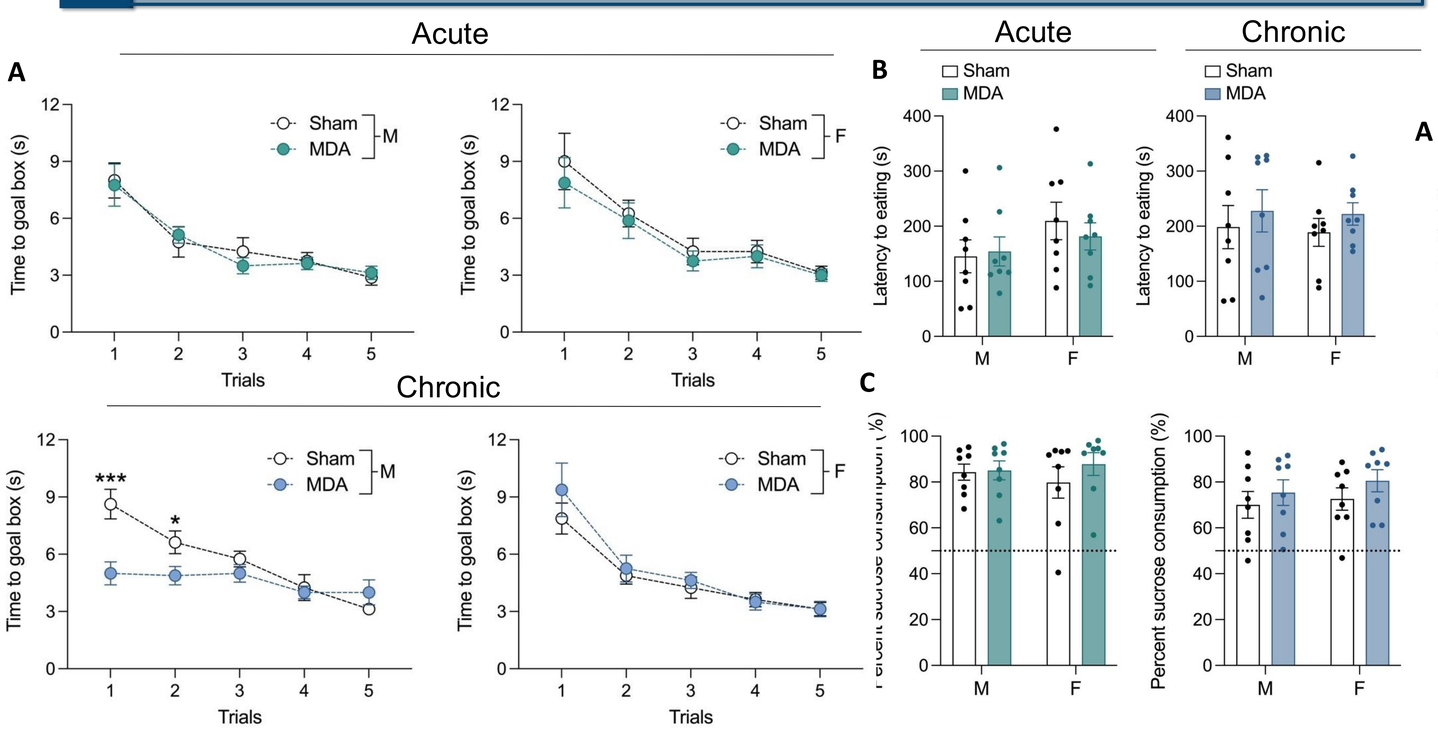


Fig. 4 Behavioral performance in reward-related tests following acute and chronic MDA treatment. (A) Time taken to reach the goal box in the incentive runway test for male (M) and female (F) mice after **acute** or **chronic** MDA treatment versus sham handling. (B) Latency to eat in the novelty-suppressed eating (NSE) test under the same conditions. (C) Percent sucrose consumption in the sucrose preference test, with the dashed line indicating chance level (50%). Data from Krzyzaniak et al., 2025.

2 MDA Achieves Therapeutic Carprofen Levels Comparable to Injection Routes

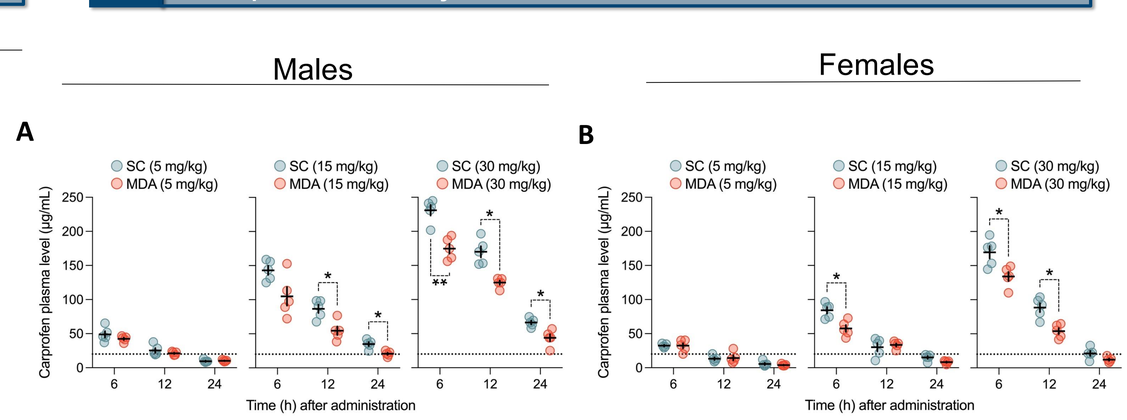


Fig. 5 Plasma concentrations of carprofen metabolites in C57BL/6N mice following administration via micropipette-guided delivery (MDA) or subcutaneous (SC) injection. (A) Male mice; (B) Female mice. Mice received 5, 15, or 30 mg/kg carprofen, and plasma samples were collected at 6-, 12- and 24-hours post-administration.

MDA enables low-stress, precise oral dosing in mice, with no major behavioral differences and lower but comparable pharmacokinetic profiles. These findings support its use as a reliable, welfare-conscious alternative and a refinement in line with the 3Rs.

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