Astrocyte-Regulated ATP Signaling on Motivational Behavior in Mice

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INTRODUCTION

- Dopaminergic neurons release dopamine at specific brain regions to regulate motivational pathways. It has been demonstrated that elevated dopamine levels further increase motivation in mice to obtain a food reward.
- Astrocytes release ATP through exocytosis to modulate neuronal activity. This mechanism occurs via the vesicular nucleotide transporter gene VNUT to provide a mechanism for the storage and release of ATP.
- A transgenic mice model in which VNUT is silenced in astrocytes is used to test the motivation of both sexes of mice compared against the wild type.

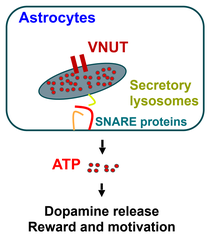
OBJECTIVE

We hypothesize that disrupting VNUT activity in male and female mice will affect motivational behavior.

METHODOLOGY

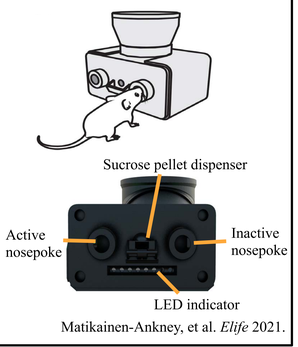
- **Generation of mouse model:**

VNUT-flox mice X *Aldh1l1*-CreERT2 mice (astrocyte-specific Cre)
↓
iA-VNUTKO mice
↓
Tamoxifen injections to activate CreERT2
↓
VNUT-flox allele recombination in astrocytes
↓
VNUT knockout specifically in astrocytes



- **Motivational behavioral assessment:**

Fixed ratio 1 (FR1) schedule 1h for 5 days
↓
Fixed ratio 5 (FR5) schedule 1h for 5 days
↓
Progressive ratio (PR) schedule for 1.5h 3 days
Formula: Effort required = $(5 \times e^{0.2n}) - 5$
↓
Breakpoint: the point where the mouse give up



Matikainen-Ankney, et al. *Elife* 2021.

RESULTS

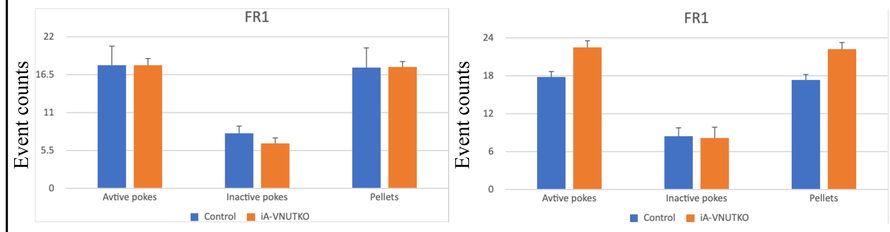


Figure 1: Performance of WT vs VNUTKO in male (left) and female (right) mice on FR1 schedule.

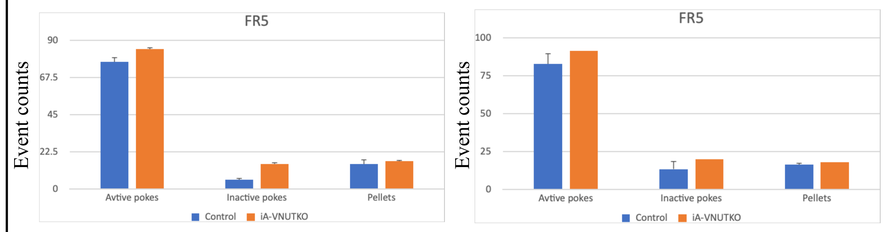


Figure 2: Performance of WT vs VNUTKO in male (left) and female (right) mice on FR1 schedule.

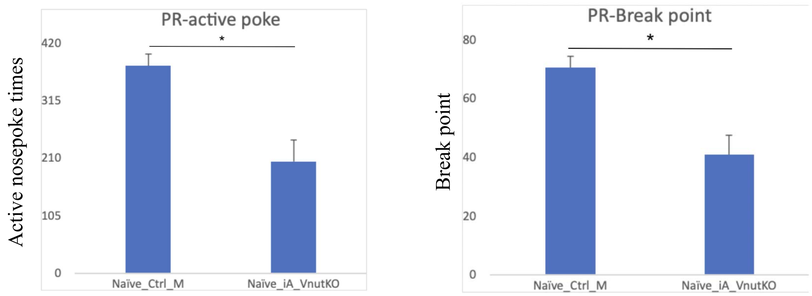


Figure 3: Performance of male mice on progressive schedule.

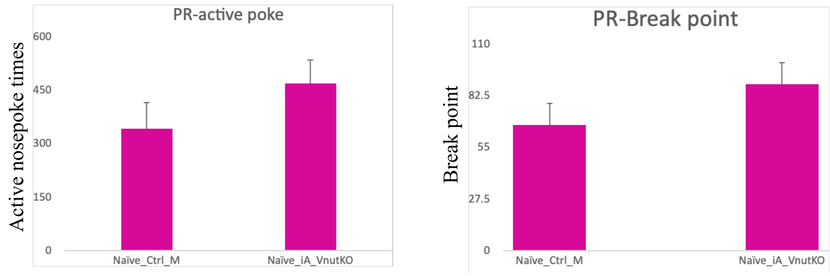


Figure 4: Performance of female mice on progressive schedule.

CONCLUSIONS

- No significant differences in associative learning were seen between the WT and VNUTKO mice in the FR1 and FR5.
- No significant differences in associative learning were seen between the male and female mice in the FR1 and FR5.
- Male VNUTKO mice exhibit significantly decreased motivational behavior compared to male WT mice.
- Female VNUTKO mice appear to have increased motivational behavior compared to female WT mice.

RECOMMENDATIONS

Future study:

- Introduce other factors that could affect motivation, such as chronic stress or depression.
- Further separate experimental groups by age.
- Associate behavioral outcomes with real-time dopamine signaling in the brain of the same mouse.

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