ABSTRACT

Efecto de la administración repetida de un precursor dopaminérgico sobre la preferencia por los refuerzos activos en ratones Pitx3-Aphakia KO en ambos sexos

Palabras clave: Dopamina, L-DOPA, Núcleo Accumbens, Conducta motivada, Pitx3-aphakia.

La conducta motivada está caracterizada por altos niveles de activación, vigor y persistencia. La toma de decisiones relacionada con el esfuerzo está regulada por la dopamina (DA) del Núcleo Accumbens (Acc). El factor de transcripción Pitx3 es necesario para el desarrollo de las neuronas dopaminérgicas del mesencéfalo, su modificación puede alterar los niveles de DA. Los ratones KO Pitx3-aphakia (APH KO), tienen bajos niveles de DA.

En el presente estudio, evaluamos el efecto de la modulación dopaminérgica en ratones macho y hembra KO Pitx3-aphakia (APH KO) y ratones control (WT). Tras la administración crónica de un precursor de DA (L-DOPA 5 mg/kg), los animales se evalúan en la preferencia por la selección de reforzadores con diferentes requerimientos de esfuerzo en la tarea del laberinto en T de tres opciones, donde estos pueden interactuar libremente con 3 reforzadores: rueda de actividad (RW), bolitas de sacarosa o un olor floral. Ambos grupos recibieron L-DOPA durante 10 días, los datos se obtuvieron el décimo día de tratamiento.

Los resultados del presente estudio muestran que hay diferencias significativas en la comparación de la LB vs el décimo día de tratamiento, ya que en los ratones macho de ambos grupos incrementó el tiempo en RW, sin embargo, las hembras de ambos grupos pasaron menos tiempo en el RW tras la administración del fármaco en comparación con los machos. Estos resultados sugieren que la L-DOPA incrementa la elección de reforzadores más activos (RW) frente a reforzadores más pasivos (bolitas de sacarosa o un olor floral) en los machos.

Esto tiene implicaciones para el desarrollo de futuros tratamientos de síntomas como fatiga o la anergia observados en gran variedad de psicopatologías.

Effect or repeated administration of a dopaminergic precursor on the preference for active reinforces in Pitx3-Aphakia KO mice of both sexes

Key words: Dopamine, L-DOPA, Nucleus Accumbens, Motivated behavior, Pitx3-aphakia.

Motivated behavior is characterized by high levels of activation, vigor and persistence. Effort-related decision-making is regulated by dopamine (DA) in the nucleus accumbens (Acc). The transcription factor Pitx3 is required for the development of midbrain dopaminergic neurons, its modification can alter DA levels. Pitx3-aphakia KO (APH KO) mice have low DA levels.

In the present study, we evaluated the effect of dopaminergic modulation in male and female KO Pitx3-aphakia (APH KO) and control (WT) mice. After chronic administration of a DA precursor (L-DOPA 5 mg/kg), animals are tested on preference for selection of reinforcers with different effort requirements in the three-choice T-maze task, where they can freely interact with 3 reinforcers: activity wheel (RW), sucrose pellets or a floral odor. Both groups received L-DOPA for 10 days, data were obtained on the 10th day of treatment.

The results of the present study show that there are significant differences in the comparison of LB vs. 10th day of treatment, as in male mice of both groups increased time in RW, however, females of both groups spent less time in RW after drug administration compared to males. These results suggest that L-DOPA increases the choice of more active reinforcers (RW) versus more passive reinforcers (sucrose pellets or a floral odor) in males.

This has implications for the development of future treatments for symptoms such as fatigue or anergy observed in a variety of psychopathologies.

EFFECT OF REPEATED ADMINISTRATION OF A DOPAMINERGIC PRECURSOR ON THE PREFERENCE FOR ACTIVE REINFORCES IN PITX3-APHAKIA KO MICE OF BOTH SEXES

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INTRODUCTION

- The **nucleus accumbens (Nacb)** is considered the neural interface between motivation and action. Nacb dopamine (DA) is involved in motivational processes, including behavioral arousal.
- **Behavioral activation** allows us to initiate and maintain goal-directed behaviors. A reduction in DA would lead to symptoms such as anergia, fatigue or psychomotor slowing. This symptomatology is typical in pathologies such as Parkinson's disease, depression or as negative symptoms in schizophrenia.
- **Pitx3-aphakia KO** (APH KO) mice are deficient in the Pitx3 transcription factor, which results in a loss of DA neurons in substantia nigra and ventral tegmental area and, as a result, in low levels of DA in Nacb and dorsal striatum.
- **L-DOPA** is the precursor of DA, the enzyme dopa decarboxylase converts L-DOPA to DA. Administration of L-DOPA is used to restore dopaminergic deficiencies.
- The **aim** of this study is to evaluate the effect of L-DOPA administration on Pitx3-aphakia KO mice of both sexes compared to wild type (WT) animals.

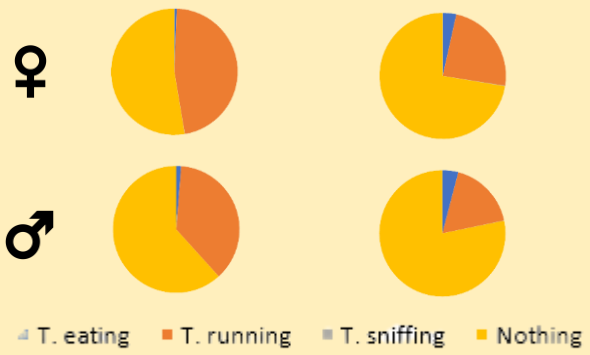
METHODS

Animals

C57BL/6J, male and female mice **Pitx3-aphakia KO (APH KO) mice** and wild type (WT) control mice were used.

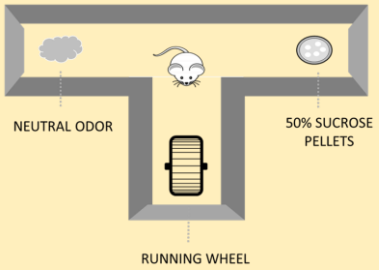
WT MICE N = 8
(3 females / 5 males)

APH KO MICE N = 14
(9 females / 5 males)



Experimental Paradigm:

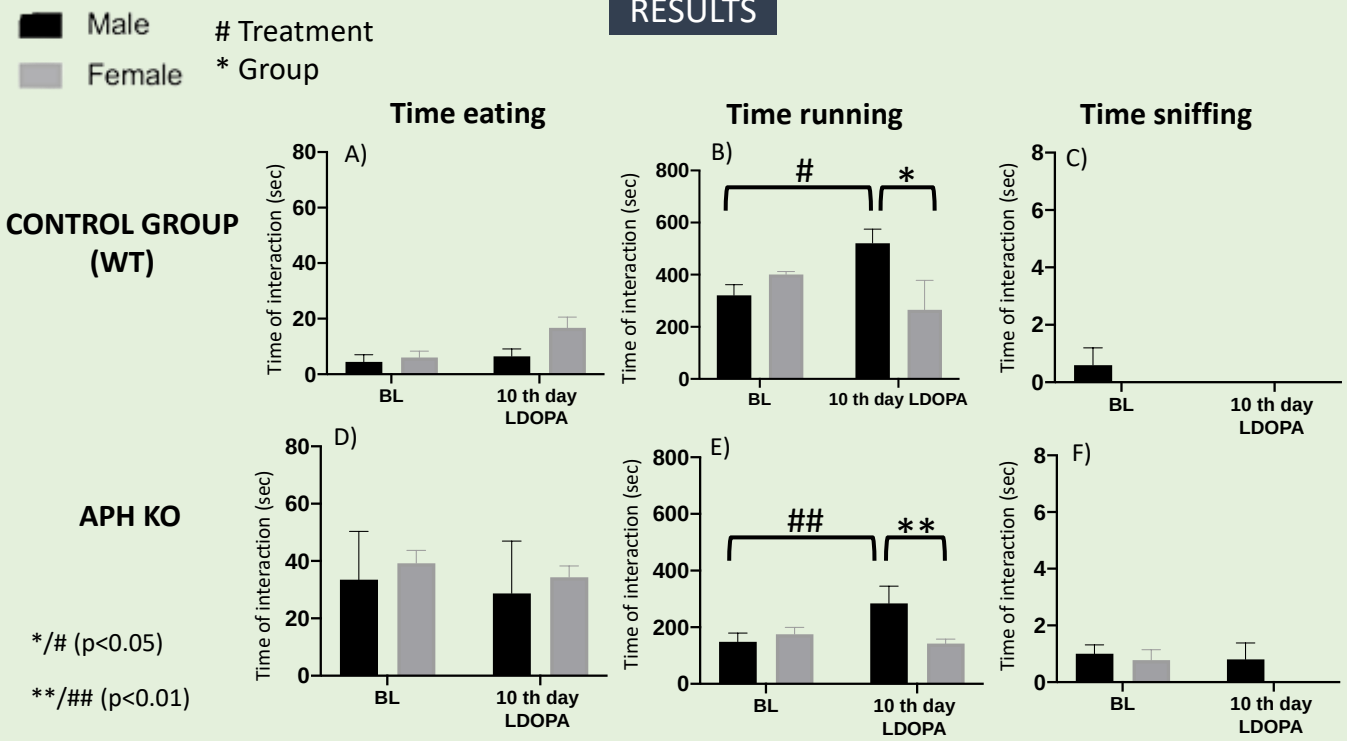
THREE-CHOICE-T-MAZE TASK



Pharmacological Treatment

Both groups received intraperitoneally (IP) **L-DOPA** (5 mg/kg) once a day, for 10 days, 1 hour before being evaluated in the Three-choice-T-maze task

RESULTS



CONCLUSIONS

- As expected, under basal conditions (BL) WT mice of both sexes spent more time than APH KO mice in the RW and less time eating or sniffing, indicting that APH KO mice show a more sedentary profile.
- L-DOPA increases the choice of more active reinforcers (RW) versus more passive reinforcers (sucrose pellets or a floral odor) in males but not in females. WT females showed a small (non-significant) reduction in time in the RW and a compensatory increase in time eating.
- These results have implications for the development of future treatments for symptoms such as fatigue or anergia observed in a variety of psychopathologies. Potential sex differences should be taken into account when given pharmacological treatments.

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