HOW DIFFERENT TETRABENAZINE (TBZ) TREATMENTS AFFECT CDNF LEVELS IN THE LATERAL AND MEDIAL DORSAL STRIATUM. DIFFERENCES BETWEEN SEXES

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ABSTRACT

Brain dopamine neurotrophic factor (CDNF) is a protein that acts as a neurotrophic factor, protecting and restoring dopaminergic (DA) neurons. CDNF has been studied primarily in nigrostriatal DA neurons in several animal models of Parkinson's disease (PD), a chronic neurodegenerative disorder that causes degeneration and death of neurons in the substantia nigra pars compacta. Tetrabenazine (TBZ), a drug that induces PD-like symptoms in rodents, inhibits the vesicular monoamine transporter type 2 (VMAT2), depleting DA in the brain and making it a common model of PD. This study examines whether DA depletion following TBZ administration affects CDNF immunoreactivity in the dorsolateral striatum (DLS) and dorsomedial striatum (DMS), regions that receive axonal projections from the substantia nigra pars compacta. We assessed the impact of an acute dose of TBZ versus repeated administration of TBZ for five days on CDNF levels and explored possible sex differences. The results show that control groups of female mice had increased CDNF immunoreactivity in both DLS and DMS, compared to male mice. However, there were no significant differences in the different TBZ treatments in sex or structures with respect to CDNF levels. Some significant trend is observed in the female group in the DMS. This suggests that TBZ does not affects CDNF levels. However, the results are not conclusive. Possible limitations of this study would be the use of a single dose of TBZ and a small animal sample, suggesting a higher dose of TBZ and the increase of subjects for future research.

Key words: *CDNF, Tetrabenazine, Dopamine, Parkinson, Dorsal Striatum*

RESUMEN

El factor neurotrófico de dopamina cerebral (CDNF) es una proteína que actúa como factor neurotrófico, protegiendo y restaurando las neuronas dopaminérgicas (DA). CDNF se ha estudiado principalmente en neuronas DA nigroestriatales en varios modelos animales de la enfermedad de Parkinson (EP), un trastorno neurodegenerativo crónico que causa degeneración y muerte de neuronas en la sustancia negra pars compacta. La tetrabenazina (TBZ), un fármaco que induce síntomas similares a los de la EP en roedores, inhibe el transportador vesicular de monoaminas tipo 2 (VMAT2), agotando la DA en el cerebro y convirtiéndolo en un modelo común de EP. Este estudio examina si el agotamiento de DA después de la administración de TBZ afecta la inmunoreactividad CDNF en el cuerpo estriado dorsolateral (DLS) y el cuerpo estriado dorsomedial (DMS), regiones que reciben proyecciones axonales de la sustancia negra pars compacta. Evaluamos el impacto de una dosis aguda de TBZ versus la administración repetida de TBZ durante cinco días sobre los niveles de CDNF y exploramos posibles diferencias de sexo. Los resultados muestran que los grupos de control de ratones hembra tenían una mayor inmunoreactividad de CDNF tanto en DLS como en DMS en comparación con los ratones macho. Sin embargo, no hubo diferencias significativas en los diferentes tratamientos de TBZ en sexo ni en estructuras respecto a los niveles de CDNF. Si se observa cierta tendencia significativa en el grupo de hembras en el DMS. Esto sugiere que TBZ no altera los niveles de CDNF. Sin embargo, los resultados no son conclusivos. Posibles limitaciones de este estudio podrían ser el uso de una dosis única de TBZ y una muestra pequeña animales. Esto sugiere utilizar una dosis más alta de TBZ y aumentar el número de sujetos para futuras investigaciones.

Palabras clave: *CDNF, Tetrabenazina, Dopamina, Parkinson, Estriado dorsal*

How different tetrabenazine (TBZ) treatments affect CDNF immunoreactivity in the lateral and medial dorsal striatum. Differences between sexes

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INTRODUCTION

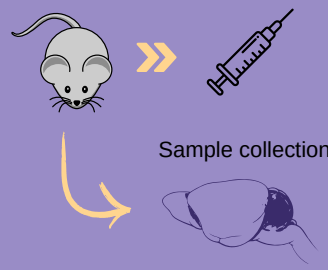
The **cerebral dopamine neurotrophic factor (CDNF)**, is a protein that acts as a neurotrophic factor (NFT) and has the ability to **protect and restore dopaminergic (DA) neurons**. CDNF has been studied mainly on nigrosestrial DA neurons (Eremin et al. 2021), using several animal models of Parkinson's disease (PD). PD is a chronic neurodegenerative disorder that affects neurons of the substantia nigra pars compacta, causing their degeneration and progressive death. **Tetrabenazine (TBZ)** is a drug known to induce PD-like symptoms, such as tremolous jaw movements in rodents (Podurgiel et al., 2013). It acts on the central nervous system by **inhibiting the vesicular monoamine transporter type 2 (VMAT2).** As a result, TBZ reduces the amount of neurotransmitter available for release at the neuronal synapse, depleting DA in the brain. Therefore, TBZ is a drug that is often used as a PD model.

METHODOLOGLY

Drug: Tetrabenazine (TBZ) administered intraperitonally (8 mg/kg)

- **Histological technique for staining**: Peroxidative Immunohistochemistry
- **Bregma coordinates**: between 0.98 and 1.34

Animals: CD1 young adults mice (6 weeks)



Sample collection

3 Groups

CONTROL	ACUTE	CHRONIC
5 days saline injection	4 days saline and 1 day TBZ injection	5 days of TBZ injection

	Control	Acute	Chronic
M	3	4	4
F	3	4	4

- **Dependent variable:** Number of cells immunoreactive to the CDNF antibody in the DLS and DMS
- **Independent variable:** Treatment (Control, Acute and Chronic) and sex (Male and Female)

OBJETIVE AND HYPHOTESIS

In the present work, we studied **if DA depletion, after TBZ administration, affects CDNF levels in two striatal areas the Dorso-Lateral Striatum (DLS) and the Dorso-Medial Striatum (DMS)** known to receive the axonal projections of the Substantia Nigra pars compacta the nuclei where DA neurons originate. We compare if an acute dose of TBZ is enough to change CDNF levels and if the repeated administration of TBZ during 5 days further produces effects on this NTF. We will also study the **potential differences between the sexes** in these effects.

RESULTS

Control group

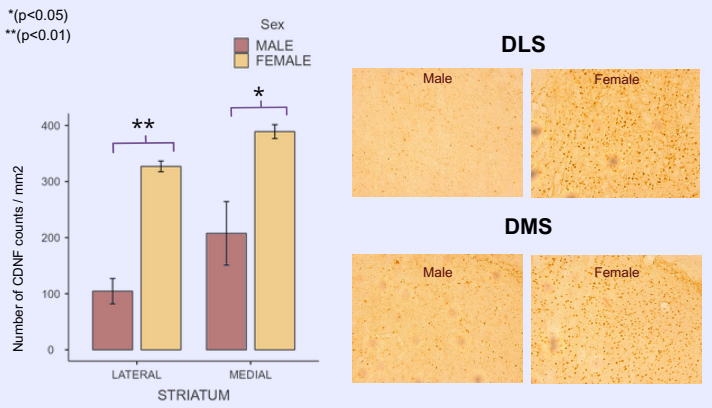


Figure 1: 2-factor ANOVA. Mean + SE of number of CDNF counts/ mm2 in control group that received vehicle.***p<0.05, **p<0.01 significant differences between sexes.**

Effect of treatment by structures and sexes

DLS

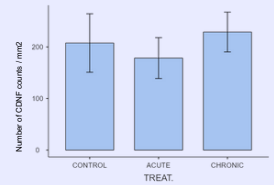


Figure 2: 1-factor ANOVA. Mean + SE of number of CDNF counts/ mm2 of the treatment effect on DLS in males (p=0.330).

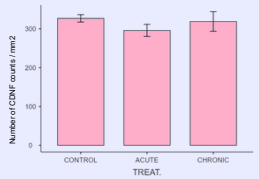


Figure 3: 1-factor ANOVA. Mean + SE of number of CDNF counts/ mm2 of the treatment effect on DLS in females (p=0.535).

DMS

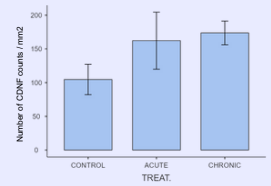


Figure 4: 1-factor ANOVA. Mean + SE of number of CDNF counts/ mm2 of the treatment effect on DMS in males (p=0.704).

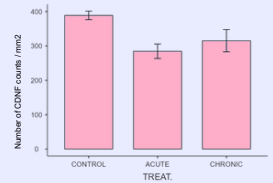


Figure 5: 1-factor ANOVA. Mean + SE of number of CDNF counts/ mm2 of the treatment effect on DMS in females (p=0.060). *Certain significant trend*

CONCLUSIONS

- In both DLS and DMS structures, **females present higher levels of CDNF immunoreactivity in the control group, compared to males.**
- There are **no significant differences between the different TBZ treatments according to structure and sex with respect to CDNF immunoreactivity**. A certain significant trend is observed in the group of females in the DMS. This could suggest that TBZ administration does not affect CDNF levels. However, as **limitations** of this work, only one dose of TBZ and the small animal sample are studied. It is proposed to study with a higher dose of TBZ and increase the number of subjects for future research.

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