

Kurkumin és ferulasav vizsgálata epilepszia modellben

**Dr. Budán Ferenc Ph.D., Szabó Péter, Dr. Szép Dávid Ph.D.,
Pál-Dittrich Bianka, Dr. Szentpéteri L. József Ph.D, Dr. Sík Attila Ph.D.**

PTE ÁOK, Transzdiszciplináris Kutatások Intézete, Pécs

PTE ÁOK, Élettani Intézet, Pécs

**MAGYAR TÁPLÁLKOZÁSTUDOMÁNYI TÁRSASÁG
XLVI. VÁNDORGYŰLÉSE
2023.10.06.**



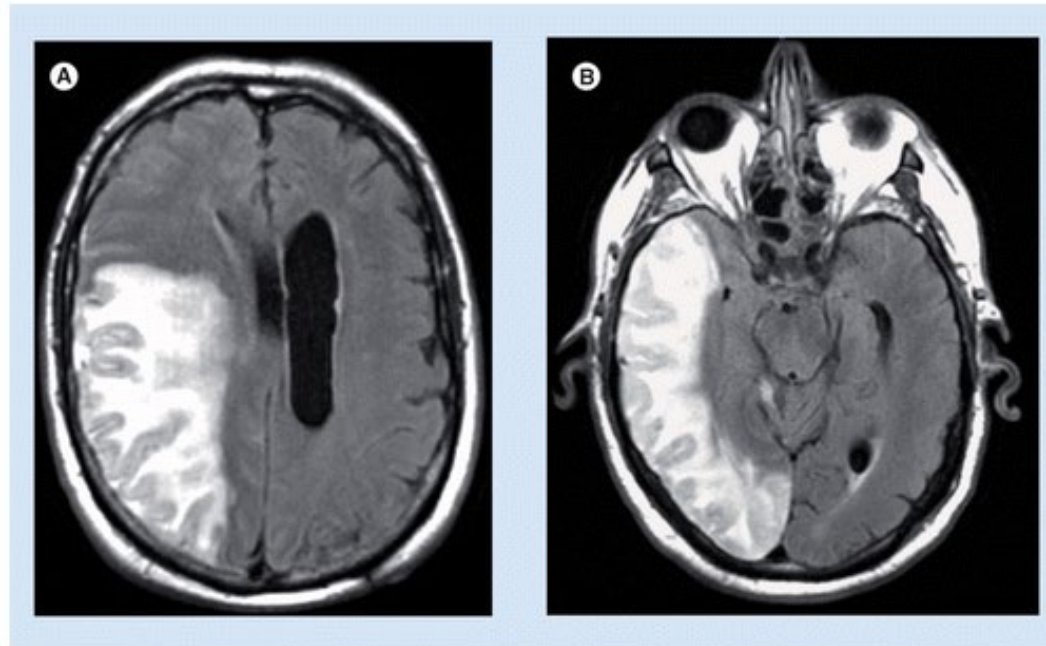


Figure 8. Epilepsy with EEG-imaging mismatch following stroke.

A 74-year-old patient presenting with a clinical EEG seizure focus within the left temporal lobe, but on MRI demonstrates large stroke within the contralateral right frontotemporal–parietal lobe as seen on fluid-attenuated inversion recovery images of the superior frontotemporal-parietal **(A)** and inferior temporal-parietal lobes **(B)**.

Epilepszia

- Prevalencia ~1 % - kb. 50 M ember
- 1/3 gyógyszeres terápia rezisztens
- Egészségkárosodással korrigált életévek 13 M/év (*Disability-adjusted life years (DALYs)*)
- Neurodegeneratív és pszichés betegségek ↑
- *Status epilepticus* életveszélyes

Epilepszia okai

- Agysérülés
- Sztrók
- Daganat
- Gyulladás
- Alkohol és kábítószeres (elvonásuk)
- Fertőzések (baktérium, vírus, parazita)
- K^+ és Na^+ ioncsatorna mutációk
- Fény inger, stb.

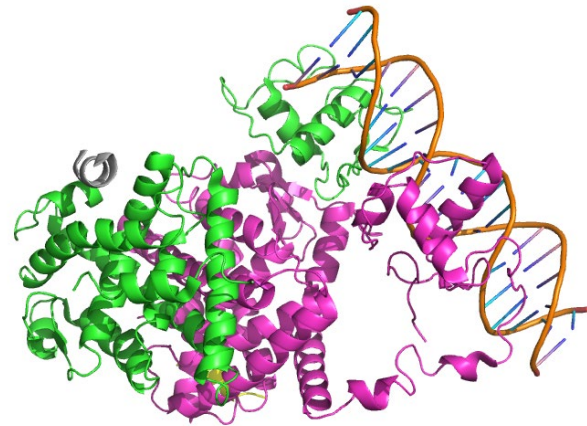


Epilepszia molekuláris okai

- KIR: K^+ ↑ ec.; ic. vagy ec. Ca^{2+} ↑
- NMDA és AMPA receptor aktiváció
- Kolinerg (M1) receptor stimuláció
- IL-1 β , IL-6, TNF- α , TGF- β 1, VEGF, MMP-9, NF- κ B, COX-2 ↑
- GABA_A receptor gátlás
- Sejt- és mitokondriális membrán sérülés

Epilepszia terápiája

- K^+ , Na^+ , Ca^{++} ioncsatorna gátlása
- GABA rec. aktiválása
- PPAR α aktiválása
- Stb



Kísérletesen:

– PPAR γ aktiválása – nem rec.-ligand kötődéssel

Chen A, et al. Am J Physiol Gastrointest Liver Physiol 2005; 288: G447-G456

Narala VR, et al. Gene Ther Mol Biol 2009; 13: 20-25

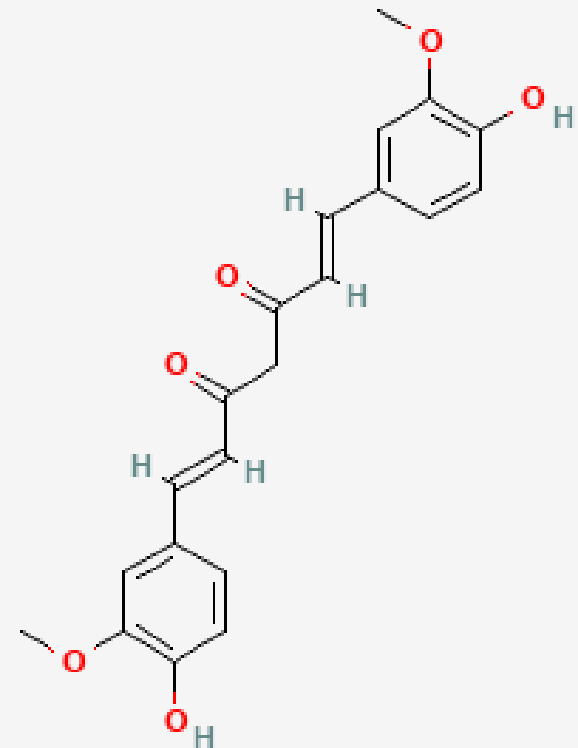
Jacob A, et al. PPAR Res 2007; 2007: 89369

Kurkumin



- Kurkumin és aktív metabolitjai (pl. ferulasav)
- Kurkuma (*Curcuma longa* Linn.)
- „Csodaszer” ...
 - kardiovaszkuláris
 - neopláziás
 - légzőszervi
 - metabolikus
 - autoimmun
 - emésztő traktus
 - neurodegeneratív
 - antimikrobiális
 - stb.

... betegségekre!



Ellentmondás

- Rossz biohasznosulás:
 - felszívódás
 - lebomlás
- Hatás helyére eljut –e?
- Hatásos dózis?
- Pleiotróp hatás
- Aktív centrum:
 - bomlik
 - rotál
 - kémiai környezetre érzékeny
- ← Aktív metabolitok, pl. ferulasav...

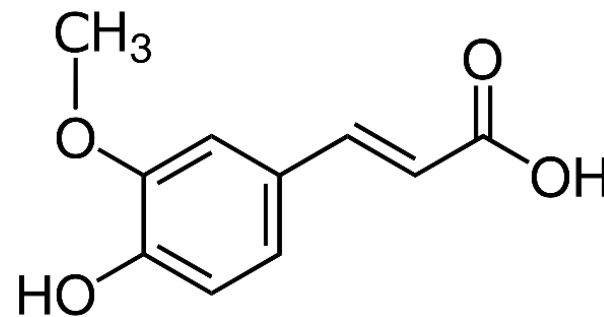


Lehetséges hatásmechanizmusok

- Antioxidáns –I ROS, NO-gyökök
- Gyulladáscsökkentő:
 - IL-ek aktivitása ↓
 - génexpressziók ↓
- Immunmoduláns
- Kolinészteráz serkentő
- Enyhe MAO gátló
- PPAR α aktivátor...

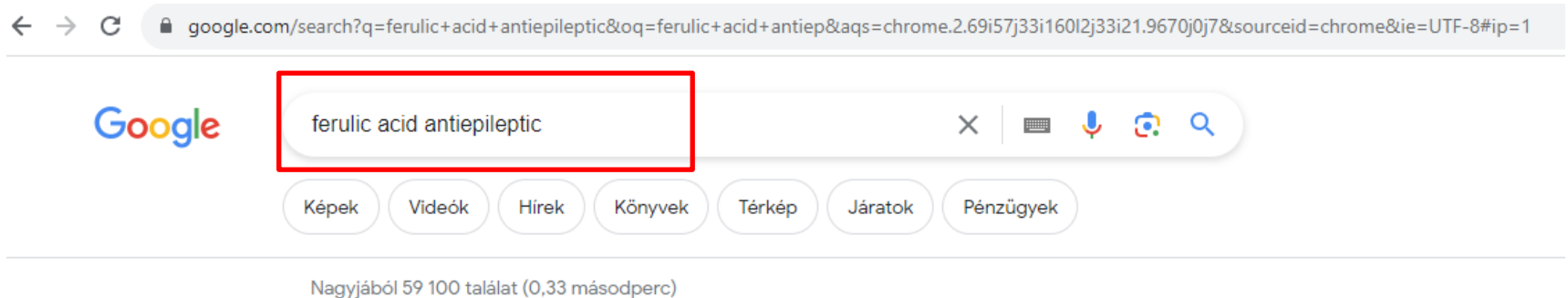
Ferulasav

- Aktív metabolit
- Antioxidáns
- LDL koleszterin ↓
- Gyulladáscsökkentő



Kérdésfelvetés

- Vajon a ferulasav önmagában mennyire epilepsziaellenes?





Nagyjából 1 550 találat (0,06 másodperc)

Bármikor
2023 óta
2022 óta
2019 óta
Egyéni tartomány...

Rendezés relevancia szerint
Rendezés dátum szerint

Bármilyen típus
Áttekinthető cikkek

szabadalmak is
 idézetek megjelenítése

Értesítés létrehozása

A review on potential footprints of **ferulic acid** for treatment of neurological disorders

[S Thapliyal](#), [T Singh](#), [S Handu](#), [M Bisht](#), [P Kumari](#)... - *Neurochemical ...*, 2021 - Springer
... and **ferulic acid**) have also demonstrated potent **anti-epileptic** effect ... **antiepileptic** and anti-epileptogenic potential of **ferulic acid**. ... over available marketed **anti-epileptic** drugs, which are ...
☆ Mentés 📄 Hivatkozás Idézetek száma: 32 Kapcsolódó cikkek Mind a(z) 6 változat

Ferulic acid exhibits antiepileptogenic effect and prevents oxidative stress and cognitive impairment in the kindling model of epilepsy

[P Hassanzadeh](#), [E Arbabi](#), [F Atyabi](#), [R Dinarvand](#) - *Life sciences*, 2017 - Elsevier
... **antiepileptic** drugs induce oxidative stress and cognitive impairment which may limit their clinical applications. **Ferulic acid** ... evaluated the effect of **ferulic acid** on pentylenetetrazole (PTZ) ...
☆ Mentés 📄 Hivatkozás Idézetek száma: 70 Kapcsolódó cikkek Mind a(z) 6 változat

Phytochemical and Network Pharmacology Based Evaluation of **Antiepileptic** Potential of Identified Metabolites in *Argimone mexicana*

[V Gahlot](#), [DK Yadav](#) - *Pharmacognosy Research*, 2021 - phcogres.com
... aimed for phytochemical and **antiepileptic** evaluation of identified ... **ferulic acid**, caffeic acid, berberine and angoline. In HPTLC quantitative analysis, the content of **ferulic acid**, caffeic acid...
☆ Mentés 📄 Hivatkozás Idézetek száma: 1 Kapcsolódó cikkek Mind a(z) 3 változat 📄

[PDF] phcogres.com

Ferulic acid supplementation for management of depression in epilepsy

[T Singh](#), [T Kaur](#), [RK Goel](#) - *Neurochemical Research*, 2017 - Springer
... Most of the **antiepileptic** drugs (AEDs) such as levetiracetam, ... , anti-inflammatory phytotherapy (**Ferulic acid**) appears a ... in combination with two doses of **ferulic acid** (40, 80 mg/kg/day/...
☆ Mentés 📄 Hivatkozás Idézetek száma: 35 Kapcsolódó cikkek Mind a(z) 4 változat

[PDF] A review on anxiolytic and **antiepileptic** effects of oleo–gum–resin of *Ferula asafoetida*

[PK Upadhyay](#), [O Singh](#), [A Yadav](#)... - *Am. J. Pharm. Heath ...*, 2014 - researchgate.net
... , **ferulic acid**, pinene, vanillin and free **ferulic acid**. **Ferulic acid** on treatment with hydrochloric acid is converted into umbellic acid, which loses water to form umbelliferone. ...
☆ Mentés 📄 Hivatkozás Idézetek száma: 3 Kapcsolódó cikkek 📄

[PDF] researchgate.net

Ferulic acid ameliorates pentylenetetrazol-induced seizures by reducing neuron cell death

[SH Zhang](#), [D Liu](#), [Q Hu](#), [J Zhu](#), [S Wang](#), [S Zhou](#) - *Epilepsy Research*, 2019 - Elsevier
... targets and to develop new **antiepileptic** drugs. **Ferulic acid** (4-hydroxy-3-methoxycinnamic acid, FA) is one of the derivatives of cinnamic acid. FA belongs to the hydroxycinnamic ...
☆ Mentés 📄 Hivatkozás Idézetek száma: 26 Kapcsolódó cikkek Mind a(z) 6 változat

[PDF] openrepository.com

Abstract

Aims

Some conventional antiepileptic drugs induce oxidative stress and cognitive impairment which may limit their clinical applications. Ferulic acid is a phenolic phytochemical with antioxidant and neuroprotective properties that prompted us to evaluate its therapeutic potential in epilepsy which is usually associated with oxidative stress and cognitive decline.

Materials and methods

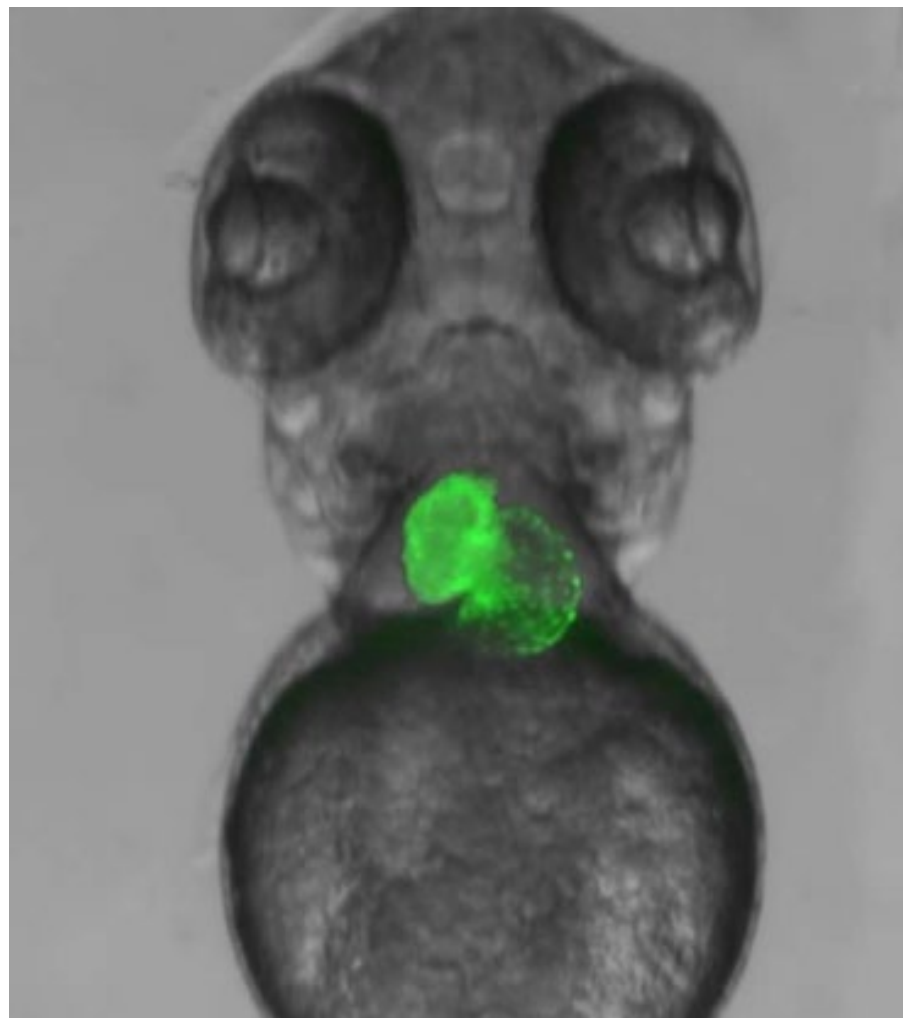
Male Wistar rats received 30mg/kg of pentylentetrazole (PTZ) intraperitoneally (i.p.) once every alternate day until the development of kindling. The locomotor activity, elevated plus maze, and passive avoidance tests were performed. Oxidative stress was evaluated by the determination of brain malondialdehyde and reduced glutathione. The effects of pre-treatment with ferulic acid (25, 50, 75, and 100mg/kg, i.p.) against PTZ-kindled seizures, cognitive impairment, and oxidative stress were investigated.

Key findings

Kindling was developed 34.18 ± 1.54 days after PTZ treatment which was associated with generalized tonic-clonic seizures (GTCS), myoclonic jerks, cognitive deficit, and oxidative stress. Ferulic acid at doses of 75 and 100mg/kg significantly reduced the seizure score, number of myoclonic jerks, cognitive decline and oxidative stress. Spontaneous locomotor activity did not significantly differ between the groups.

Zebradánió lárva modell

- Epilepszia vizsgálatára in vivo nem állat modell!
- High through put
- Olcsó
- Gyors
- 5 naposak, nem kell etikai engedély!
- Átlátszó - Ca szenzor neuronokba 3 D mikroszkóppal vizsgálható, hogy melyik idegsejt
- Excitatórikus sejteket gátol, vagy inhibitoros sejtet aktivál védő anyag? – Klasszikus farmakológia!



Pentilén-tetrazol

PTZ:

- GABA_A gátlása

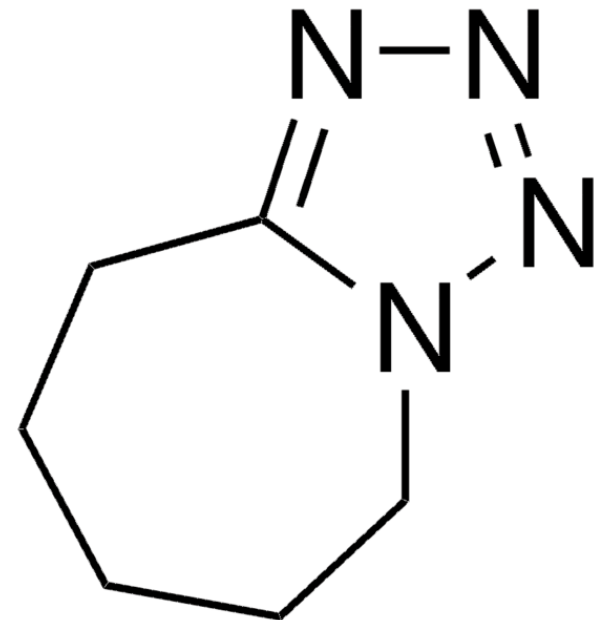
← Modulálja:

- 5-HT_{1A}, 5-HT₃

- NMDA

- glicin

- L-típusú Ca-csatorna



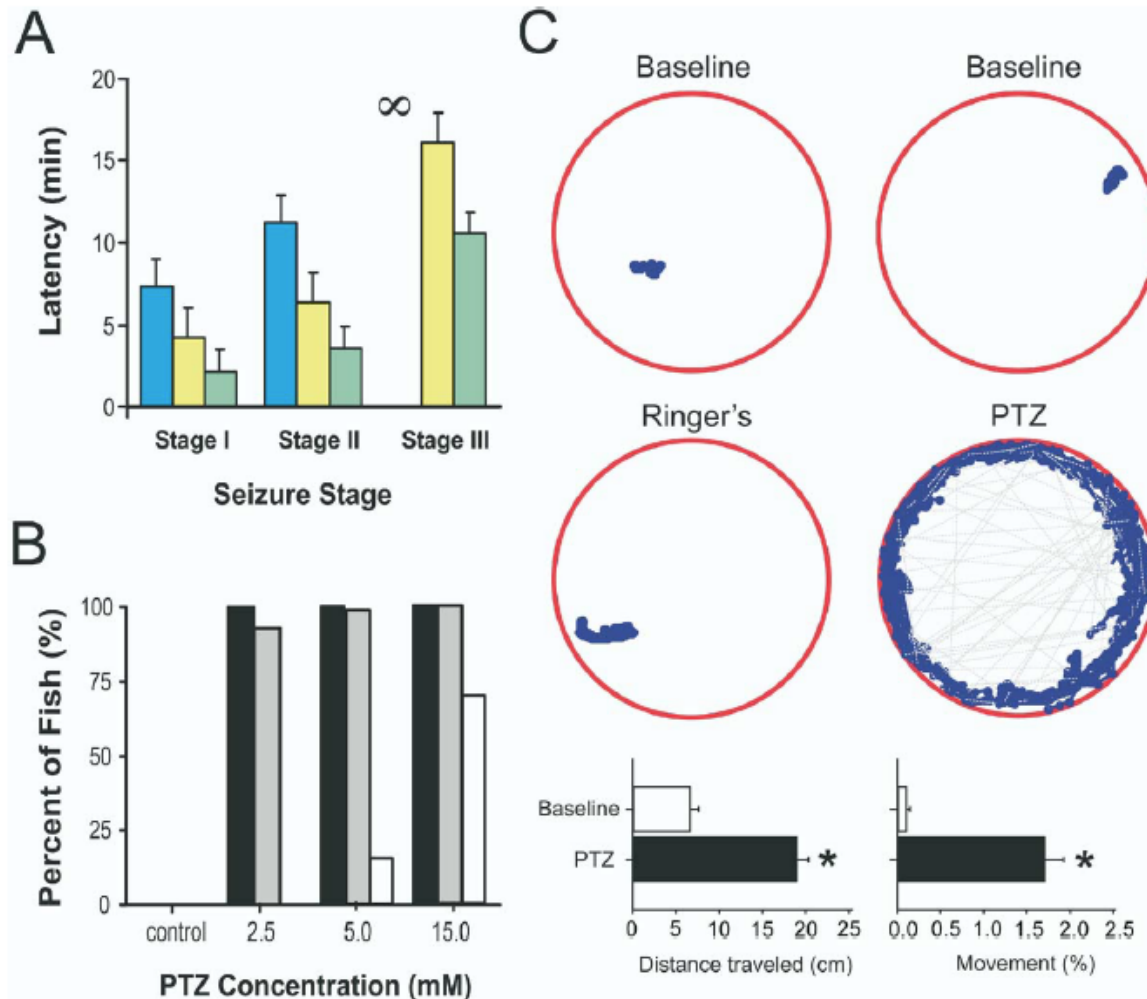
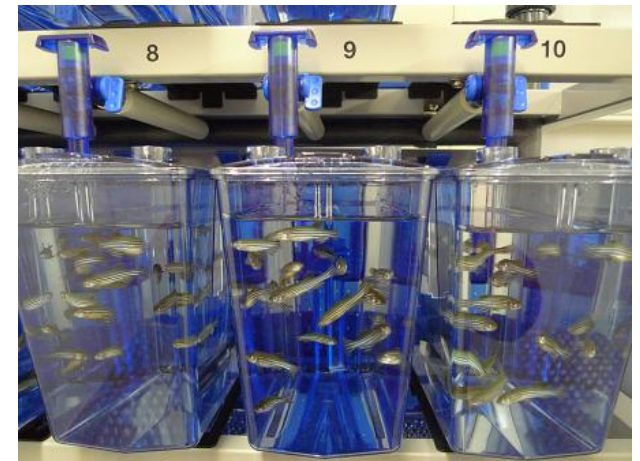


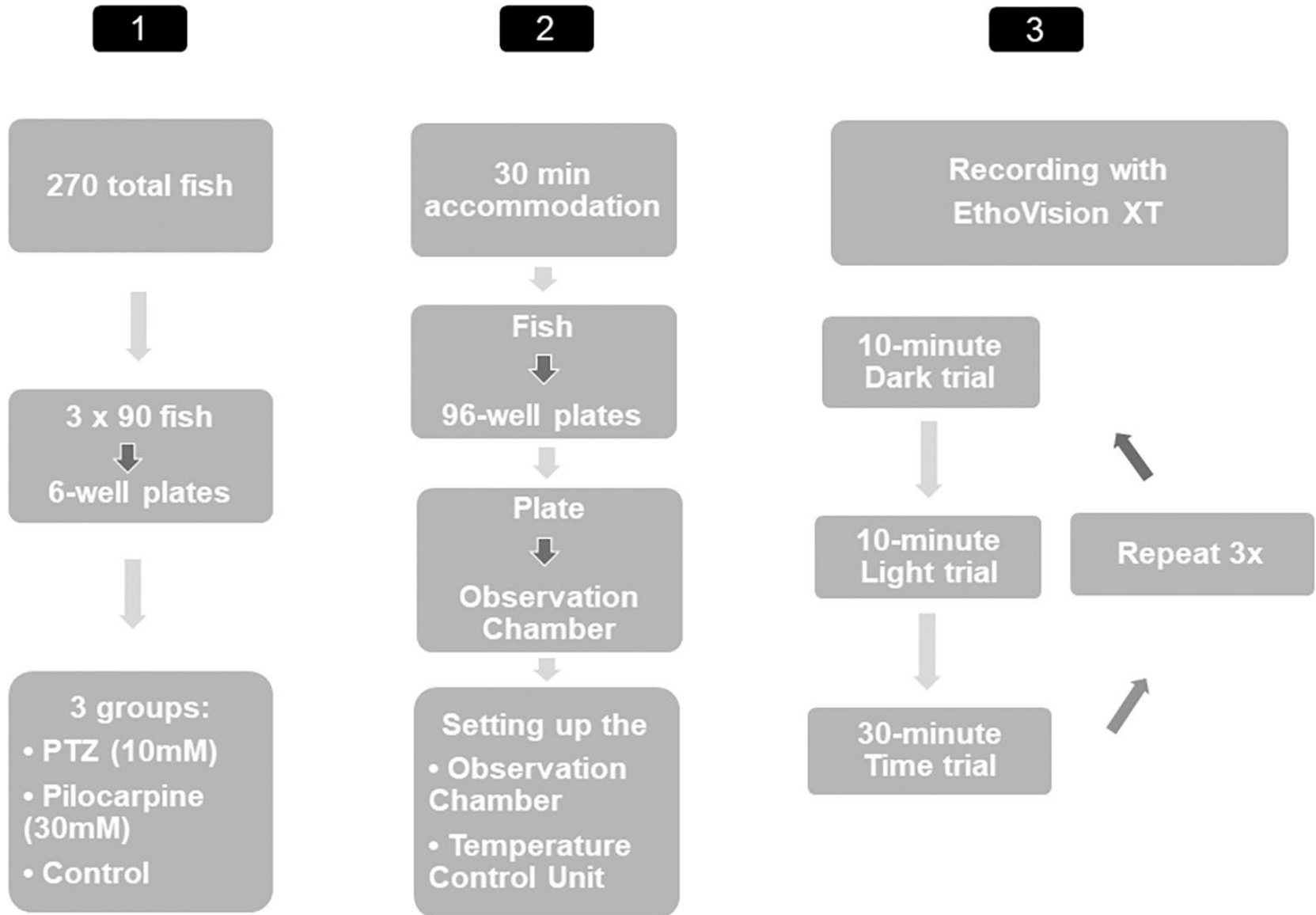
Fig. 1. Behavioral seizure scoring in zebrafish larvae. (A) Plot of the latency to first sign of seizure behavior for three different stages of behavior vs. PTZ concentration ($n=96$ fish per drug). Note that PTZ evokes seizure-like behaviors in a concentration-dependent manner. Fish were placed in a 96-well Falcon dish, videotaped and scored by an experimenter blind to the status of the animal. Infinity symbol (in A) denotes that no fish reached Stage III seizure behavior at this PTZ concentration. Plots (in A) are means \pm S.E.M. PTZ concentrations are as follows: 2.5 mM (blue), 5 mM (yellow), 15 mM (green). (B) Plot of the percentage of zebrafish larvae exposed to a given concentration of PTZ vs. the seizure stage reached ($n=96$ fish per drug concentration). Stage I (black bar), Stage II (gray bar), Stage III (open bar). (C) Sample locomotion tracking plots are shown for individual zebrafish in normal bathing medium (baseline) and 10 min after exposure to fresh Ringer's or 15 mM PTZ. Blue dots indicate movement; dashed lines indicate rapid convulsive seizure activity (this fish exhibited >30 convulsive episodes). Plots were obtained from recording epochs 2 min in duration. Bar plots (bottom) are shown for the total distance traveled and percent of time fish spent moving in a user-defined arena. Plots (in C) are means \pm S.E.M; baseline recording (open bars); 15 mM PTZ (closed bars).

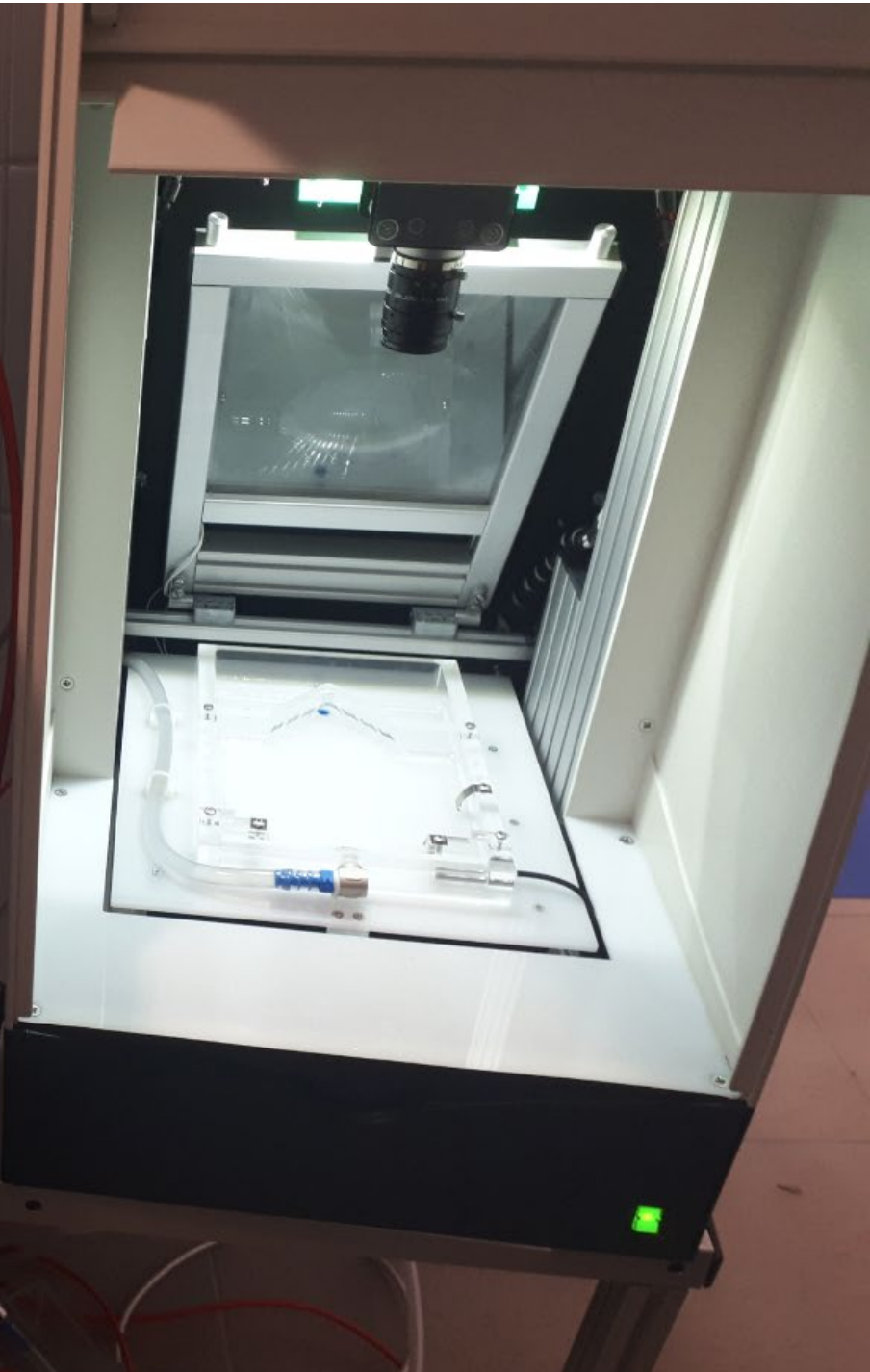
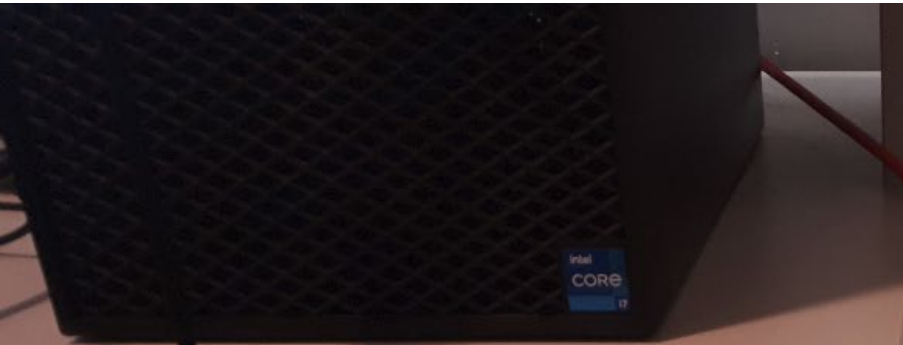
Anyagok és módszer

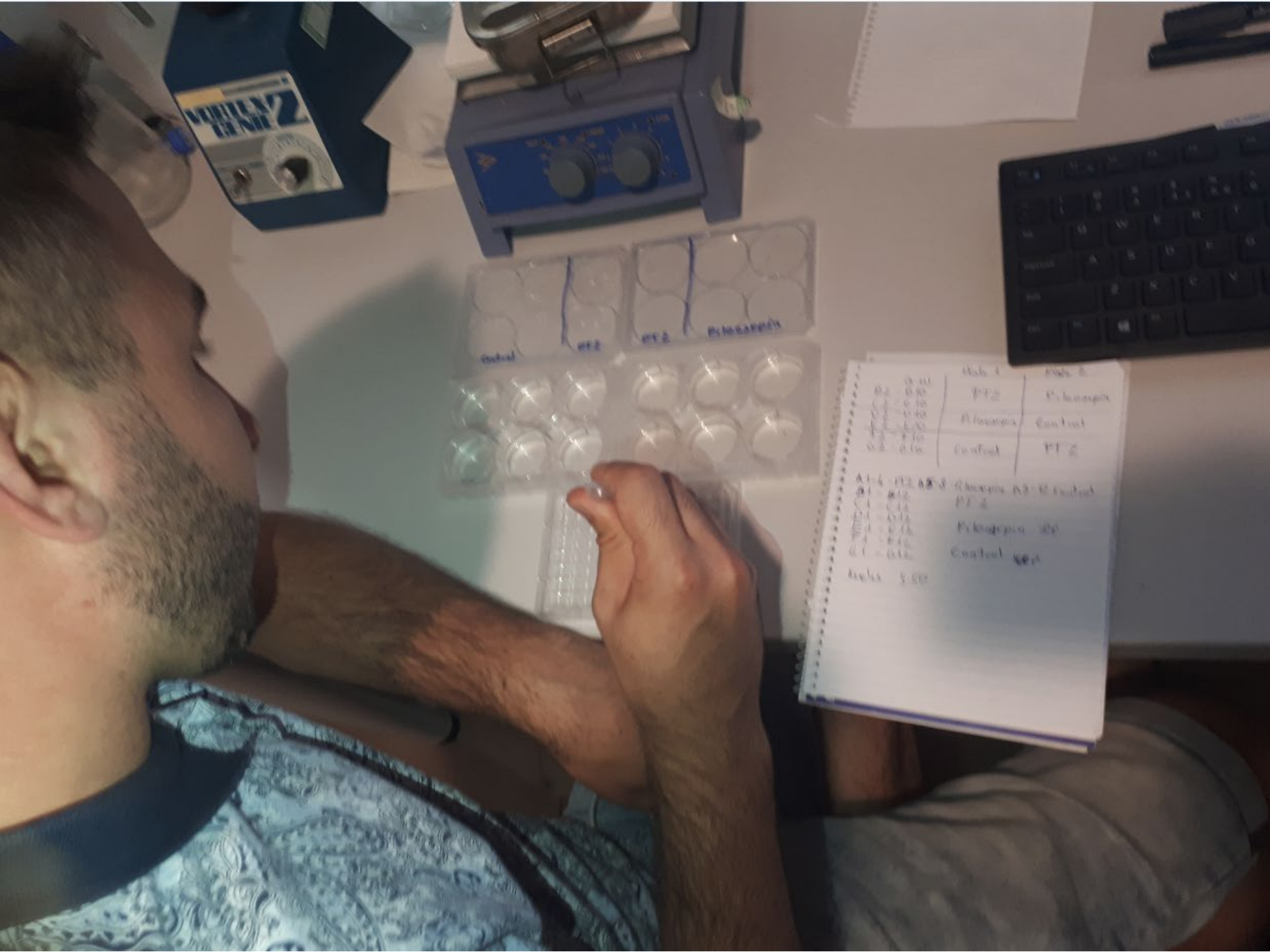
- $n = 16$
- 3 párhuzamos mérés
- Kurkumin koncentrációja: 0,025 μM
- Ferulasav koncentrációja: 0,2 μM
- PTZ kezelés: 10 mM
- Megj: kurkumin (PEG-400)
- DanioVision berendezés
- EthoVision XT szoftver



Módszer fejlesztése



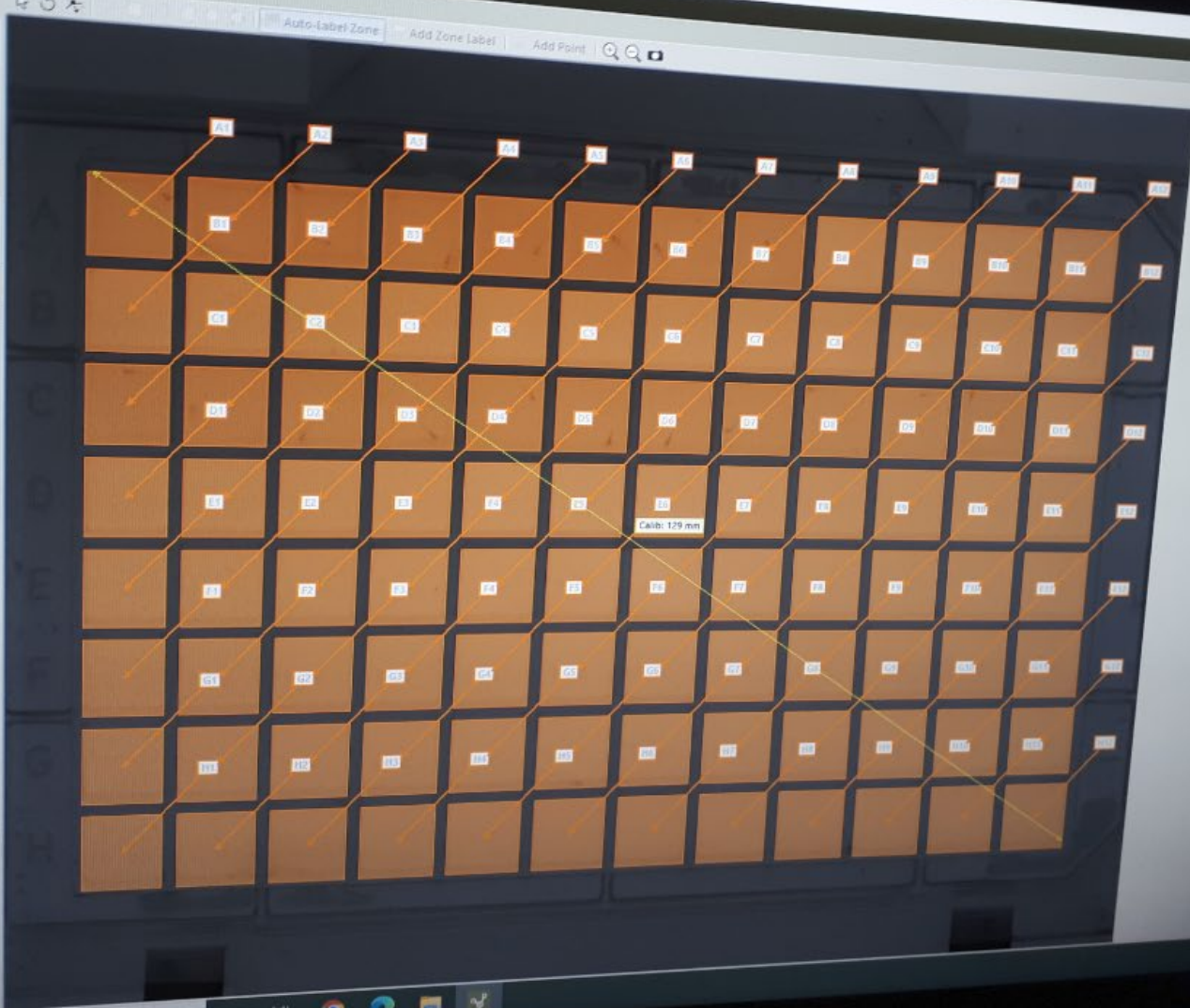




Handwritten notes on a notebook page:

	Plate 1	Plate 2
B2	0.11	PF2
B3	0.10	Pilocarpin
C1	0.10	Control
C2	0.10	PF2
D1	0.10	Control
D2	0.10	PF2
E1	0.10	Control
E2	0.10	PF2
A1-4	PF2	Control
B1	0.12	PF2
C1	0.12	PF2
D1	0.12	Pilocarpin 0.5
E1	0.12	Pilocarpin 0.5
F1	0.12	Control 0.5
G1	0.12	Control 0.5
Angles	9.00	

- Setup
 - Experiment Settings
 - Arena Settings (1)
 - Arena Settings 1
 - Trial Control Settings (2)
 - Detection Settings (1)
 - Trial List
- Acquisition
 - Acquisition (0 acquired)
 - Track Editor
 - Track Smoothing Profiles (1)
- Analysis
 - Data Profiles (5)
 - Analysis Profiles (1)
 - Results
 - Statistics & Charts
 - Track Visualization
 - Heatmap Visualization
 - Integrated Visualization
 - Export
 - Raw Data
 - Statistics



Arena Settings (Arena Settings 1)

Arenas and Zones

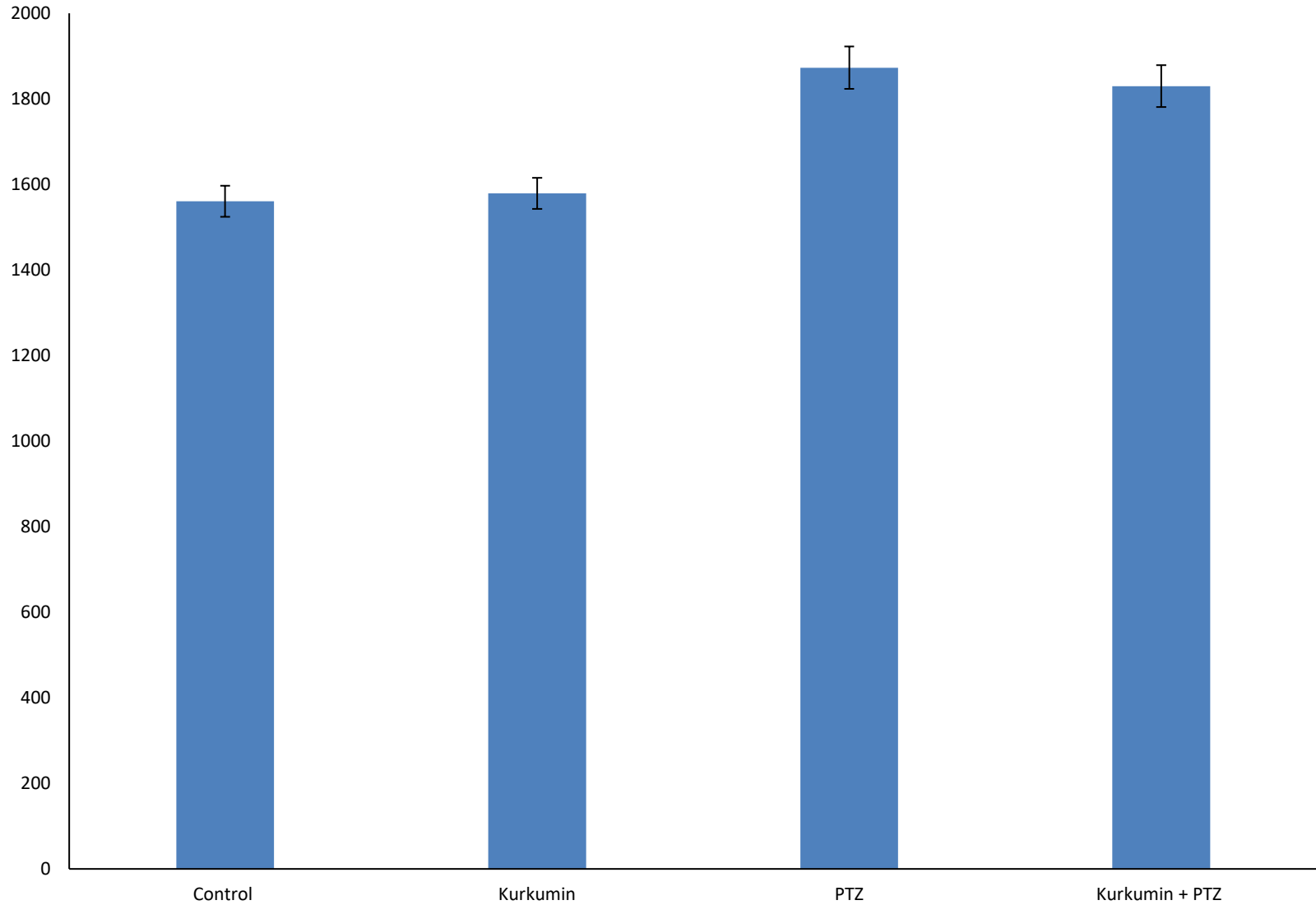
- 1 Draw Scale to Calibrate
- 2 Select Shape and Draw Area
- 3 Select Shape and Draw Zones (Editorial)
- 4 Copy Name
- 5 Arrange Areas
- 6 Validate Setup

Background	Color	View
Calibration	Black	<input type="checkbox"/>
A1	Orange	<input type="checkbox"/>
A2	Orange	<input type="checkbox"/>
A3	Orange	<input type="checkbox"/>
A4	Orange	<input type="checkbox"/>
A5	Orange	<input type="checkbox"/>
A6	Orange	<input type="checkbox"/>
A7	Orange	<input type="checkbox"/>
A8	Orange	<input type="checkbox"/>
A9	Orange	<input type="checkbox"/>
A10	Orange	<input type="checkbox"/>

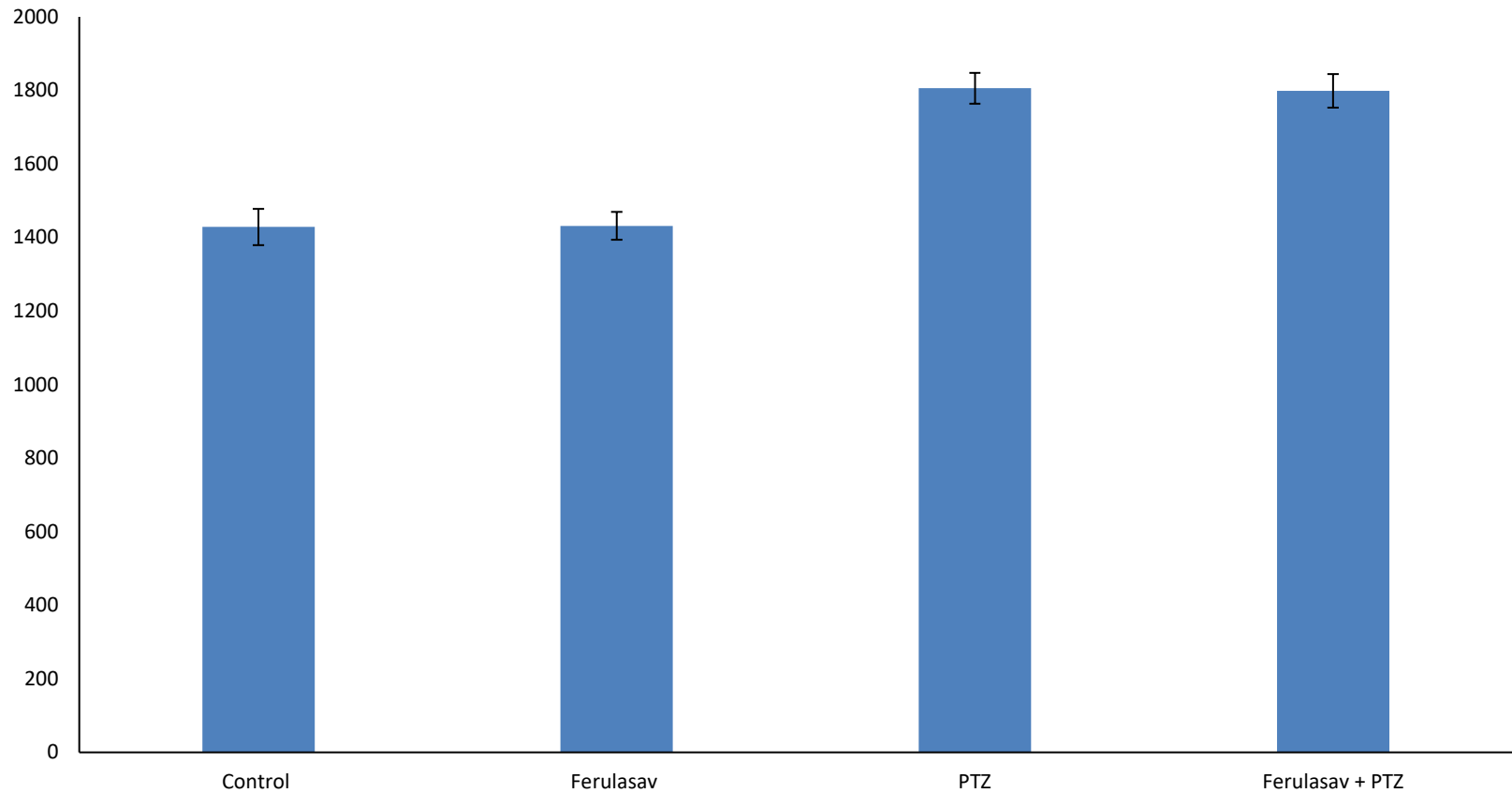
Shape Size and Position

Heatmap Plotting

Eredmények kurkumin



Eredmények ferulasav



Eredmények

Kiszámoltuk a kontroll úthossz arányában is:

- Kurkumin: - 4,8 %
- Ferulasav: - 0,1 %

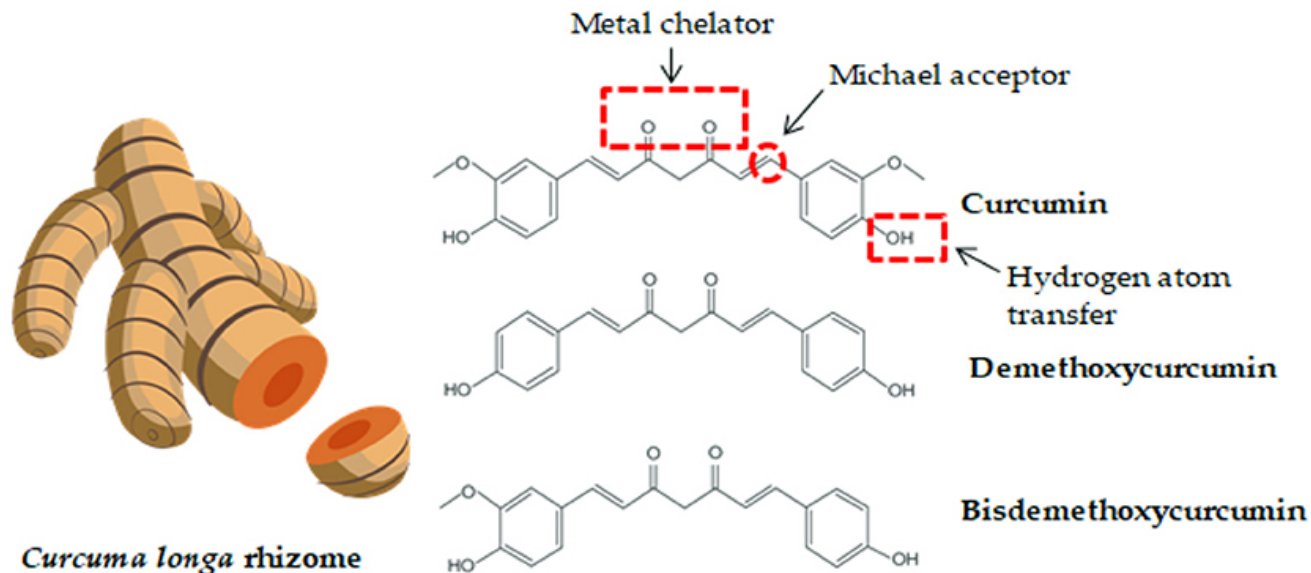


Következtetés

- Egyik anyag sem szignifikánsan, de a kurkumin erőteljesebben gátolta a 10 mM PTZ hatására kiváltott mozgás növekedést, mint a ferulasav.
- A vizsgált anyagok közt átfedő, direkt antioxidáns hatás modellünkben nem volt jelentős.
- Feltehetően a két vizsgált anyag nem átfedő hatásmechanizmus(ai) okozhatták a különbséget (pl. PPAR rec. aktiválás).
- További vizsgálatot, pl. EEG-t tervezünk

Kurkumin és PPAR γ

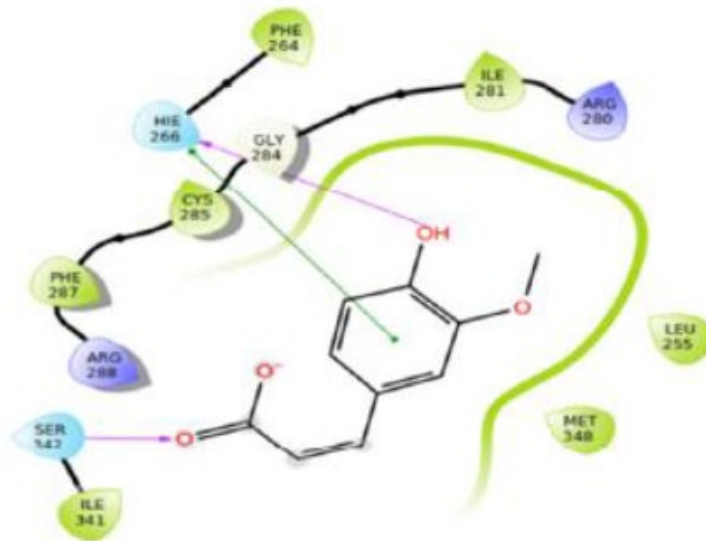
- Kurkumin PPAR γ aktiváláson keresztül Akt, NF- κ B, AP-1, és JNK jelátvivőket gátol.



Jacob, A., et al. (2008). *PPAR research*, 2007.

Surma S., et. al. (2022) *Front. Nutr.*

Ferulasav és PPAR γ



A kutatócsoport



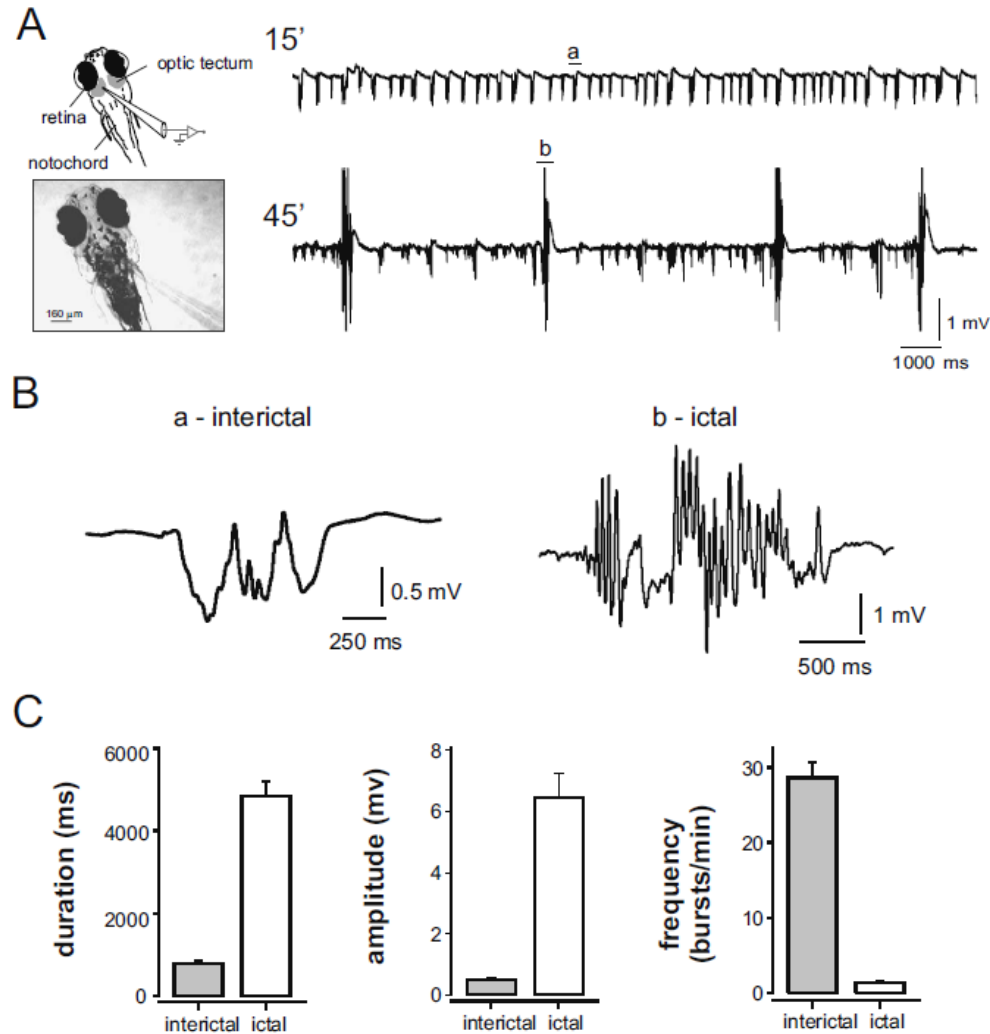


Fig. 2. Epileptiform-like electrographic activity in zebrafish larvae. (A) Schematic of the configuration used to obtain tectal field recordings from agar-embedded zebrafish larvae. Top left: schematic showing the location of the optic tectum, and other relevant brain structures as well as the position of a glass microelectrode. Bottom left: a frame-grabber image showing the placement of an electrode in the zebrafish optic tectum. Top right: Representative field recording from a zebrafish larvae exposed to 15 mM PTZ for 15 min. Bottom right: a second trace of field recording from the same fish after 45 min of PTZ exposure is also shown. Note the presence of interictal- and ictal-like epileptiform discharges. (B) An isolated "interictal-like" burst at a faster time resolution as indicated by the letter "a" (in A); an isolated "ictal-like" burst (b in panel A) is also shown. (C) Bar graphs of the cumulative data obtained from all wild-type fish exposed to 15 mM PTZ. In each plot we measured 10 individual interictal or three to five ictal bursts for each fish and data are presented as mean \pm S.E.M.

EEG
vizsgálatot
tervezünk
a jövőben

Köszönjük a figyelmet!



Pótdia

PEG-400 szolubilizáló szer

