

Kurkuminoidok lehetséges antiepileptikus hatásai

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**MAGYAR TÁPLÁLKOZÁSTUDOMÁNYI TÁRSASÁG
XLV. VÁNDORGYŰLÉSE
2022.10.20**



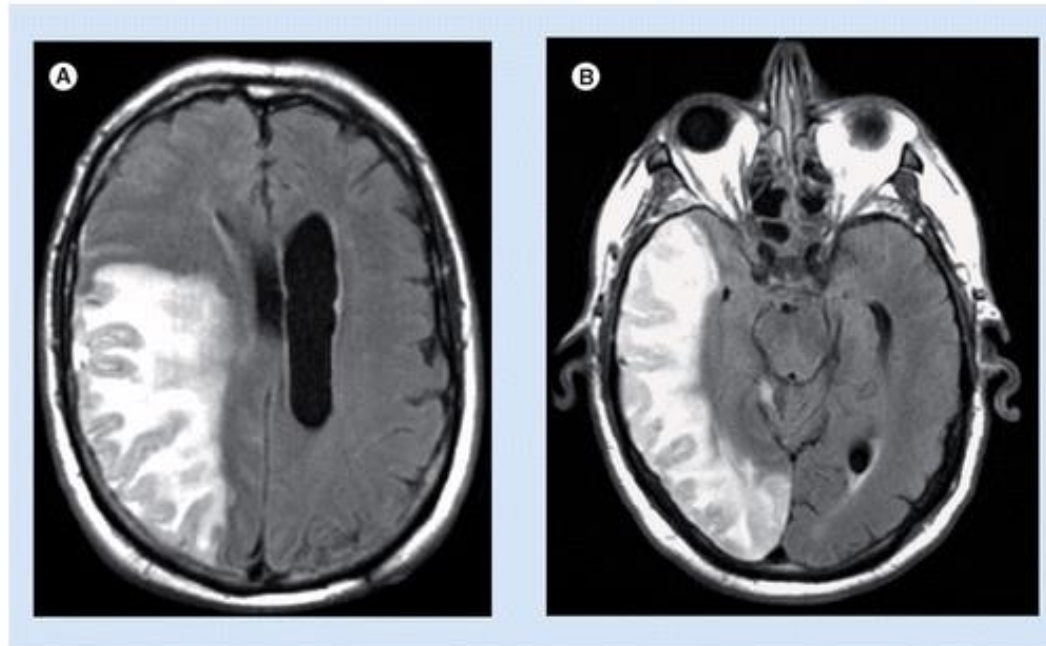


Figure 8. Epilepsy with EEG-imaging mismatch following stroke.

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+} ↑
- 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

PTZ és pilokarpin

- PTZ:
 - GABA_A gátlása
 - ← Modulálja:
 - 5-HT_{1A}, 5-HT₃
 - NMDA
 - glicin
 - L-típusú Ca-csatorna
- Pilokarpin:
 - Kolinerg (M1) receptor stimuláció

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

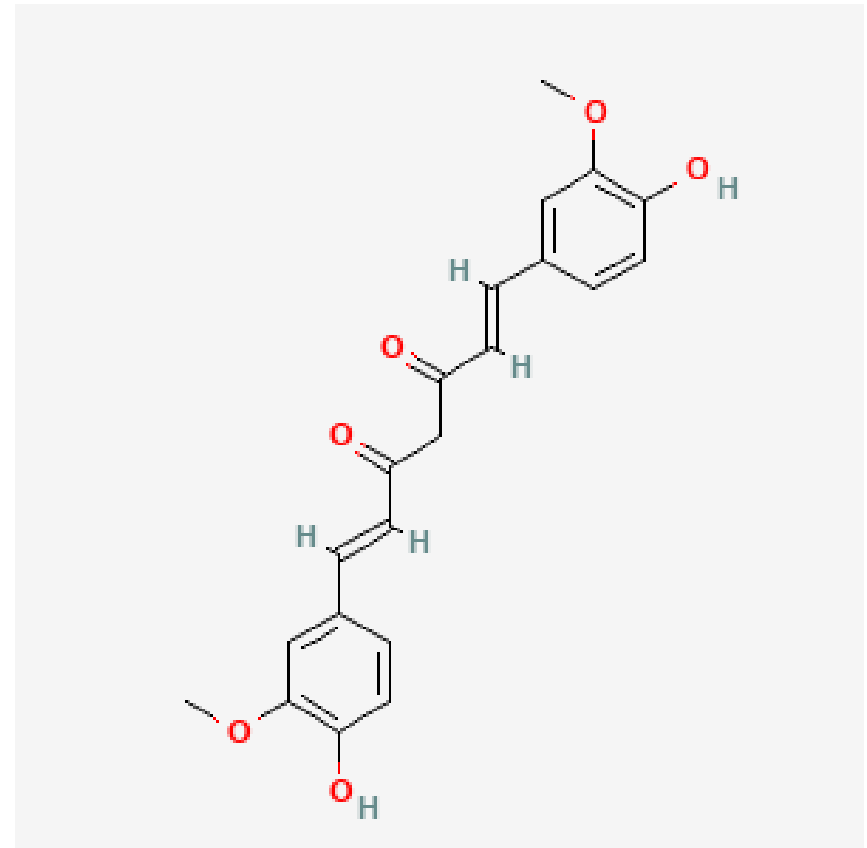
Jacob A, et al. PPAR Res 2007; 2007: 89369

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?
- Aktív centrum:
 - bomlik
 - rotál
 - kémiai környezetre érzékeny
- ←Aktív metabolitok, pl. ferulasav...



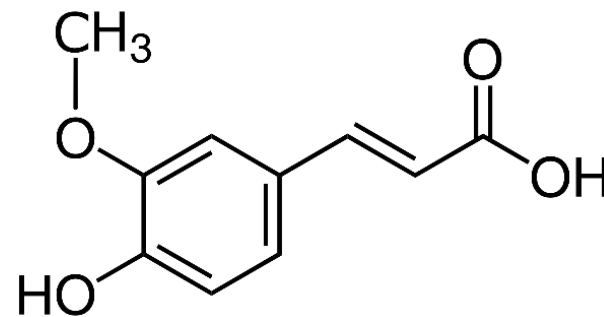


Lehetséges hatásmechanizmusok

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

Ferulasav

- Aktív metabolit
- Antioxidáns
- LDL koleszterin ↓
- Gyulladáscsökkentő



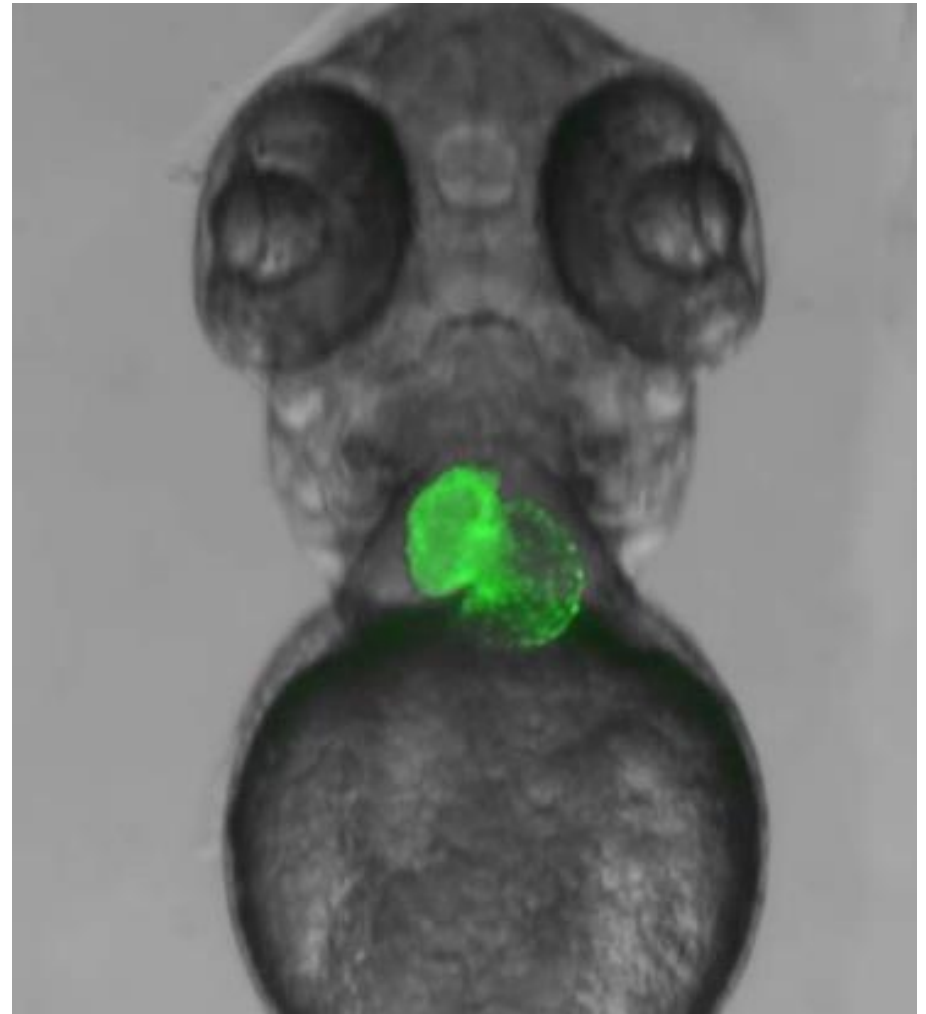
Miért éppen zebraahal?

- gerinces
- átlátszó
- könnyű mikromanipuláció
(grafting, fenotípus meghatározás)
- több toxicitás hatás hasonló a halban és az emlősökben
- gyors 'gene-knock down'
- genetikailag ismert
- kevés vizsgálati anyag
- bőrön át felszívódás
- génmódosított epilepsziás is



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!



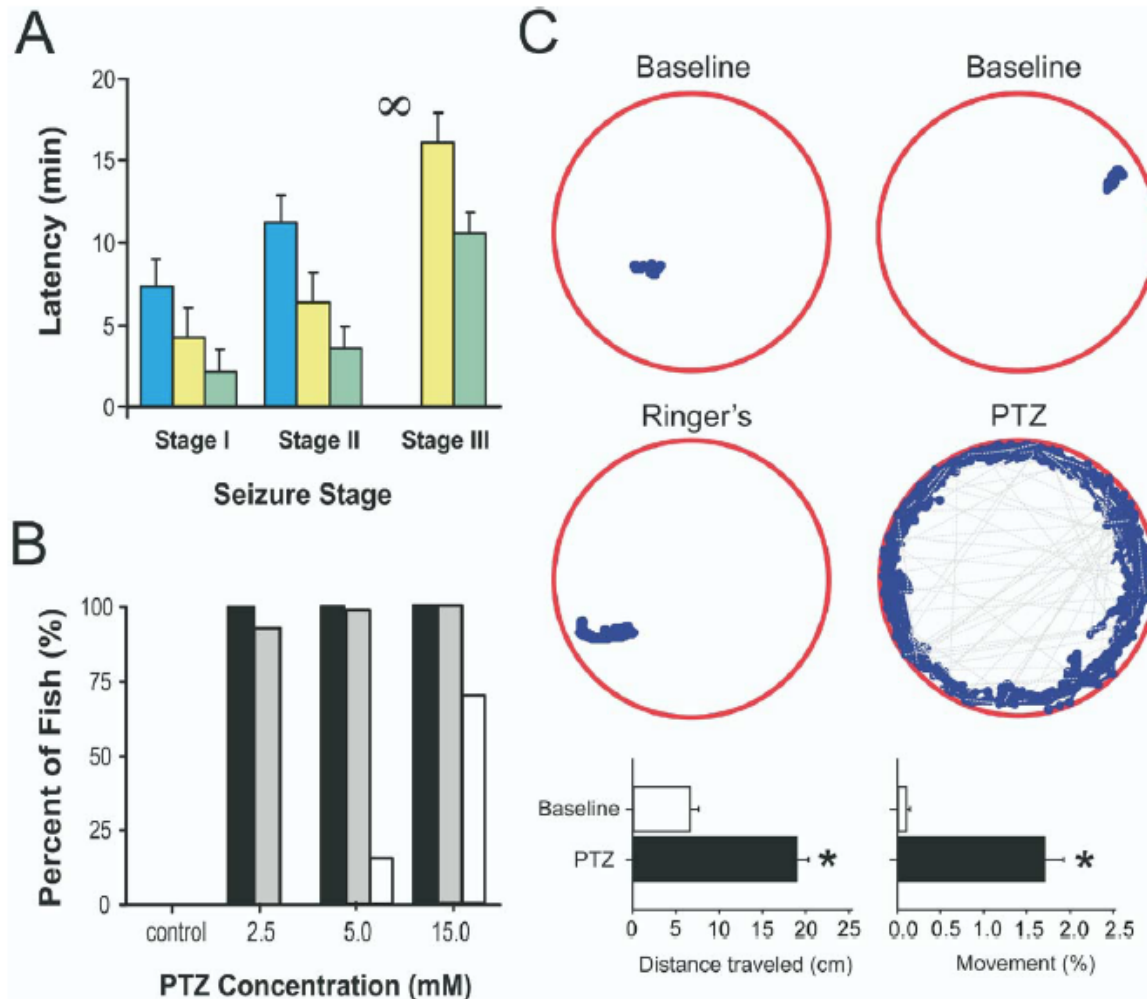
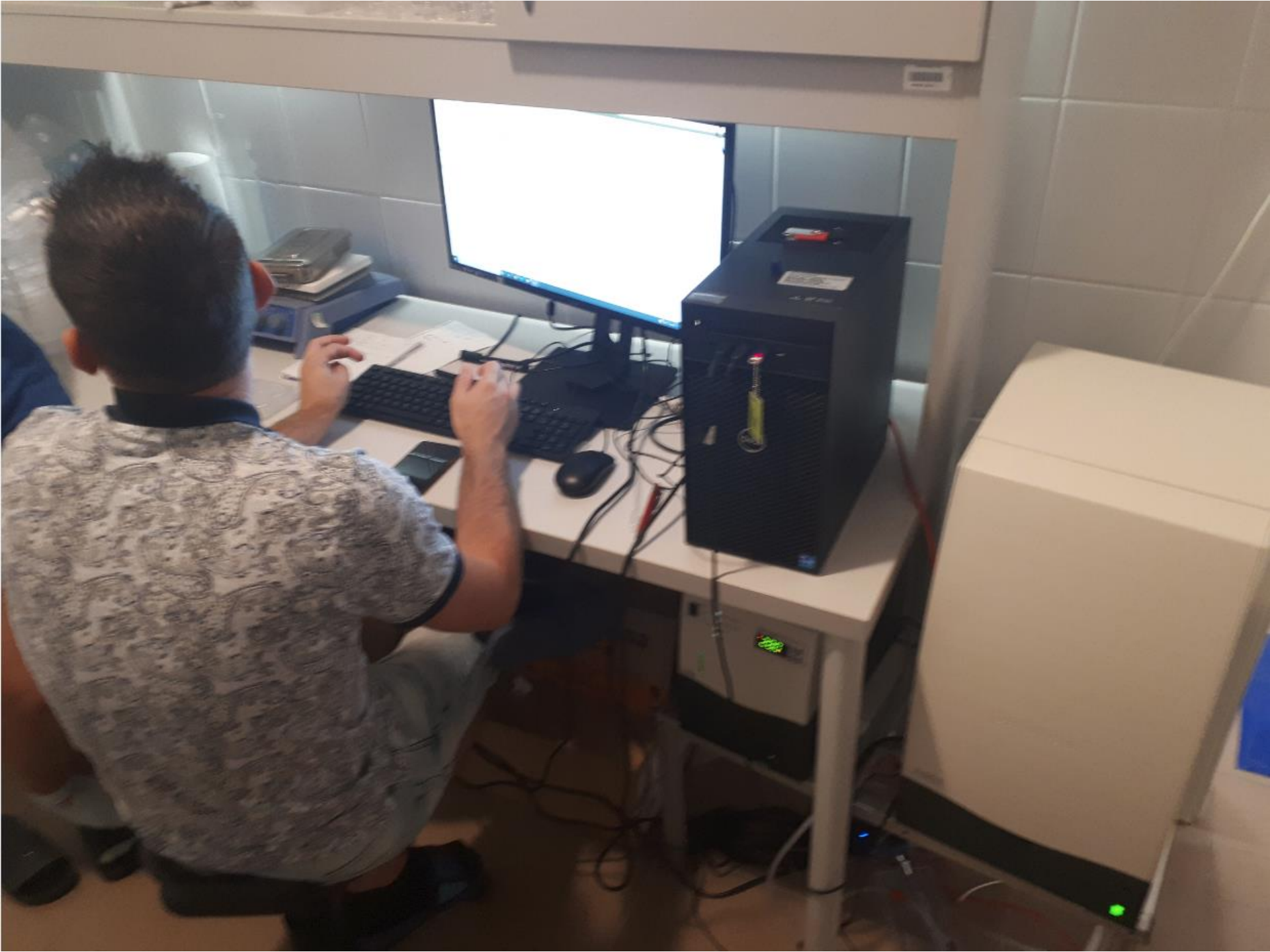
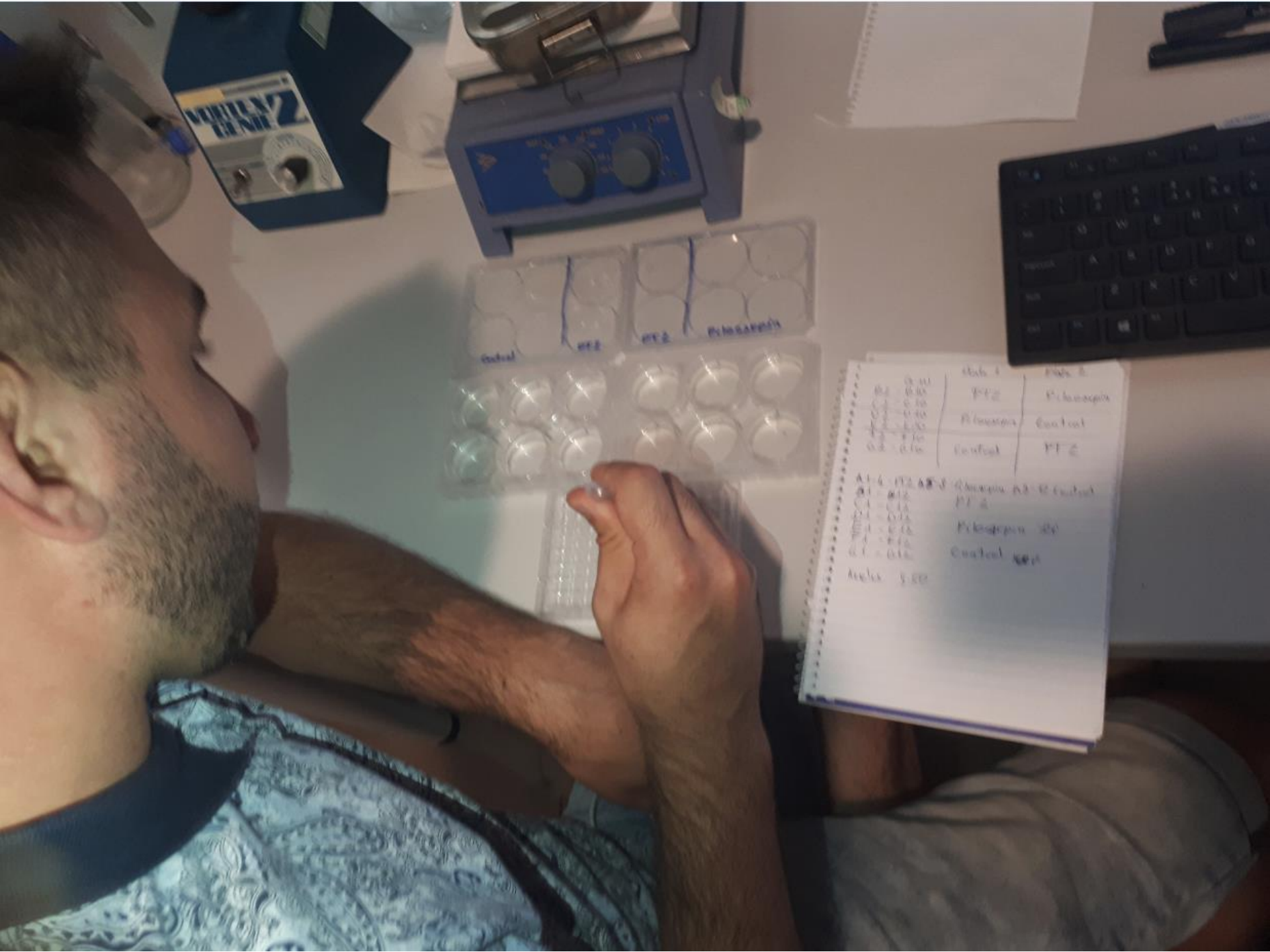


Fig. 1. Behavioral seizure scoring in zebrafish larvae. (A) Plot of the latency to first sign of seizure behavior for three different stages of behavior vs. PTZ concentration ($n=96$ fish per drug). Note that PTZ evokes seizure-like behaviors in a concentration-dependent manner. Fish were placed in a 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).







Handwritten notes and a table on a notebook page:

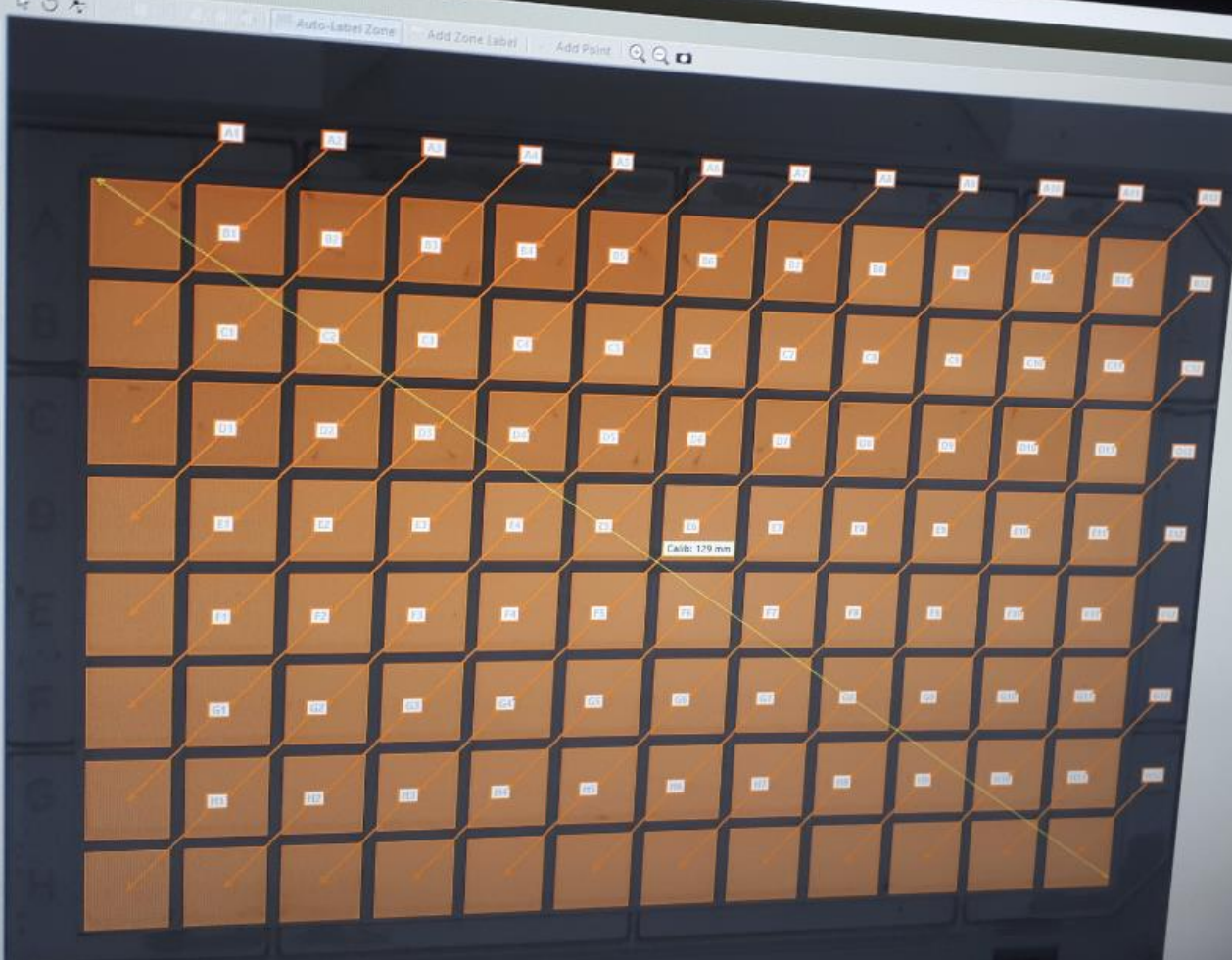
	Plate 1	Plate 2
B2 - 0.11	PT 2	Pilocarpin
B3 - 0.22		
C1 - 0.10	Pilocarpin	Control
C2 - 0.20		
D1 - 0.10	Control	PT 2
D2 - 0.20		

Additional handwritten notes:

- A1 - 0.12 - Pilocarpin 0.5 - Control
- A2 - 0.12 - PT 2
- B1 - 0.12 - Pilocarpin 0.5
- C1 - 0.12 - Control 0.5

At the bottom of the page, it says: "At the 5.00"

- Experiment Explorer
- 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 Items
- 5 Arrange Areas
- 6 Validate Setup

Background	Color	View
Calibration	Black	<input type="checkbox"/>
A1	Orange	<input type="checkbox"/>
Zone Group 1	Green	<input type="checkbox"/>
A2	Orange	<input type="checkbox"/>
Zone Group 1	Green	<input type="checkbox"/>
A3	Orange	<input type="checkbox"/>
Zone Group 1	Green	<input type="checkbox"/>
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A9	Orange	<input type="checkbox"/>
Zone Group 1	Green	<input type="checkbox"/>
A10	Orange	<input type="checkbox"/>
Zone Group 1	Green	<input type="checkbox"/>

Shape Size and Position

Heatmap Mapping

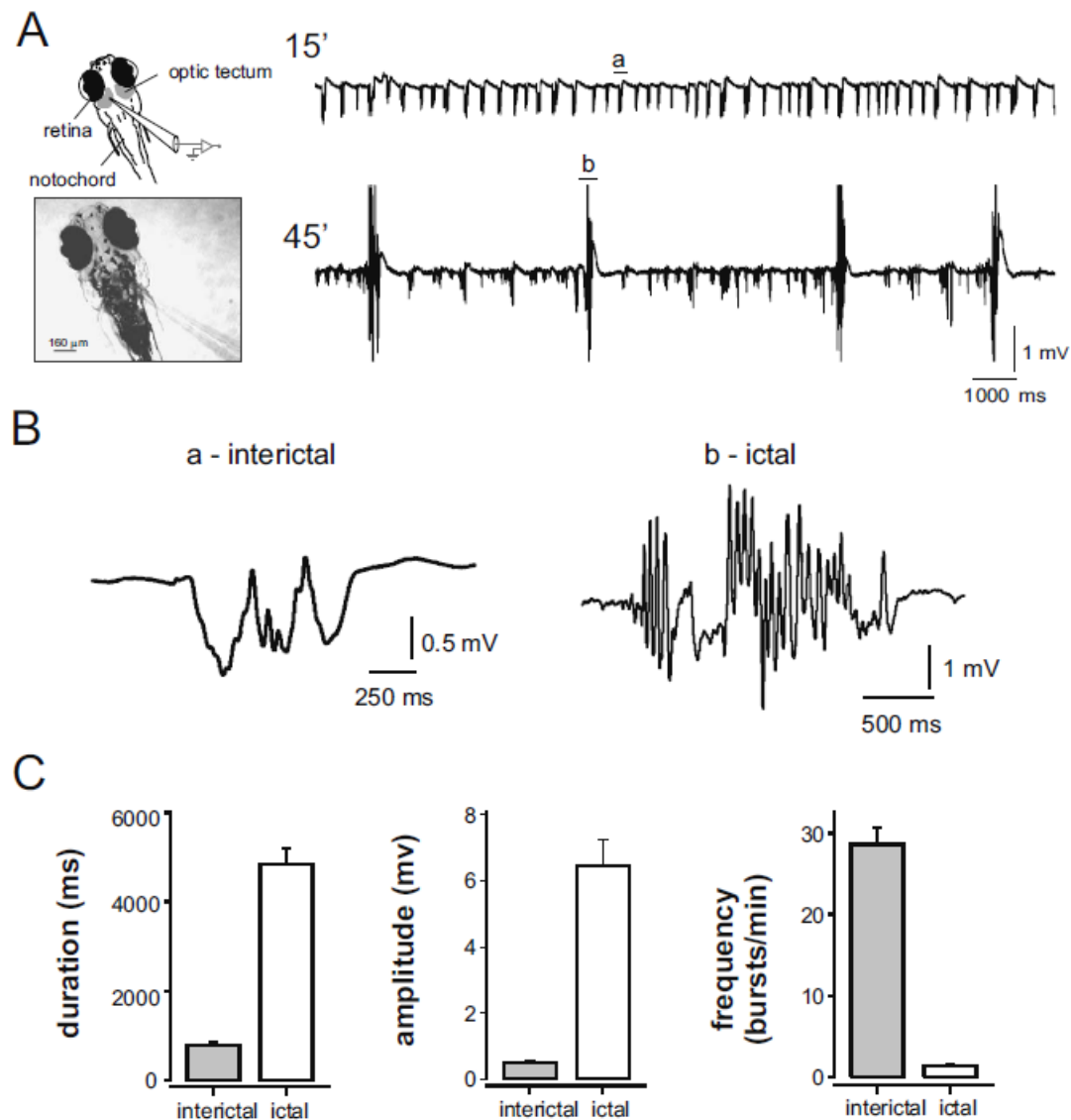


Fig. 2. Epileptiform-like electrographic activity in zebrafish larvae. (A) Schematic of the configuration used to obtain tectal field recordings from agar-embedded zebrafish larvae. Top left: schematic showing the location of the optic tectum, and other relevant brain structures as well as the position 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.

A kutatócsoport





Oldékonyság

- PEG-gel jobban oldatba vihető