

Propojení výuky oborů Molekulární a buněčné biologie a Ochrany a tvorby životního prostředí
OPVK (CZ.1.07/2.2.00/28.0032)

Nibbled to death

Markéta Kovalová

Nancy Guillén .

Nature vol 508

Trogocytosis by *Entamoeba histolytica* contributes to cell killing and tissue invasion by Kathrine Ralton *et al.*

- Trogocytosis, a process in which one cell 'takes a bite' out of another, had previously been seen only in immune cells.

Entamoeba histolytica

- Parasite
- Causes amoebiasis – potential fatal diarrhoea
- One third of children get infected in developing world
- Connected with malnourishment and stunting
- Symptoms:
 - Non symptomatic
 - Diarrhoea, colitis, extraintestinal disease

How kills *Entamoeba histolytica*

- 2 hypothesis
 - Attaches itself to the host cell → insertion of peptides → lysis of the cell
 - Phagocytosis – ingest dying enterocytes
- Can also ingest pieces of the host cell → death of the cell

Trogocytosis

- Expected only in immune cells
- Principle:
 - Early immune response
 - Antigen molecule captured by antigen presenting cell → displaying on surface → recognized by lymphocytes' receptor → activation of specific immune response

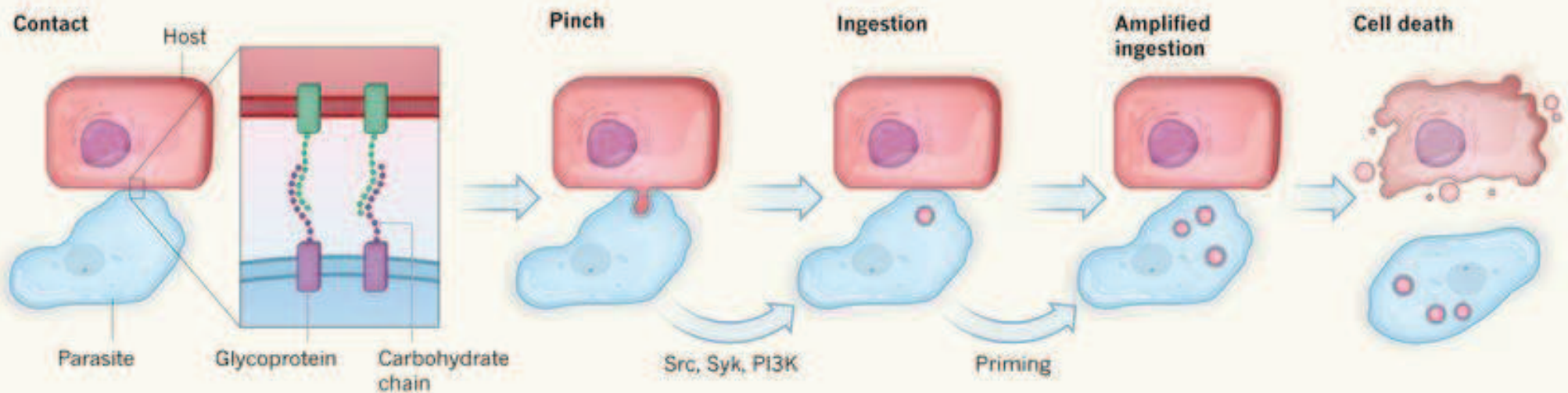
Trogocytosis

- Requires transduction of signals
- Kinase enzymes – Src, Syk, PI₃K
- Modulation of cytoskeleton and intracellular calcium-ion levels
- Rapid process
- No cell dies

Trogocytosis by *Entamoeba histolytica*

- General components of the cell surface
 - Glycocalyx rich in glycoproteins and glycolipids
- Most important glycosylated components
 - Lipopeptidophosphoglycans and Gal/GalNAc lectin = essential for the process

Trogocytosis by *Entamoeba histolytica*



Fagocytosis or trogocytosis?

- How parasite chose is still unknown
- Once use trogocytosis – next killing is more effective than killing of parasite which it didn't use yet
- Trogocytosis change parasite behavior
- Trogocytosis is necessary for ability to invade the tissue
- Can use for lot of types of cell

Immune cells vs. *Entamoeba histolytica*

Immunne cells

- Mediated by receptors (TCR)
- Low affinity of antigen to TCR
- Associated with Src-kinase activity

Entamoeba histolytica

- Mediated by general components
- Low interaction between Gal/GalNAc lectin and glycosylated residues
- Associated with Src-kinase activity

- No homology

What can other experiments bring?

- Why is important to amplify the trogocytosis?
 - Surface components activates signaling pathways → increase affinity for extracellular carbohydrates
- Does fagocytosis and trogocytosis occurs at the same time?
- This new concept is important for understanding amoebiasis, host-pathogen interactions, immune-cell function and interactions

Thank you for your attention

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Dynasty of the plastic fish

Daniel Malíšek

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John Hutchinson

History

Napoleon Bonaparte's military excursions into Egypt in 1798 – 1799 led a young French naturalist Geoffroy Saint-Hilaire, to cross paths with a strange fish that had paired lungs and could walk on land on its stubby.

In 1802 he named this fish „*Polyptere bichir*“ today known as the Nile bichir.



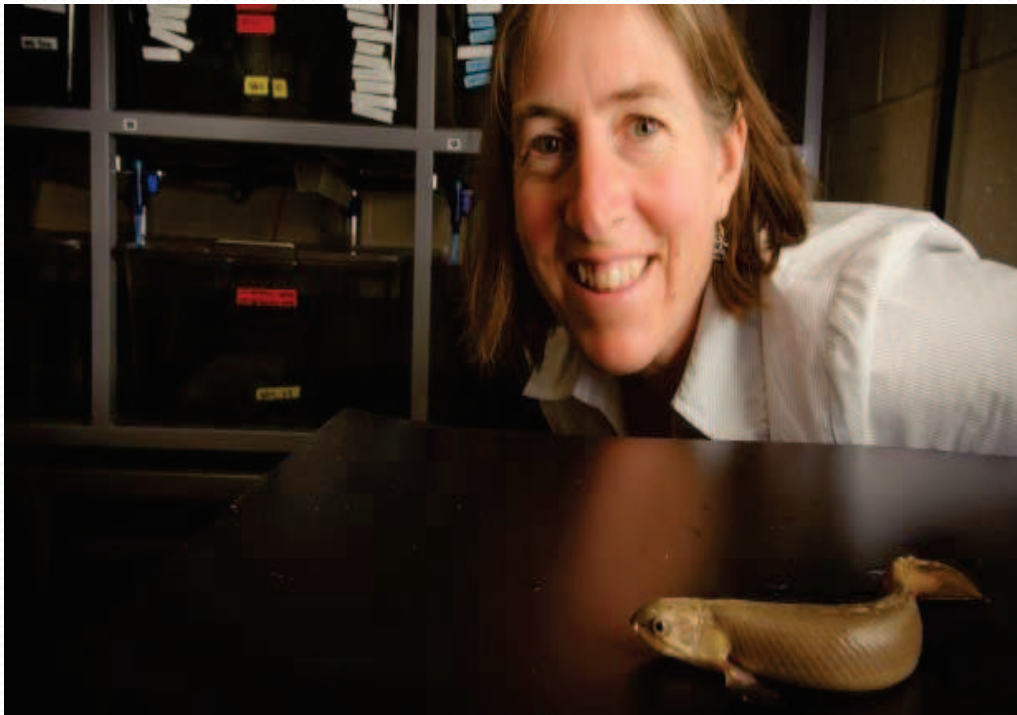
Present

- Nowadays, Standen and colleagues focus on *Polypterus* in their own excursion. They suggest that remarkable plasticity of the skeleton of *Polypterus senegalus*(*) reveals a key part of the mechanism that might have facilitated the gradual transition of limbed vertebrates from water to land.

Research

- In experiment, Standen and colleagues reared a group of bichirs on land for eight months and compared them with bichirs that had developed in their normal aquatic environment.
- Then they studied how the fish from two groups moved on land, and how the shape of the skeletal elements of their paired front fin bases different.

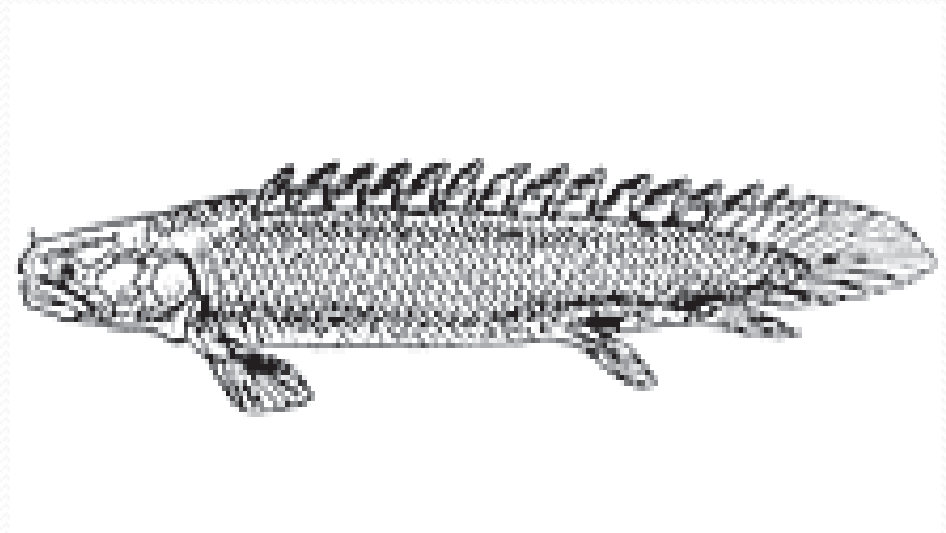
Research



- They found out that differences between water and land bichirs are that land bichirs took faster steps, their fins slipped across the substrate less frequently, they held their fins closer to their bodies, their noses stayed more aloft and their tails undulated less, with less-variable motions overall.

Research - skeleton

- However, the bones of the neck and shoulder region in the land-reared fish had altered in shape to produce a more mobile fin base with greater independence of motion between the fin and the neck, along with improved bracing of the ventral collarbone region.



Research

- These environmentally induced traits probably fostered the locomotor changes observed in the land-reared fish and helped the animals to resist gravity, thereby representing a common biological phenomenon termed developmental plasticity.
- Surprisingly, the land-reared fish could swim just about as well as the aquatic cohort, so there was no clear trade-off between being a good swimmer and a good walker.

Research

- The nature of the genetic and developmental mechanism by which bichirs achieve developmental plasticity is unclear.
- If the plasticity is heritable enough, then it might be selected for in multi-generational experiments, such that we could directly test the hypothesis that the animals plastic response to a terrestrial environment can become genetically assimilated.
- Such a study could thus become an exemplar of how genetic assimilation can contribute not only to microevolutionary events, as has been previously suggested.

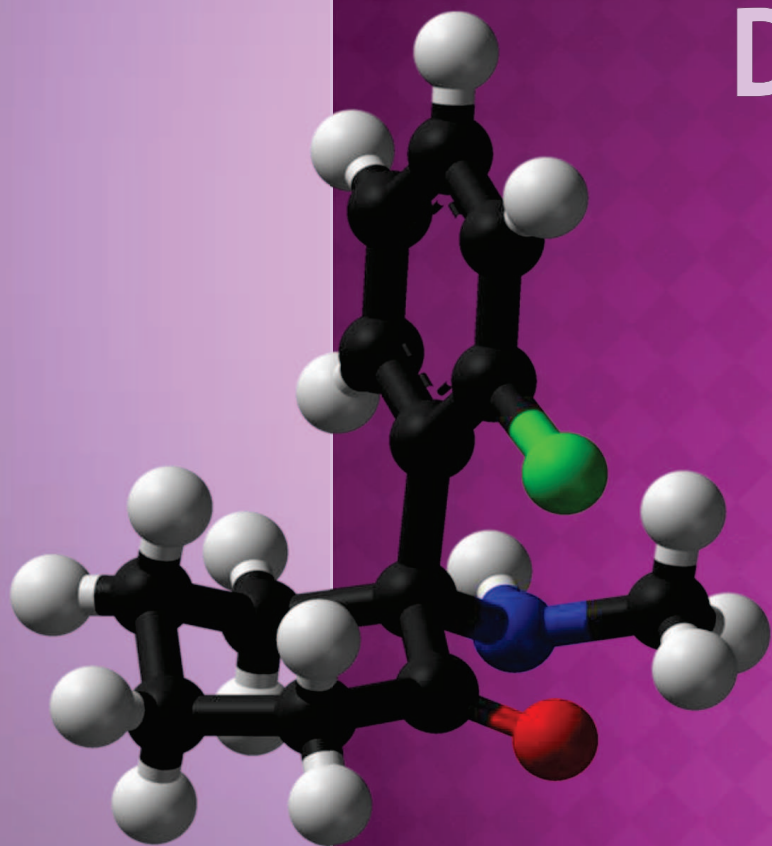
Research

- Geoffroy would probably have applauded Standen and colleagues study of developmental plasticity, all the more for involving his beloved bichirs.
- Much as Napoleon's land-fall in Egypt was not a lasting succes, bichirs never produced wholly terrestrial descendants, despite their malleable locomotor system.
- But the same type of plastic developmental mechanism that bichirs use today to make tentative, floppy incursions of the terrestrial realm might have been harnessed by our own fishapod forebears, leaving a much more revolutionary dynasty on the Earth.

Thank you for attention

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RAVE DRUG HOLDS PROMISE FOR TREATING DEPRESSION FAST



Veronika Neoralová

Molecular and Cell Biology
Palacký University Olomouc

written by Sara Reardon
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KETAMINE

(*RS*)-2-(2-Chlorophenyl)-2-(methylamino) cyclohexanone

- ◉ a psychoactive 'party drug' known as Special K, Super K, Kitty, Horse...
- ◉ recreational use has been associated with several deaths
- ◉ its hydrochloride salt is sold as Ketanest, Ketaset, Ketalar
- ◉ used clinically as an **anaesthetic** in animals and humans
- ◉ It has proved an effective **treatment for depression, bipolar disorder and suicidal behaviour**. It works really fast!
- ◉ It induces a **trance like state** while providing **pain relief, sedation, and memory loss**. Heart function and breathing remain functional.



MORE INFORMATION:

- ◉ At therapeutic doses, it often produces a dissociative, out-of body sensation that lasts less than an hour.
- ◉ At higher doses, recreational users report experiencing a 'K-hole', a deeply disoriented state with hallucinations.
- ◉ Unlike other antidepressants (which take weeks to start working) ketamine lifts depression in as little as 2 hours.

"It blew the doors off what we thought we knew about depression treatment,"
psychiatrist James Murrough (Mount Sinai Hospital, NY)

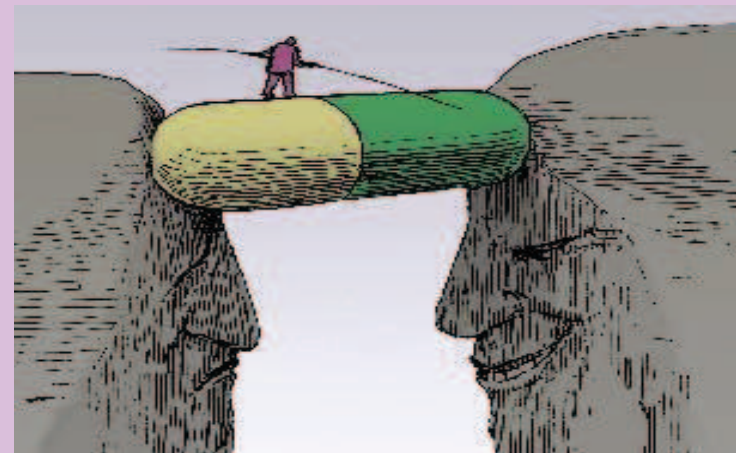
- ◉ companies are racing to develop patentable form of the drug
- ◉ researchers are trying to understand how it affects the brain
- ◉ some clinicians are prescribing ketamine off-label for their patients
- ◉ some of them worry that **too little is known about long-term effects!!!**

SITUATION TODAY:

- Many drug companies have closed their mental-health divisions in the past 5 years, and there have been no significant advances in medication for depression in decades.
- Today's most common antidepressants target the brain's **serotonin or noradrenaline pathways**.
- Ketamine acts on the NMDA receptor, a component of the **glutamate pathway**, which is involved in memory and cognition.

„The excitement over ketamine shows how badly new depression drugs are needed.“

Thomas Insel, director of the US National Institute of Mental Health



DR. MURROUGH'S RESEARCH:

- ◉ In 2013, Dr. Murrough's group published the largest trial of off-label ketamine carried out so far, with 73 participants.
- ◉ Ketamine reduced depression 24 hours after treatment in 64% of patients who had tried 3 or more other medications with unsuccessful results.
- ◉ A second group received the sedative midazolam. The reduction was 28%.
- ◉ Murrough's group is now imaging the brains of patients receiving ketamine treatment to try to dissect just how the drug works.



IN THE FUTURE:

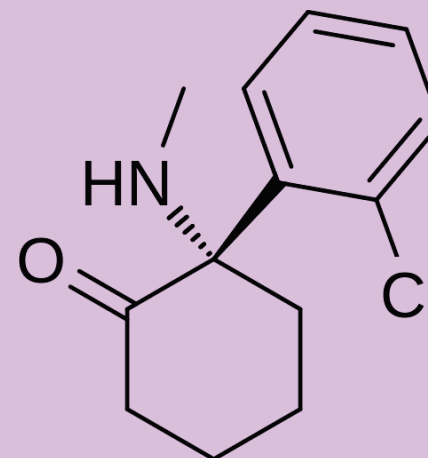
Long-term studies should be done before its use becomes widespread!!

- ◉ The way in which ketamine should be administered still needs to be worked out.
- ◉ Companies hope to profit by developing patentable variations on ketamine.



ESKETAMINE:

- Johnson & Johnson company designed a nasal spray containing a structural variant called **esketamine**.
- The company plans to release the results of a 200-person study this year.



LATEST RESEARCHES:

- ◉ **Naurex** company released results from a 386-person trial. Ketamine-like drug, **GLYX-13**, successfully treated depression in about half of patients, without hallucinatory side effects.
- ◉ **Roche** of Basel is also expected to release results this year from a 357-person trial of a drug called **decoglurant**, which targets the glutamate pathway.

Many scientists disagree that ketamine's psychoactive effects are a drawback. They questions the ethics of making patients pay more for a patented, non-dissociative drug if unmodified ketamine works just as well.



SUICIDE PREVENTION:

- ◉ Ketamine's fast action is particularly promising for **suicide prevention**, says **Carlos Zarate** of the NIMH.
- ◉ Instead of being committed to institutions for weeks of treatment, people might be treated with ketamine and released in days or even hours.
- ◉ Zarate has found that ketamine seems specifically to affect the desire to attempt suicide, whether a person is clinically depressed or not.
- ◉ That observation suggests that **suicidal behaviour might be distinct from depression**.

DR. ZARATE'S RESEARCH:

- ◉ Zarate is using ketamine to treat 50 people with depression and to study these effects.
- ◉ This year, his group will begin a multiyear study.
- ◉ Zarate hopes to learn more about what an actively suicidal brain looks like.

