KING'S College LONDON

INSTITUTE OF PSYCHIATRY,
PSYCHOLOGY & NEUROSCIENCE

Module:
Biological foundations of mental health

Week 2:
Building blocks of the brain

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Topic 1
Neuron-glial interactions and mental health

Part 2 of 2

Introduction

Astrocytes play an active, informational processing role in CNS

Astrocytic dysfunction may contribute to mental health disorders

A more gliocentric approach may lead to more effective therapeutic strategies

Figure 11: Mental health

Syndrome characterised by clinically significant disturbance in:
- Cognition
- Emotion
- Regulation
- Behaviour

Dysfunction in:
- Psychological
- Biological
- Developmental processes

Associated with significant distress in :
- Social
- Occupational
- Other important activities

Examples:
- Depression
- Bipolar disorder
- Schizophrenia
- Autism

Difficulties studying mental health in humans

Very difficult to study in humans

Figure 12: Mental health

Main lines of evidence

Human studies: mainly post-mortem

Animal studies, including use of genetically modified animals

In vitro studies

Focus on Major Depressive Disorder but information will also be provided of evidence available for schizophrenia.

What is depression?

A common mental disorder that causes people to experience *depressed* mood

Loss of interest or pleasure

Feelings of guilt or low self-worth

Disturbed sleep (insomnia or excessive sleep)

Low energy

Poor concentration.

What are the neurophysiological processes underlying a depressed state?

Astrocytes may play a role in depression?

Evidence comes from:

- Studies in animal models
- Post-mortem human tissues
- Astrocytes in culture (in vitro)

Examples of studies

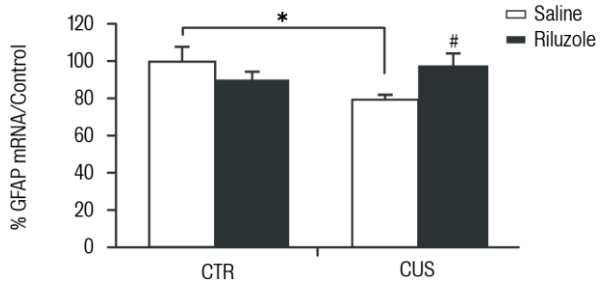
Figure 13: Mouse

Astrocyte pathology is present in animal models of depression

Treatments that revert astrocyte pathology also revert symptoms of depression in animal models

Chronic unpredictable stress (CUS; a model of depression)

Stressors
- Cage rotation
- Light on
- Light off
- Cold stress
- Isolation
- Crowding
- Cold swim stress



- A significant decrease of mRNA levels is seen for the glial-specific marker GFAP.
- The effect of stress can be reversed by the glutamate-modulating drug riluzole.

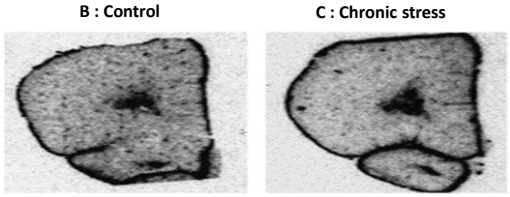


Figure 14: Effects of chronic unpredictable stress (CUS) and riluzole on mRNA levels of glial-specific markers measured by in situ hybridization

Animals are subjected to a sequence of two stressors per day over an extended time period

Sucrose preference test

Anhedonia is considered a symptom of depression

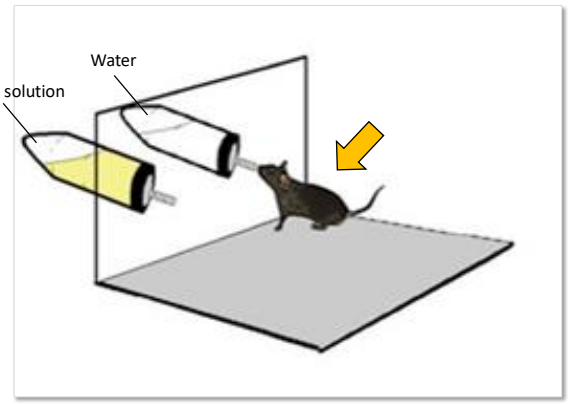
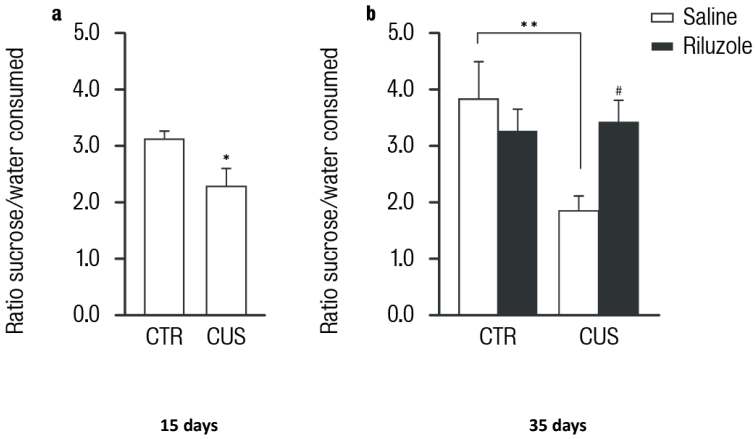


Figure 15: Sucrose preference test

Reduced preference for sucrose solution represents anhedonia

Chronic unpredictable stress causes anhedonia in rodents



- Chronic unpredictable stress affects animal behaviour in the sucrose preference test, leading to anhedonia.
- This is reversed by riluzole, in parallel with the reduction observed in glial pathology.
- Rilusole increases glutamate uptake by astrocytes
- and this results in increased glutamine production.

Figure 16: Chronic unpredictable stress effects animal behaviour in sucrose preference test, leading to anhedonia.

Examples of studies

Human Post-mortem material

Decreased GFAP expression in depression suicides

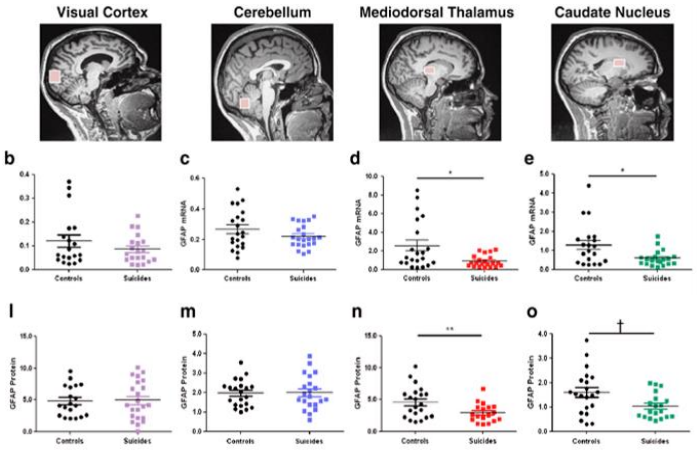


Figure 17: Decreased GFAP expression is also observed is observed in the medio dorsal thalamus and caudate nucleus but not in the primary motor and visual cortex of depressed suicides.

- Decreased GFAP expression (mRNA and protein) is also observed in depressed suicides.
- This loss is present in the mediodorsal thalamus and caudate nucleus but not in the primary motor and visual cortex, nor in the cerebellum.

Example of studies - 3

Studies conducted on cultured astrocytes.
Various types of pharmacological and non pharmacological treatments for depression can act directly on astrocytes.

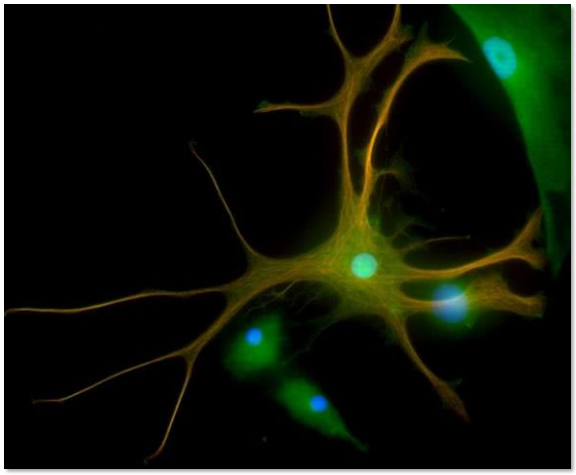


Figure 18: Glial cell (astrocyte)

Direct effect of fluoxetine on cultured astrocytes

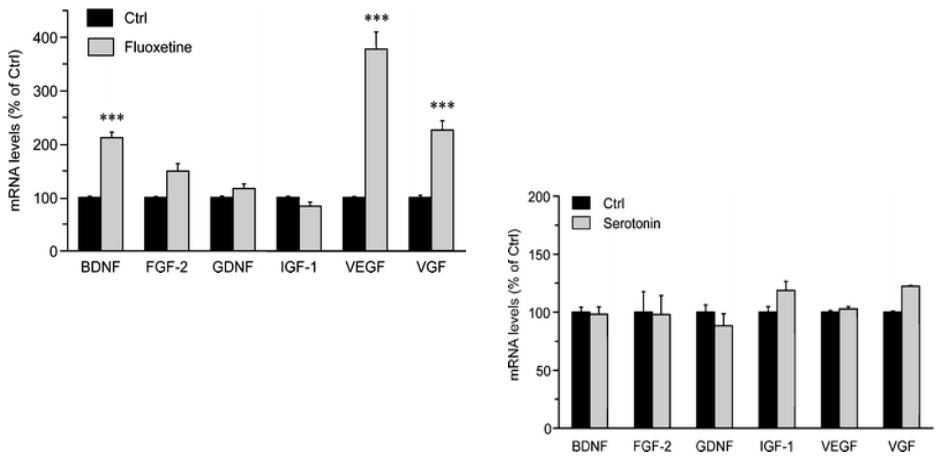


Figure 19: Fluoxetine induces the production of trophic factors by cultured astrocytes

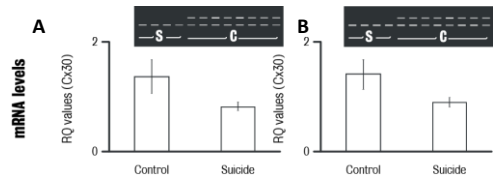
Fluoxetine (Prozac), a commonly used antidepressant, induces the production of trophic factors by cultured astrocytes in serotonin independent manner.

Astrocytic networks in Major Depressive Disorder

A role for astrocytic networks in Major Depressive Disorder (MDD)?

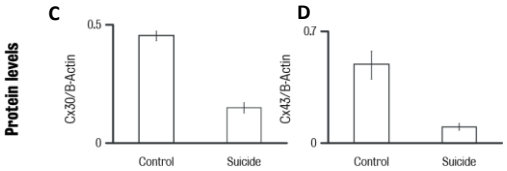
Evidence from studies on post-mortem human material and animal models of depression

Disruption of astrocytic networks play a role in depression



C: control
S: suicide case

Quantitative polymerase chain reaction (PCR) data from Cx30 **(A)** and Cx43 **(B)**



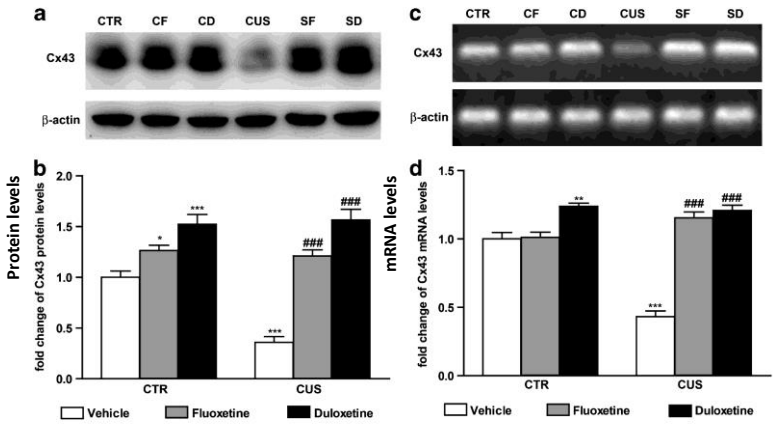
Quantitation of band intensity of western blot images for Cx30 **(C)** and Cx43 **(D)** with β-actin used as a loading control.

NB: suicide completers had diagnosis of MDD, Bipolar disorders or schizophrenia. There was no difference in Cx30 and 43 levels between pathologies.

Figure 20: Dysfunction of connexins in the dorsal Lateral prefrontal cortex of suicide completers

The expression of the components of astrocytic GAP junctions Cx30 and Cx43 is reduced in dorsal lateral prefrontal cortex from suicide completers compared with control subjects, suggesting a dysfunction of astrocytic networks in depressed individuals.

Antidepressants reverse connexin 43 decrease in the prefrontal cortex of stressed rats

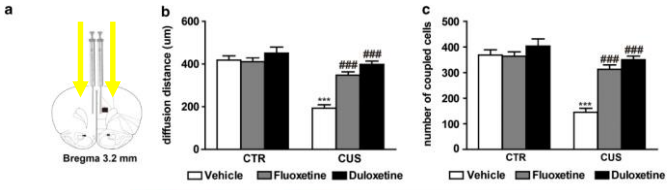


CTR: control group
CUS: Chronic unpredictable stress group
CF: CTR+fluoxetine group
SF: CUS+fluoxetine group
CD: CTR+duloxetine group
SD: CUS+duloxetine group

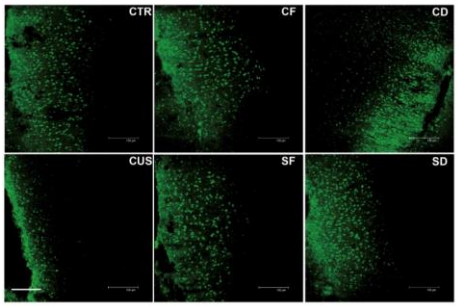
Figure 21: Antidepressants reverses connexin 43 decrease in the prefrontal cortex of stressed rats

Chronic unpredictable stress in rats causes decreased connexin 43 (Cx43) protein and mRNA levels in the prefrontal cortex (PFC), analogous to what was observed in suicides. Antidepressants reverse this decrease.

Chronic unpredictable stress disrupts astrocytic networks



Representative dye coupling images from animals of all groups



CTR: control group
CUS: Chronic unpredictable stress group
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CD: CTR+duloxetine group
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Figure 22: Chronic unpredictable stress disrupts astrocytic networks

Chronic unpredictable stress (CUS) disrupts astrocytic networks, as shown by a significant decrease in the distance of diffusion and the number of coupled cells in the prelimbic cortex of CUS-exposed rats as compared with control group, following Lucifer yellow dye injection. Treatment with antidepressants significantly reversed the effect of CUS on intercellular coupling.

Gap junction induces depressive-like behaviour

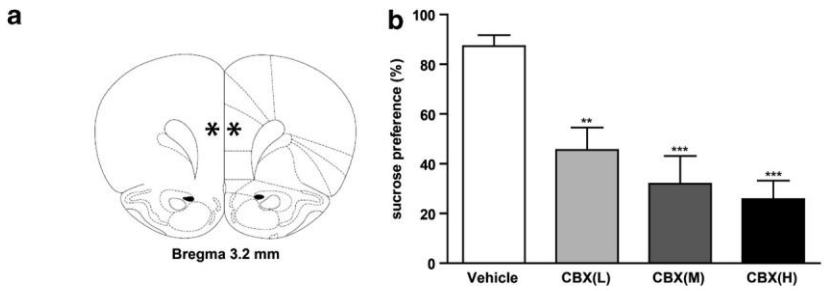

Figure 23: Gap junction induces depressive-like behaviours

Gap junction blockade in the prefrontal cortex (PFC) with carbenoloxone induces depressive-like behaviors.

A role for astrocytic networks and/or gliotransmission?

Decreased levels of connexins were identified in both MDD and in experimental stress.

Fluoxetine and other antidepressants can reverse these changes in animal models.

Blocking GAP junctions in the prefrontal cortex is sufficient to induce depressive behaviour in animals, suggesting astrocytic network dysfunction may be **sufficient** to induce the onset of depression.

The mechanisms whereby dysfunctional astrocytic networks may affect mood have not been established yet.

Therefore astrocytic network dysfunction may be **sufficient** to induce the onset of depression.

Sleep deprivation is a potent, if short-term, antidepressant. The antidepressant effects of sleep deprivation require astrocyte-dependent adenosine mediated signalling, i.e. gliotransmission.

What causes astrocyte pathology in depression?

- Stress (acting on the Hypothalamic-Pituitary-Adrenal Axis) may be a causative factor in depression

  - Acute and chronic stress alter astrocyte morphology and physiology,
and most of these alterations can be prevented by antidepressants or other protective treatment

Further, correlative, evidence supports a role for astrocytes in most if not all psychiatric disorders

In conclusion

- Much circumstantial evidence supports the hypothesis of a role for astrocytic dysfunction in psychiatric disorders
  - Often the most obvious astrocyte pathology appears to be atrophy
- It is currently impossible to determine whether astrocytic pathology is the primary cause of psychiatric disorders or it is secondary to neuronal pathology
  - Targeting astrocytic pathology appears in some cases to be sufficient to ameliorate behavioural disturbances
- Future research into the neurobiology of psychiatric disorders should shift its focus from a neurocentric perspective to, at least, a neuro-glial one

Figure references (1)

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