Depression

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Erich Seifritz
Klinik für Psychiatrie, Psychotherapie und Psychosomatik | Psychiatrische Universitätsklinik Zürich
erich.seifritz@bli.uzh.ch

Inhalt

• Glutamaterges System:
  – Veränderungen bei Depression (MDD)
  – Ketamin
• Ausblick
~ 60-80% of the total energy consumption appears to be devoted to functions directly involved in neurotransmission.

Glutamate (Glu): Wichtigster exzitatorischer Neurotransmitter

Neuro-Glial Homeostasis

effective Glu clearance is essential for neuronal function.
Glu/Gln Cycling ist stark energieabhängig und ca. 1:1 mit dem Glucosemetabolismus gekoppelt (verbraucht ca. 60-80% des gesamten Energiehaushalts des Gehirns): 1 Glu : 3 Na~ ~ 1 Glc : 2 ATP
1 Glu reuptake requires 1 Glc mol equals 2 ATP

Price and Drevets, 2010

Glucose Metabolismus und MDD

Brain regions with Hyper- and Hypometabolism in MDD

FDG-PET

Price and Drevets, 2010

Neuropsychopharmacology

doi: 10.1038/npp.2009.104
**MDD: Molecular Mechanismen an der Glu Synapse**

- $^1$H-MRS => Glu, Gln levels
- negative feedback
- $^{13}$C-MRS => Gln/Glu cycling
- PET => mGluR5

**MDD: Histopathology**

Glia and neurons in layer 6 of the anterior cingulate cortex

Cotter et al.
Arch Gen Psychiatry, 2001

Sanacora et al.
Nat Rev Drug Discovery, 2008
Stress und Neurodegeneration / -plastizität

MDD: Multimodale Bildgebung (fMRI & MRS)

Figure 1. Glutamin (Gln) in major depressive disorder (MDD). A. Placement of the magnetic resonance spectroscopic voxel (orange frame, upper panel) in the anterior cingulate cortex. Functional magnetic resonance imaging analysis revealed decreased negative blood oxygenation level-dependent responses in patients with MDD within this region compared with controls (difference map, P<.001, uncorrected, lower panel). B. Mean Gln concentrations (relative to creatine [Cr]) ± standard error of the mean measured in the magnetic resonance spectroscopic voxel depicted in A in MDD patients with high anhedonia (MDDHA) (n=8) and low anhedonia, (MDDLA) (n=6) and healthy controls (n=14), C. In healthy controls, Gln and glucose (Glc) levels (relative to Cr) show a significant correlation (r=0.886, P<.001), whereas in patients with MDD, Gln and Glc levels are uncorrelated.

in MDD, no correlation Gln:Glc => decoupling

Walter et al., Arch Gen Psychiatry, 2009
MDD: 1H-MRS: Glu und Krankheitsstadien

Ventromedial prefrontal spectroscopic abnormalities over the course of depression: A comparison among first episode, remitted recurrent and chronic patients

Glu

NAA

Cho


• Glutamaterges System:
  – Veränderungen bei Depression (MDD)
  – Ketamin

• Ausblick
The depressive state of depressed patients (n=35) administered ketamine improved after surgery

*P < 0.05 between Group A and B.

Kudoh et al., Anesth Analg 2002

**NMIDA Antagonist Ketamin**

- hypnotic
- analgesic
- amnesic
- psychotomimetic

R(-) ketamine

S(+) ketamine: 3-4 times higher affinity
Psychologische Effekte von Ketamin

- Ketamine 6 µg per kg per min (n = 42)
- Ketamine 12 µg per kg per min (n = 92)

Ketamine blocks GABA-ergic subcortical and cortical interneurons => increased firing in Glu projection neurons => increased extracellular Glu in PFC.
Ketamine blocks cortical NMDAR => increased AMPAR stimulation. Increased AMPAR/NMDAR mediated throughput => increased expression of BDNF

Ketamine: BDNF↑

Ketamine blocks GABA-ergic subcortical and cortical interneurons => increased firing in Glu projection neurons => increased extracellular Glu in PFC. Ketamine blocks cortical NMDAR => increased AMPAR stimulation. Increased AMPAR/NMDAR mediated throughput => increased expression of BDNF

Vollenweider & Kometer, Nat Rev Neurosci 2010
**1H-MRS nach Ketamin**

Robust and rapid antidepressant effect resulted from a single i.v. dose of the NMDA receptor antagonist ketamine; onset occurred within 2 hours postinfusion and continued to remain significant for 1 week.

**Ketamin: antidepressive Wirkung**

Rowland et al., Am J Psychiatry, 2005

Zarate et al., Arch Gen Psychiatry, 2006
RCT mit Ketamin bei TRD

Antidepressent Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial

Murrough et al.

FIGURE 1. Change in Depression Severity Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam

- Modified intention-to-treat group. MDRS scores range from 0 to 60, with higher scores indicating a greater severity of symptoms.
- Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group (p=0.002).

Akute und langdauernde Effekte mit wiederholter Ketamin i.v. Gabe bei TRD

Murrough et al., Biol. Psychiatry 2014
**Ketamin intranasal bei MDE (RTC, 20 pts, i.n. 50 mg)**

Lapidus et al, Biol Psychiatry 2014

**Low-dose Ketamin bei Suizidgedanken**

Ibrahim et al.
Prog Neuropsychopharmacol Biol Psychiatry, 2011

* single i.v. bolus of ketamine (0.2 mg/kg) over 1-2 min
* Patients were monitored for 4 h, then re-contacted daily for 10 d.
Metaanalyse der antidepressiven Effekte von Ketamin

Glutamaterges System:
- Veränderungen bei Depression (MDD)
- Ketamin

Ausblick
Pharmazeutische Pipeline Antidepressiva

**Monoaminergic**
- **Cholinergic**
- **Glutamatergic**

**HPA Axis Modulation**

**Neurotrophic compounds**

**Melatonin Modulation**

**Neuropeptide Galanin 3R**

**NMDA receptor antagonists**
- Maeng & Zarate, 2007
- Moryl et al., 1993
- Papp & Moryl, 1994, 1996
- Przegalinski et al., 1997
- Trullas & Skolnick, 1990

**NR2B subunit-selective antagonist CP-101,606**
(allosteric mechanism)
- Preskorn et al., 2008

**AMPA receptor potentiators**
- inhibitors of glutamate-release agents
- enhancers of glutamate transporters

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Danke für die Aufmerksamkeit
Longer-term antidepressant effects of repeated i.v. Ketamine

Response prediction

Participants meeting response criteria were monitored for relapse for up to 83 days from the last infusion.

The overall response rate at study end was 70.8%.

Response at study end was strongly predicted by response at 4 hours (94% sensitive, 71% specific).

Among responders, median time to relapse after the last ketamine infusion was 18 days.
Intermittent oral ketamine augmentation in chronic suicidality

Letters

Oral ketamine augmentation for chronic suicidality in treatment-resistant depression
Angelo De Giannis and Diego De Leo

and the current regime of amitriptyline (200 mg nocte) and quetiapine (100 mg bid) he remained depressed, with scores of 36 on the Montgomery-Asberg Depression Rating Scale (MADRS) and 4/6 on the suicide item. Following written informed consent, oral ketamine was added. The treatment involved fortnightly doses of a ketamine solution (100 mg/ml) ingested orally with a flavoured drink. Starting with an initial dose of 0.5 mg/kg and the scores decreased to 10 on the MADRS and 2 on the suicide item. She continued to receive monthly doses of oral ketamine and her mental state continued to improve with no suicide ideation between treatments. Pretreatment blood tests included liver function tests and complete blood count with differential. Blood pressure and pulse rate were monitored before and 30 minutes after each dose. Neither patient experienced adverse

Perspective - Ketamine for a personalized treatment

The Relationship Between Aberrant Neuronal Activation in the Prefrontal Anterior Cingulate, Altered Glutamatergic Metabolism, and Anhedonia in Major Depression

Does ketamine have the potential to compensate for lower Gln levels in anhedonic patients?

Quantitative J-resolved 1H-MRS in the pgACC

Walter et al., Arch Gen Psychiatry, 2009
**Ketamine: Preclinical studies -> Glu**

Ketamine i.p. increases brain glutamate levels  
*(in vivo microdialysis in rats)*

**EAAT: anhedonia and depression**

**Animal model::** Blocked astrocytic glutamate clearance (EAAT) in rats induces signs of anhedonia and impaired spatial memory

**Postmortem depressive brain::** mRNA reduction of astrocytic Gln-synthetase and Glu-transporter (EAAT)

Bechtolt-Gompf et al 2010, Neuropsychopharmacology 35, 2049-59  
Choudary et al 2005, Altered cortical glutamatergic and GABA-ergic signal transmission with glial involvement in depression, PNAS 43, 15653-8
Major Depressive Disorder: 1H-MRS

Reduced Prefrontal Glutamate/Glutamine and γ-Aminobutyric Acid Levels in Major Depression Determined Using Proton Magnetic Resonance Spectroscopy

Georg Hasler, MD, Jan Willem van der Veen, PhD, Toshi Tamamio, MD, Noah Meyers, RN, Jun Shen, PhD, Wayne C. Drevets, MD

<table>
<thead>
<tr>
<th>Voxel and Participants</th>
<th>GABA</th>
<th>Coiled Gla†</th>
<th>Choline</th>
<th>NAA</th>
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<tbody>
<tr>
<td>DM/DA-PF ROI</td>
<td></td>
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<tr>
<td>Patients with MDD (n = 20)</td>
<td>0.89 (0.11)</td>
<td>2.30 (0.38)</td>
<td>1.55 (0.18)</td>
<td>10.31 (1.10)</td>
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<tr>
<td>Controls (n = 20)</td>
<td>1.02 (0.11)</td>
<td>2.67 (0.54)</td>
<td>1.55 (0.29)</td>
<td>9.97 (0.99)</td>
</tr>
<tr>
<td>Statistics (df = 38)</td>
<td>t = 2.54</td>
<td>t = 2.25</td>
<td>t = -0.12</td>
<td>t = -1.63</td>
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<tr>
<td>P = .02</td>
<td></td>
<td>P = .59</td>
<td>P = .90</td>
<td>P = .11</td>
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| VM-PF ROI              |      |            |         |     |
| Patients with MDD (n = 20) | 0.94 (0.14) | 2.65 (0.39) | 1.59 (0.21) | 9.57 (0.76) |
| Controls (n = 20)       | 0.95 (0.12) | 2.96 (0.47) | 1.57 (0.25) | 9.75 (0.74) |
| Statistics (df = 38)    | t = 0.35 | t = 2.30 | t = -0.29 | t = 0.76 |
| P = .72                |        | P = .02    | P = .37   | P = .43  |

Abbreviations: DM/DA-PF, dorsomedial/dorsal anterolateral prefrontal; GABA, γ-aminobutyric acid; SIx, glutamate/glutamine; MDD, major depressive disorder; NAA, N-acetylaspartate; ROI, region of interest; VM-PF, ventromedial prefrontal.

*The creatine concentration was set at 93 mg/dl (7100 μmol/L).
†Coiled Gla represents a fraction of the total Gla concentration (see the "Methods" section).

Immunmodulation by ketamine in mice astroglia cells

Yuhas et al 2015, J Neuroimmunology