Department of Child and Adolescent Psychiatry/Psychotherapy

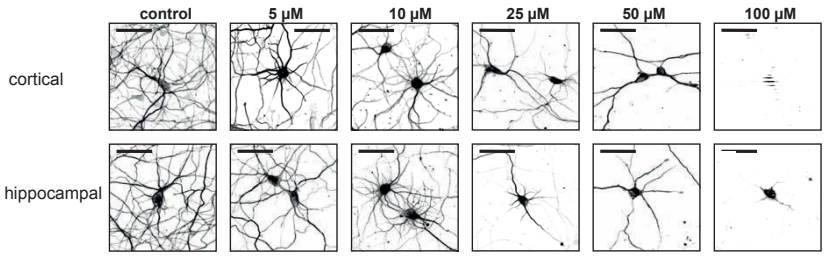
Age-dependent Cell Biological Effects of Psychotropic Substances in Maturing Neuronal Systems

Head: Jörg M. Fegert

If the prevalence of psychiatric disorders in childhood and adolescence is increasing, then this has been intensively debated for many years now. In contrast, it is undoubtedly true that the frequency of prescriptions of psychotropic medications for minors is significantly increasing. Most psychotropic substances are used “off-label” meaning there is a huge lack of knowledge about the cell biological effects of the prescribed compounds in the developing brain. Pediatric psychopharmacology can only be properly understood within the context of developmental neurobiology.

The Team:
Head of Department: J. M. Fegert
Group Leaders/Postdocs: A. G. Ludolph
PhD Student: P. T. Udvardi
Additional Member of Thesis Advisory Committee:
A. Storch (Dresden)

In a joint venture between the Clinic of Child and Adolescent Psychiatry and the Institute of Anatomy and Cell Biology, we are conducting in vitro studies in neuronal cell cultures and in vivo studies in rodents to assess the potential impact of psychotropic substances on cell development. We are interested in the effects of the substances most frequently used in child and adolescent psychiatry: methylphenidate, a psychostimulant and dopamine transporter inhibitor; atomoxetine, a selective norepinephrine transporter inhibitor (both compounds are used in the treatment of attention deficit hyperactivity disorder); and fluoxetine, a selective serotonin transporter inhibitor and antidepressant. Besides their well-known effects on the presynaptic monoaminergic transporter molecules, all three substances seem to have an impact on cell plasticity. Our working group was able to detect neuroprotective effects of methylphenidate. Fluoxetine and atomoxetine exerted a dose-dependent effect on cell viability and a reduction of neuronal arborisation and synaptic density. In collaboration with the Department of Anesthesiology, we were able to show that atomoxetine inhibits the NMDA-receptor, a mechanism that influences apoptosis in the developing brain. We are currently investigating a possible age-dependency of the effects of atomoxetine and fluoxetine not only on the expression of various monoaminergic transporters and subunits of the NMDA-receptor (PhD work Patrick Udvardi) but also, since the NMDA-receptor is embedded in a much larger complex of proteins associated with the post-synaptic density (PSD), on the expression of PSD scaffolding proteins.



Effect of atomoxetine on cortical and hippocampal neurons. The neuronal cells were treated on DIV 5 for 72 h with the indicated concentrations of atomoxetine. The neurons were immunolabeled with antibodies against MAP2 (microtubular-associated protein 2). Bar = 20 µm. Loss of sprouting emerged in cortical and hippocampal neurons dose-dependently. The impairment of the dendritic network starts at an atomoxetine concentration of 5 µM.

Ulm University
Department of Child and Adolescent Psychiatry/
Psychotherapy
Prof. Dr. Jörg M. Fegert
Steinhövelstraße 5
89075 Ulm, Germany
Tel. +49 (0)731 500 61600
Fax +49 (0)731 500 61602
joerg.fegert@uniklinik-ulm.de
www.uni-ulm.de/klinik/kjp/

Selected Publications:

- *Ludolph AG, Schaz U, Storch A, Liebau S,Fegert JM, Böckers TM (2006): No neurotoxic but neuroprotective effects of Methylphenidate in primary mesencephalic cultures, J Neural Transm 113, 1927-34.*
- *Ludolph AG, Kassubek J, Schmeck K, Glaser C, Wunderlich A, Buck AK, Reske SN, Fegert JM, Mottaghy FM (2008): Dopaminergic dysfunction in attention deficit hyperactivity disorder (ADHD), differences between pharmacologically treated and never treated young adults: A ···3,4-dihdroxy-6-[18F]fluorophenyl-L-alanine PET study, NeuroImage 41, 718-727.*
- *Schaz U, Ludolph AG, Udvardi PT, Schaz U, Henes C, Adolph O, Weigt HU, Fegert JM, Boeckers TM, Föhr KJ: Atomoxetine acts as an NMDA receptor blocker in clinically relevant concentrations, Br J Pharmacol 160, 283-91.*
- *Schaz U, Föhr KJ, Liebau S, Fulda S, Koelch M, Fegert JM, Boeckers TM, Ludolph AG (2010): Dose-dependent modulation of apoptotic processes by fluoxetine in maturing neuronal cells: an in vitro study. World J Biol Psychiatry. 2010 Aug 24. Epub ahead of print*