involved in spatial coding and spatial memory. Genetic manipulations included ablations of glutamate receptors or electrical coupling in GABAergic interneurones in the whole forebrain, or locally in the hippocampal-entohinal formation. Our studies underline the functional role of local GABAergic interneurones for spatial or temporal coding in the hippocampus. The genetic manipulations were always associated with distinct spatial memory deficits. These results will be summarized and discussed in the context of current models of memory formation and storage.

In addition I will present data demonstrating the presence of long-range GABAergic cells that bilaterally connect the hippocampus and entorhinal cortex[3]. Also these data will be discussed in a larger context, since there is good reason to believe that long-range GABAergic neurones are more abundant in the forebrain as previously thought. By virtue of their connectivity – the target cells are most often local interneurones – this class of cells is ideally suited to synchronize brain regions over long distance. Like local GABAergic interneurones, long-range GABA cells do not constitute a homogenous cell population. Thus, we identified long-rang GABA cells expressing somatostatin that project from the hippocampus to the medial entorhinal cortex and long-range parvalbumin-positive cells that project from the medial entorhinal to the hippocampus. Of note, in both brain regions there are additional long-range GABA cells whose neurochemical identity remains to be established.

References

[1] Fuchs, E. C., Zivkovic, A. R., Cunningham, M. O., Middleton, S., LeBeau, F. E., Bannerman, D. M., Rozov, A., Whittington, M. A., Traub, R. D., Rawlins, J. N., Monyer, H., 2007. Recruitment of parvalbumin-positive interneurons determines hippocampal function and associated behavior. Neuron 53, 591–604.
[2] Allen, K., Fuchs, E.C., Jaschonek, H., Bannerman, D.M., Monyer, H., 2011. Gap Junctions between Interneurons Are Required for Normal Spatial Coding in the Hippocampus and Short-Term Spatial Memory. J. Neurosci. 31, 6542–6552.
[3] Melzer, S., Michael, M., Caputi, A., Eliava, M., Fuchs, E.C., Whittington, M., Monyer, H., 2012. Long-range Projecting GABAergic Neurons Modulate Inhibition in Hippocampus and Entorhinal Cortex, Science 335, 1506–1510.

S.28.03 Schizophrenia-related behavioural deficits caused by hippocampal and prefrontal disinhibition

T. Bast[1]*, S. McGarrity[1], R. Mason[2], K.C. Fone[2], M. Pezze[1] [1]*Nottingham University, Psychology & Neuroscience@Nottingham, Nottingham, United Kingdom;* [2]*Nottingham University, Biomedical Sciences & Neuroscience@Nottingham, Nottingham, United Kingdom*

Disinhibition, i.e. deficient GABA function, in prefrontal cortex and hippocampus has emerged as a key neuropathological feature of schizophrenia. However, the contribution to symptoms remains to be clarified. Disinhibition of a brain region, interfering with spatio-temporal tuning of neural activity, is likely to disrupt regional function; moreover, causing aberrant drive of functional connectivity, regional disinhibition may disrupt processing in efferent sites.

Considering function and connectivity of prefrontal cortex and hippocampus, disinhibition of these regions may play a key role in cognitive deficits, including attentional and memory deficits, which are resistant to current treatments [1,2].

To test these ideas, we began to examine the neuro-behavioural effects of acute prefrontal and hippocampal infusion of the GABA-A antagonist picrotoxin in rats. Using in vivo electrophysiology, we showed increased neural firing in the vicinity of the infusion sites, consistent with disinhibition. Prefrontal disinhibition also increased LFP power within prefrontal cortex, resembling increased frontal EEG power in schizophrenia [3]. Our behavioural studies focused on key cognitive deficits. Both prefrontal and hippocampal disinhibition caused attentional deficits on the 5-choice-serial-reaction-time task (with the weaker deficits from hippocampal disinhibition presumably mediated by hippocampo-prefrontal connectivity, compare [1]). Hippocampal disinhibition also caused deficits on the watermaze delayed-matching-to-place memory test (akin to everyday memory problems in schizophrenia patients, compare [1]). Moreover, prefrontal and hippocampal picrotoxin caused moderate dose-dependent locomotor hyperactivity, consistent with psychosis-related dopamine hyperfunction.

Our findings reveal that prefrontal and hippocampal disinhibition can cause attentional and memory deficits. Thus, novel treatment strategies targeting such disinhibition may ameliorate cognitive deficits.

References

[1] Bast, T., 2011, The hippocampal learning-behavior translation and the functional significance of hippocampal dysfunction in schizophrenia. Curr Opin Neurobiol 21, 492–501.
[2] Lewis, D.A., Moghaddam, B., 2006, Convergence of γ-aminobutyric acid and glutamate alterations. Arch Neurol 63: 1327–1376.
[3] Venables, N.S., Bernat, E.M., Sponheim, S.R. (2009) Genetic and disorder-specific aspects of resting state EEG abnormalities in schizophrenia. Schizophr Bull 35: 826–839.

Disclosure statement: On invitation by Abbott Neuroscience Laboratories (Ludwigshafen, Germany) and Elli Lilly (Windlesham, Surrey, UK), I have given research seminars to employees of these companies and discussed my research with them.

S.28.04 New pharmacological treatment strategies targeting GABAergic dysfunction in schizophrenia

C.H. Vinkers[1]* [1]*Rudolf Magnus Institute of Neuroscience, Deptartment of Psychiatry A01.468, Utrecht, The Netherlands*

There is evidence that the inhibitory GABA system is involved in schizophrenia, and various GABAergic deficits are present in schizophrenia patients. If a dysfunctional GABA system is present in schizophrenia, therapeutic strategies to correct or modulate disrupted GABAergic pathways may be used to treat this disorder. However, classical benzodiazepines produce cognitive impairments and are associated with side effects. This unfavorable side effect profile introduces clinical risks, negatively influences compliance, and the development of tolerance may interfere with the required chronic use. The development of GABAergic compounds with selective efficacy for different alpha subunits at the benzodiazepine site of the $GABA_A$ receptor has renewed interest for the therapeutic potential of GABAergic drugs in schizophrenia. Specifically, two important classes of selective GABAergic drugs have been proposed to be value in schizophrenia, alpha5-selective inverse agonists and alpha2/3-selective agonists. This presentation will summarize the evidence for the use of GABAergic modulators in the treatment of schizophrenia and discusses the role of putative (selective) GABA-modulating drugs in clinical practice.