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Environmental modulation of phenotype in neuregulin 1 mutants

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Results: Normal anatomical distribution showed for NRG-1α only few immunopositive interneurons located in the prefrontal gray and white matter, whereas NRG-1β revealed a widespread immunoreactivity in pyramidal cells and interneurons in the gray matter of DLPCF and anterior cingulate cortex (ACC). In schizophrenia stereologic analysis revealed a significant reduction of NRG-1α cells in the white as well as in the gray cortical matter. In patients with unipolar depression the density of NRG-1α immunoreactive neurons was also significantly reduced in the prefrontal gray matter. In contrast to the 1α-isoform, NRG-1β immunopositive interneurons and pyramidal cells in DLPCF and ACC were significantly increased in schizophrenics in comparison to controls. Interneurons of the DLPCF differed significantly between cases of affective disorders and schizophrenics.

Conclusion: The diminished expression of NRG-1α in interstitial white matter neurons supports a neurodevelopmental component to schizophrenia (disturbed migration). With regard to NRG-1β we assume that the increase of the immunopositive neurons in schizophrenics leads to a hypofunction of NMDA-receptors via enhanced binding of this NRG-1 isoform to its receptor, ErbB4 (Hahn et al. 2006). However the increased expression of NRG-1β could also be due to the chronic administration of antipsychotics.

ISS-01.04 Testing the functional impact of at-risk haplotypes for schizophrenia with neuroimaging measures

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Neuregulin 1 has been identified as a potential susceptibility gene for schizophrenia. As with other candidate genes, initial findings have been difficult to replicate, because across studies different haplotypes were associated with the disease (Munafo et al., Schizophrenia Bulletin, 2008). SNP8NRG221533 was the single most significant variant in the original Icelandic haplotype and was included in several replication studies since then. Because neuregulin is implicated in neuronal development and synaptic transmission, we examined the impact of SNP8NRG221533 on neuropsychological, volumetric and functional measures of the brain in schizophrenia. In a study of 100 patients with first-episode of schizophrenia, SNP8_221533 was significantly associated with several measures of executive function (Trail making test B, Digit Symbol Substitution, Word fluency). A subsample of these first episode patients also underwent fMRI with an n-back paradigm. Patients without the at-risk allele at SNP8_221533 showed stronger activations in the left parahippocampal gyrus, the superior frontal gyrus, lateral temporal lobe, precuneus and the right anterior cingulate. In a separate study, we found that hippocampal brain volumes in schizophrenic patients and also in their relatives were affected by the core Icelandic haplotype comprising the same NRG1 SNP (Grueter et al., J. Psychiat Res., in press). Thus, while the association of specific SNPs and haplotypes of the NRG1 gene with schizophrenia may appear less convincing than some years ago, NRG1 variants appear to affect brain functional and structural measures in patients and their relatives, corroborating that frequent polymorphisms (and possibly also rare mutations) in this gene impact on intermediate phenotypes of schizophrenia.

ISS-01.05 Environmental modulation of phenotype in neuregulin 1 mutants


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Objective: Schizophrenia with its multi-factorial etiology has a concordance rate of 30–50% for monozygotic twins highlighting the fact that neither environment nor genetics alone are sufficient to cause schizophrenia but a combined action is likely. There is strong evidence that the human neuregulin 1 (NRG1) gene is a schizophrenia candidate gene and mice mutant for transmembrane domain (TM) Nrg1 exhibit a marked schizophrenia-related behavioural phenotype.
A variety of environmental risk factors have been proposed as contributing to the development of schizophrenia, including stress and chronic use of drugs of abuse. We hypothesise that subjects with a pre-existing genetic vulnerability for schizophrenia may be more susceptible to these environmental factors.

Methods: Using a multi-factorial animal model strategy, we investigated the neurobehavioural phenotype of male heterozygous TM Nrg1 mutant mice (Nrg1 HET) and their wild-type-like (WT) littermates, which (i) were kept in different housing conditions (i.e. standard vs. enriched housing), or (ii) were treated acutely with drugs of abuse (i.e. amphetamine (AMP; 5 mg/kg body weight) or the psychoactive constituent of cannabis, delta-9-tetrahydrocannabinol (THC; 5/10 mg/kg body weight)). All mice were tested in a variety of tasks for locomotion, exploration, anxiety, working memory and sensorimotor gating. Expression analyses were performed for a variety of receptor systems. Furthermore, c-Fos expression analysis determined neuronal correlates for the behavioural effects of acute THC.

Results: Nrg1 mutants were more susceptible to the stimulation of motor activity and exploration induced by environmental enrichment and its anxiolytic-like effects. Acute AMP treatment induced similar locomotor hyperactivity and disruptions of PPI as well as working memory performance in mutant and WT mice. However, Nrg1 HETs were more sensitive to the locomotor suppressant actions of THC and expressed a greater THC-induced enhancement in %PPI compared to WT mice. Mutants were also more susceptible to the anxiogenic effects of THC. Nrg1 hypomorphs expressed greater basal c-Fos levels in the shell of the nucleus accumbens and the ventral lateral septum (LSV) and a global increase in cortical serotonin 2A receptors. THC selectively increased c-Fos expression in the LSV, the central nucleus of the amygdala and the paraventricular nucleus of Nrg1 HETs.

Conclusion: These data suggest an interaction between Nrg1 and environmental factors. It appears that variation in the Nrg1 gene alters the sensitivity to the neurobehavioural effects of environmental enrichment and cannabinoids. Importantly, our study adds evidence to face and construct validity of this genetic animal model for schizophrenia.

Objective: To establish an animal behavioural model of depression an attention has to be paid to behavioural changes that can be monitored objectively and are reversed by the same treatment that is effective in clinics. The most recognized animal behavioural models of depression in historical sequences are: (a) Bilateral Olfactory Bullectomy in rodents, (b) Mother-Infant Separation in monkeys, (b) Learned Helplessness in dogs and rats (inescapable electric shocks), (c) Forced Swim Test in rodents, (d) Chronic Mild Stress in rodents, (e) Drug-withdrawal-induced anhedonia (f) Tail Suspension Test in mice, (g) Psychosocial stress in rodents (Resident-Intruder test; agnostic behaviour). The results received in potential antidepressant-like activity testing of selected drugs in rodent models of (a) olfactory bulbectomy, and (b) social stress in repeatedly defeated mice on pared agonistic interactions will be presented.

Methods: The bilateral ablation of the olfactory bulbs was performed by aspiration in the anaesthetized rats as described by Leonard and Tuite [1981]. The sham operated rats underwent the identical anesthetic and drilling procedures as olfactory bulbectomized (OB) animals, but their bulbs were left intact. Experiments were carried out 3 weeks after the surgery. The characteristic locomotor hyperactivity in the open-field test showed by OB rats was measured in the open field (Aeti-track infra-red beam based system, Panlab, s.l., Spain).

Results: (a) At the doses used none of drugs tested for their potential antidepressant-like effects (e.g. felbamate, tiagabine, sertraline, amisulpride) changed locomotor behaviour of sham-operated rats, however they inhibited locomotor hyperactivity in the open field test in OB rats. (b) Compared to control individuals the group-housed mice repeatedly defeated on interaction with aggressive singly-housed male mice exhibit significantly higher depression of ambulation in the open field test. This was normalized by clinically proven (e.g. citalopram, valproate) as well as potential antidepressants (e.g. felbamate, rimobabant).

Conclusion: In conclusion, it is believed that drug testing in both in results presented models could predict their beneficial effect on depression. The work was supported by the research project MSM60021622404.