Phenotyping ENU-mutagenized rats

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A major challenge in post-genomics is the systematic determination of mammalian gene function. A better insight in the causes of disorders in brain function may lead to more effective therapeutic treatments and interventions of human psychiatric disorders. As the rat is currently the most widely studied experimental animal in biomedical research, "knock-out" rat models are of major importance in gene function studies. "Phenotype-driven" approaches can be performed to generate knock-out rat models. Advantage is that no a priori assumptions are made about the underlying genes or pathways.
Novel rat phenotypes can be created using N-ethyl-N-nitro-sourea (ENU), a powerful germ-line mutagen. Extensive phenotyping of F1 offspring may result in the identification of behavioural abnormalities. Such phenotypic screens are especially challenging, as behavioural profiles have to be identified in single individuals.
To induce germ-line mutations, male founder rats (Wistar) were treated with three repetitive doses of ENU (35 or 40 mg/kg i.p., one week intervals). Fertile animals were crossed with wildtype females to generate offspring (F1) that was expected to be heterozygous for many independent random point mutations. Besides being genetically screened for mutations using a high-throughput pipeline based on endonuclease CEL-I-mediated heteroduplex DNA cleavage (see poster of Homberg et al.), these F1 animals are phenotyped in extensive behavioural screens assessing various brain functions. The "primary" screening test-battery includes the open field test, the elevated T-maze test, the spontaneous alternation test, the Nijmegen swim test, the pre-pulse inhibition test, the shock-prod burying test with a retention test after a 48 hr interval and the sucrose preference test. Animals that behaviourally deviate from their siblings are also subjected to a 'basal' screen assessing motor, autonomic and sensory function, based on the SHIRPA protocol. Mendelian inheritance of deviating behavior will be confirmed by breeding. Eventually, the responsible mutation will be mapped and cloned by traditional forward genetic cloning.

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Poster graag naast die van JR Homberg