

PRECLINICAL RESEARCH

S.20 Adult neurogenesis in anxiety and mood disorders Hall A3 Monday 14:45 – 16:25

The HABs and the HAB-nots

New findings in anxiety and depression

A symposium on the relationship between adult neurogenesis and anxiety and depression takes place this afternoon, giving delegates an insight into the latest knowledge that has accumulated as a result of studies in both animals and humans.

Speaking to *ECNP Daily News*, Nicolas Singewald (University of Innsbruck, Austria) described the work he has been doing in deciphering the maze that connects anxiety and depression with neurogenesis and the hippocampus, with the hope that, in this way, it will be possible to improve the understanding and treatment of these conditions.

Along with fellow colleagues, Professor Singewald is involved in two Austrian network initiatives, SFB-F44 (Cell Signalling in Chronic CNS Disorders) and SPIN (Signalling Processing in Neurons), that take cross-disciplinary approaches to studying the involvement of mechanisms such as epigenetics, non-coding RNAs, and inflammation.

“The beauty there is actually that we have members that study completely different things to what we are classically studying in the anxiety and depression field. So you go into these questions with an unbiased approach. We came up with really interesting stuff that we would never have looked at had we not been in this network”

The principle of the lab, explained Professor Singewald, is to approach clinical reality as closely as possible by using psychopathologically-relevant animal models. The ways in which, for example, deficient fear regulation (evident in PTSD, phobia or panic disorder), could be rescued in a model via numerous pharmacological means provides valuable information as to the mechanisms involved in this recovery process.

“We have identified a number of pharmacological ways to rescue such deficits and build long-term fear inhibitory memories,” he continued. “The idea is then to team up with clinicians and try to translate such findings into man. We were successful last year, showing that such a fear extinction-boosting approach that worked in mice also worked in humans.”

The majority of experiments thus far that have looked at neurogenesis in mental illnesses such as depres-

sion, anxiety and schizophrenia, have used naïve animals under baseline conditions, noted Professor Singewald. He went on: “This was initially very important in order to find the basic mechanisms. I think the step forward now is to model risk factors for developing those disorders, rather than focusing on naïve animals. There has been a lot of work done on the stress side, for example, which we know is a triggering factor and an important epidemiological factor. But much less has been done with the genetic risk factors, and that is exactly what we are doing now.”

Professor Singewald will present work on models of enhanced anxiety and comorbid depression, arguing that, because this comorbidity is the rule rather than the exception, it is necessary to take a deliberate look at them in tandem – in contrary to what most research thus far has done.

“This comorbidity has been shown to complicate therapy and worsen treatment prognosis,” he said. “Although anxiety and depression clearly have distinct features and are distinct diagnostic categories, this high comorbidity points to shared underlying mechanisms, including genes and epigenetics.”

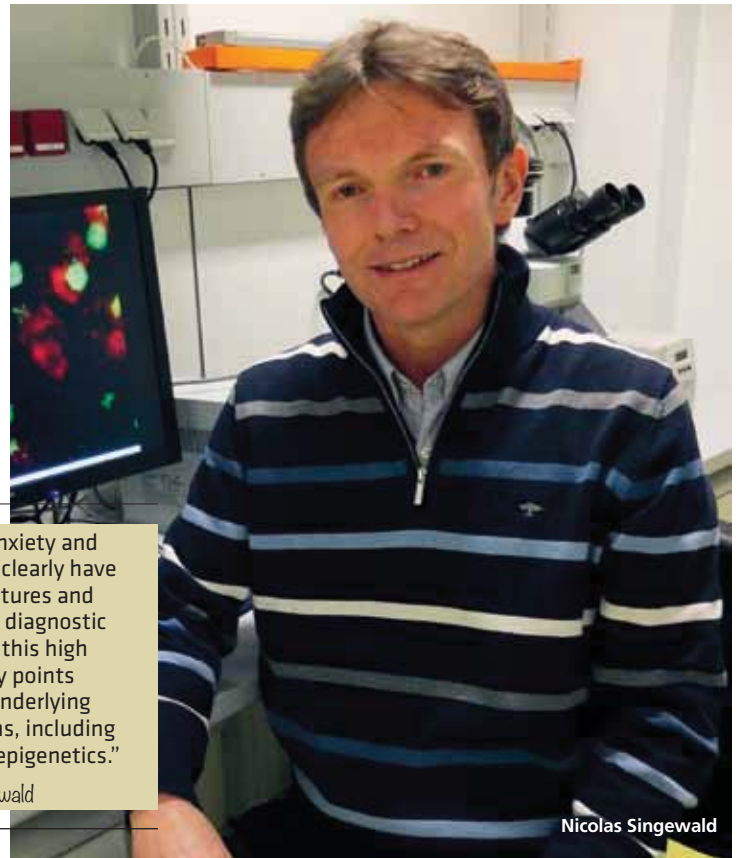
“Experimentally, we have shown that nutritional issues can support the development of anxiety and depression, for example Mg²⁺ deficiency, and we have identified underlying mechanisms such as altered neuronal activation in key nodes of anxiety and depression-related circuitries, including the amygdala and paraventricular nucleus.”

The group is studying a special rodent (both rat and mouse) model of trait anxiety and comorbid depression, the HAB (high anxiety-related behaviour) model, developed some years ago by Rainer Landgraf and colleagues at the Max Planck Institute of Psychiatry in Munich.

Twin, and twin versus separated sibling studies, along with other work, have demonstrated that complex gene-environment interactions are responsible for the expression of anxiety and depression-related disorders. Moreover,

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explained Professor Singewald, it has been estimated that the genetic contribution is indeed considerable (30-60%). Fraternal studies in twin populations with anxiety and depressive disorders have shown that nearly a third to a half (33-46%) of the variance could be explained by genetic factors alone.

These findings are pertinent when designing an animal model; such a polygenic disorder in which each gene contributes in a small way to the phenotype can present difficulties, especially when only a small proportion of these contributing genes are known. “Therefore, we use a trick – selective breeding,” explained Professor Singewald. “This is thought to accumulate relevant gene variants and produces a stable phenotype, in this case hyperanxiety with comorbid depression-related behaviour.”

“An advantage is that the high anxiety/depression HAB mouse can be compared to mice with normal anxiety/depression (NAB) or even with low anxiety/depression mice (LABs), which all in principle have diverged from the same mouse strain. While a lot has been done looking into the environmental mechanism – in particular stress (a predisposing and triggering factor) – the effect of genetic risk and vulnerability for the development and maintenance of anxiety and depression symptoms is less studied.

“Due to the selective enrichment of

the genetic risk factors related to anxiety across generations, the HAB/NAB/LAB mouse model is a robust system for studying genetically inherited behavioural extremes of trait anxiety and comorbid depression.”¹

The group and their collaborators found that HAB animals undergo a number of changes that reflect the progression of anxiety/depression patients. These include altered stress coping ability, anhedonia (a hallmark of depression in humans), altered effects of therapeutic treatments, altered anxiety-related physiology (e.g. heart rate responses, heavily fragmented sleep patterns), and dysregulated brain neurotransmitter systems (e.g. neuropeptides and the GABA system, particularly the GABA-A subunit).

Further investigations using brain imaging identified aberrant activation, including amygdala hyperactivity, and prefrontal cortex and dentate gyrus hypoactivity. “We wanted to go into this hypoactivity in the dentate gyrus in more detail, to see whether it can be modulated or normalised by successful treatment – by pharmacological and also environmental manipulations,” explained Professor Singewald. “We also wanted to see whether there are morphological changes in this area and whether neuroplasticity and/or neurogenesis are altered in HABs, since the dentate gyrus is host

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to the subgranular zone, the main neurogenic region of the hippocampus.

“Since comorbidity lowers the chances of remission from both anxiety and depression, the final aim was to investigate in this animal model whether long-term benefits of antidepressant treatment are observed – and if so, whether this is associated with long-term alterations in dentate gyrus activity.”

A number of key findings emerged from the group's investigations. They showed that various antidepressant drugs with a high anxiolytic component (e.g. tianapine, NK1R antagonist) can normalise both the hyperanxiety and enhanced depression-like behaviour of HABs, while not affecting the NABs, indicating that pathophysiologically deranged systems are a primary target of these drugs. Environmental interaction (both positive, such as environmental enrichment, and negative, such as stress), was found to normalize the anxiety- but not the depression-like phenotype in HABs as well as LABs – thus providing good evidence that even a strong genetic predisposition to anxiety can be influenced via environmental manipulations.

Noting further findings of the group, Professor Singewald explained that hypoactivation of the dentate gyrus was normalised by successful antidepressant treatment, as well as by successful deep brain stimulation in SSRI treatment-resistant HABs.

“In work performed by Anupam Sah in the lab, we found reduced hippocampal neurogenesis and impaired functional integration of newly born neurons in HABs, which may contribute to the hypoexcitability and hypoactivation of dentate gyrus neurons,” he said. “In other words: selective enrichment of the genetic risk factors related to anxiety and possibly comorbid depression predisposes to reduced birth and integration of newly born neurons, with possible consequences like impaired pattern separation, cognitive disturbances, and anxiety/depression circuitry changes.”

The fundamental finding that blunted hippocampal neurogenesis is not permanent, i.e. that it can be rescued by pharmacological and environmental interventions, provides an impetus to shift the emphasis of treatment approaches in patients with anxiety and depression.

While neurogenesis seems to be largely altered with changes in anxiety, the therapeutic modulation of depression-like behaviour is dissociated from changes in neurogenesis. This, explained Professor

Singewald, indicates that neurogenesis may be an intermediate process followed by neurogenesis-independent processes governing the final antidepressant behavioural effect. He continued: “The therapeutic rescue of enhanced depression-like behaviour was associated with the normalisation of blunted dentate gyrus activity, indicating a close correlation with the ultimate behavioural

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response, rather than with (possibly intermediate) neurobiological changes.²

“What we can say from our data is that positive experience in these predisposed animals – an enriched environment – rescues the blunted neurogenesis that we have seen that is associated with a strong genetic predisposition to anxiety. So that is good news, that it is not permanent. We are investigating at the moment whether it helps to prevent the development of comorbid depression if we attenuate hyperanxiety by the identified means early on.

“There is more and more evidence that these patients should work out physically, because this also increases neurogenesis. We haven't got the causal link between these – it could be epigenetic – but it is really good news that you can do a lot with a positive experience, and by running or jogging to the extent that you might increase neurogenesis. The other positive aspect of this is that it may help to set the scene for better efficacy of other treatments you are using. In the future, this should be included much more in the therapy, because it is an easy thing to do. The step to boost neurogenesis pharmacologically as well in a specific and safe, well-dosed way, to ultimately possibly prevent hyperanxiety and depression in vulnerable patients, still needs a lot of joint basic work efforts.”

References

- Landgraf et al. Candidate genes of anxiety-related behavior in HAB/LAB rats and mice: focus on vasopressin and glyoxalase-I. *Neurosci Biobehav Rev.* 2007;31(1):89-102. Epub 2006 Aug 28.
- Sah et al. Anxiety- rather than depression-like behavior is associated with adult neurogenesis in a female mouse model of higher trait anxiety- and comorbid depression-like behavior. *Transl Psychiatry.* 2012 Oct 16;2:e171.

