WEB WATCH

- Webvision: http://webvision.med.utah.edu/

20/20 vision

We know a lot about the anatomy, physiology and development of the retina. So much, in fact, that this structure is arguably the part of the central nervous system that we understand best. A cursory visit to the Webvision web site will quickly show you that this is no exaggeration. This fantastic site, which is maintained by Helga Kolb, Eduardo Fernández and Ralph Nelson at the University of Utah, has very detailed information on the retina at all levels of analysis and depth.

In addition to basic concepts on the structure and function of the retina, Webvision includes more advanced sections on retinal neurochemistry, colour vision and psychophysics. The authors provide a good deal of background information, including milestones in the history of the field, which makes the site extraordinarily accessible and an invaluable educational resource. The quality of their illustrations is also high, and links to higher-resolution versions are bound to prove useful in lectures and seminars. The site is very well referenced, and constitutes an ideal platform from which to search for further information.

Webvision is so comprehensive that there is even an abridged version in Spanish, which is hosted at the Universidad Miguel Hernández in Alicante, Spain. Although it might be a tall order, we hope that, in future, all of the sections will be fully translated for the benefit of the Spanish-speaking scientific community.

With these solid foundations in place, the authors have started to extend the site beyond the retina to include a section on the primary visual cortex. We look forward to this expansion — and parallel improvements in our understanding of human vision — which will undoubtedly embrace the high standards of quality that Webvision currently enjoys.

Juan Carlos López

PSYCHIATRIC DISORDERS

Less stress?

A potential new approach to the development of anxiolytic and antidepressant drugs might emerge from results showing that an antagonist of the vasopressin V_{1b} receptor is effective in rodent models of both anxiety and depression. Griebel *et al.* tested the antagonist SSR149415 in a variety of rat and mouse models, and concluded that it shows both anxiolytic- and antidepressant-like properties.

Although arginine vasopressin (AVP) is produced in the hypothalamus and is involved in the regulation of the secretion of corticotropin by the pituitary gland, the presence of AVP-containing neurons that project to the limbic system, and of vasopressin receptors (V_{1a} and V_{1b}) in structures such as the septum and hippocampus, has led to the idea that AVP might also be important in emotional processes such as stress responses. In support of this, a mixed ($V_{1a/b}$) peptide vasopressin receptor antagonist has anxiolytic effects in rats, and stress resulting from chronic immobilization increases the levels of V_{1b} receptor messenger RNA. These results indicate a possible role for the V_{1b} receptor in emotional processes.

Now, the availability of a selective antagonist for the V_{1b} receptor has allowed Griebel *et al.* to test this idea. They used a battery of mouse and rat models of anxiety and depression to test the effects of SSR149415. In 'classical' models of anxiety, such as the elevated plus-maze and the light/dark test (which measures how long mice spend in a lit box as opposed to a dark one), the new compound was less effective than the benzodiazepine anxiolytic diazepam. But in models of exposure to traumatic stress, such as the social-defeat paradigm (in which a mouse is exposed to aggression from a resident mouse in a test cage, which normally increases anxiety as assessed in the elevated plus-maze), SSR149415 had clear anxiolytic effects. The authors suggest that V_{1b} receptor antagonists might be useful as a treatment for stress disorders that result from traumatic events, rather than for generalized anxiety disorder.

To test the antidepressant effects of SSR149415, Griebel and colleagues used two models of depression: the acute forced-swimming test, and the chronic mild-stress test (in which a mouse is exposed to a sequence of mildly stressful events, such as water deprivation and restraint, for several weeks, leading to a decline in grooming that is thought to parallel the reduction in personal hygiene in depressed humans). SSR149415 reduced all of the measures of 'depression' in these rodent models, which are normally good predictors of antidepressant efficacy in humans.

Although these results might be therapeutically useful, they do not tell us where in the brain SSR149415 acts to reduce anxiety or depression. However, the fact that it is still effective in hypophysectomized rats indicates that the effects do not depend on blocking the hypothalamic V_{1b} receptors, and supports the idea that the receptors in limbic structures are more important for these effects.

NEURAL INDUCTION

Tempting fate

The central tenet of the default model of neural induction states that ectodermal cells are fated to become neural unless they are instructed by bone morphogenetic proteins (BMPs) to take on an epidermal fate. This indicates that there must be transcriptional repressors that act downstream of the BMPs to inhibit the expression of neural-specification genes, and Bakkers and colleagues have now identified a strong candidate for such a repressor. The zebrafish ΔNp63 protein is a homologue of the mammalian p63, which is a close relative of the tumour-suppressor protein p53. Alternative splicing generates at least six different isoforms of ΔNp63, all of which function as transcriptional activators or repressors. Mutation of p63 in mice revealed defects in epithelial development and indicated a possible role in the maintenance of epithelial stem cells, but these new studies in zebrafish imply a much earlier role in ectodermal cell-fate choice.

First, the authors looked for evidence that ΔNp63 acts downstream of BMP signalling. They showed that the promoter region of the *ΔNp63* gene contains binding sites for the BMP-signalling mediators Smad4 and Smad5. They also showed that *ΔNp63* expression could be upregulated by increasing the level of BMP signalling, an effect that was abolished if the Smad binding sites were mutated.

Next, the authors examined the role of ΔNp63 in dorsoventral patterning. In the gastrulating zebrafish embryo, ΔNp63 transcripts are confined to the ventral ectoderm, which gives rise to epidermis. Bakkers *et al.* inactivated ΔNp63 at this stage of development using antisense oligonucleotides. In the resulting embryos, the neuroectoderm was expanded, and there was a concomitant reduction in expression of non-neural

A headless zebrafish larva 120 hours after fertilization, obtained by ectopic expression of ΔNp63, which blocks neural specification in the anterior neuroectoderm. Courtesy of Matthias Hammerschmidt, Max Planck Institute for Immunobiology, Freiburg, Germany.

Further studies using selective vasopressin receptor antagonists, perhaps targeted to specific regions such as the amygdala, septum or hippocampus, should help to clarify the role of AVP in anxiety and stress.

Rachel Jones

References and links

ORIGINAL RESEARCH PAPER Griebel, G. *et al.* Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V_{1b} receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. *Proc. Natl Acad. Sci. USA* **99**, 6370–6375 (2002)

FURTHER READING Wong, M.-L. & Licinio, J. Research and treatment approaches to depression. *Nature Rev. Neurosci.* **2**, 343–351 (2001)

ectodermal markers. Inhibition of BMP signalling also causes expansion of the neuroectoderm, and the authors found that this phenotype could be rescued by forcing the expression of ΔNp63. Overexpression of ΔNp63 in wild-type embryos, by contrast, led to a reduction in the amount of neural tissue.

So, ΔNp63 acts downstream of BMP signalling and it seems to be involved in ectodermal cell-fate specification, but how does it work? Bakkers *et al.* found that if the DNA-binding domain of ΔNp63 was linked to the repressor domain of a different protein, overexpression of the resulting chimeric protein could produce the same phenotype as ΔNp63 overexpression. This implies that ΔNp63 normally functions as a transcriptional repressor, with its DNA-binding domain conferring target specificity.

Taken together, these lines of evidence point towards ΔNp63 acting in the ventral ectoderm, downstream of BMP signalling, to repress genes that promote neural cell-fate specification. To complete the picture, it will be necessary to identify the target genes of ΔNp63, and to find out more about the mechanisms by which it achieves this repression.

Heather Wood

References and links

ORIGINAL RESEARCH PAPER Bakkers, J. *et al.* Zebrafish *ΔNp63* is a direct target of Bmp signaling and encodes a transcriptional repressor blocking neural specification in the ventral ectoderm. *Dev. Cell* **1**, 617–627 (2002)

FURTHER READING Muñoz-Sanjuán, I. & Brivanlou, A. H. Neural induction, the default model and embryonic stem cells. *Nature Rev. Neurosci.* **3**, 271–280 (2002) | Yang, A. & McKeon, F. P63 and P73: P53 mimics, menaces and more. *Nature Rev. Mol. Cell Biol.* **1**, 199–207 (2000)

WEB SITES

Encyclopedia of Life Sciences:
http://www.els.net/
BMP antagonists and neural induction

IN BRIEF

BEHAVIOURAL GENETICS

Influence of gene action across different time scales on behavior.

Ben-Shahar, Y. *et al*. *Science* **296**, 741–744 (2002)

Different alleles of the *foraging* gene (*for*) in *Drosophila* cause flies to be either 'rovers' (foraging over a wide area) or 'sitters' (feeding more locally). Ben-Shahar *et al.* show that increased expression of the same gene is associated with the age-related transition from hive work to foraging in honeybees. The *for* gene encodes a cyclic-GMP-dependent protein kinase (PKG), and the authors found that increasing PKG activity could increase precocious foraging.

ADDICTION

Psychostimulant-induced behavioral sensitization depends on nicotinic receptor activation.

Schoffelmeer, A. N. M. *et al. J. Neurosci.* **22**, 3269–3276 (2002)

The authors found that repeated exposure to nicotine enhanced the psychomotor effects of amphetamine, and that nicotinic antagonists prevented the development of amphetamine- and cocaine-induced behavioural sensitization. Nicotinic antagonists also prevented the increase in dopamine release that was found in the nucleus accumbens after treatment with the psychostimulant drugs. The results indicate that nicotine might enhance the long-term effects of amphetamine and cocaine, and alter their addictive properties.

NEUROLOGICAL DISEASES

Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis.

Lock, C. *et al*. *Nature Med.* **8**, 500–508 (2002)

Lock *et al.* compared the gene expression profiles of 'active' and 'silent' multiple sclerosis (MS) lesions to identify genes that are expressed at different stages of the disease. Several genes that were differentially expressed had not previously been associated with MS. By modulating the expression of two of these genes, the authors reversed the symptoms of EAE (experimental allergic encephalomyelitis), a mouse model of MS. This approach might help in the development of therapies to treat specific aspects of MS.

PSYCHIATRIC DISORDERS

Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism.

Torrente, F. *et al. Mol. Psychiatry* **7**, 375–382 (2002)

The authors describe a systematic study of lymphocytic colitis in children with regressive autism, comparing duodenal biopsies from these individuals with those from both normal and disease control groups. Their findings confirm the presence of a new form of enteropathy in autistic children, including increases in mucosal lymphocyte density, crypt cell proliferation, and epithelial deposition of IgG with complement C1q. They point to a possible autoimmune lesion in regressive autism.

Biotech/Pharmaceutical

New stress reducer

16 April 2002 - Proc. Natl. Acad. Sci. U.S.A.

The drug SSR149415 blocks a subtype of a receptor found in brain areas associated with anxiety and depression. Researchers showed that animals given the drug were less anxious and less depressed than untreated animals. Compared to traditional antianxiety drugs, the new compound was less effective at reducing anxiety caused by dangerous situations or aversive stimuli, but it was just as effective at reducing stress caused by traumatic social encounters. However, unlike traditional anxiolytics and antidepressants that can disturb sleep, impair memory, and reduce locomotor activity, the drug has few side effects.

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ABSTRACT FULL TEXT $

Reference: Griebel, G., Simiand, J., Gal, S.-L. et al. 2002. Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. *Proc. Natl. Acad. Sci. U.S.A.* (online), April 16.

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BioMedNet *Proc. Natl. Acad. Sci. U.S.A.* (Online), April 16.

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Volume 3, Number 48 - April 26, 2002

Step Toward Reducing Stress

A new drug has been shown to cut down on stress. It may offer a way to treat emotional disorders, such as anxiety and depression, researchers said in the Proceedings of the National Academy of Sciences.

The drug is called SSR149415. It was tested on mice and rats exposed to acute and chronic stress. Animals getting the drug showed less anxiety and depression than animals left to fend for themselves, said the scientists from Sanofi-Synthelabo in France.

When the researchers compared the compound to traditional anti-anxiety drugs, they found it was less effective in reducing anxiety caused by dangerous or aversive situations but worked just as well in ameliorating stress caused by traumatic social encounters. Unlike medications aimed at the same ends, the new drug has few side effects, said study co-author Guy Griebel.

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Sanofi Researchers Say Anxiety Drug Shows Promise in Mice

By Kristin Reed

Washington, April 15 (Bloomberg) -- Sanofi-Synthelabo SA researchers said an experimental anti-anxiety compound appeared promising in mouse studies that will appear tomorrow in the Proceedings of the National Academy of Sciences.

Researchers said the compound, dubbed SSR149415, appeared to ease trauma-related anxiety in mice without triggering the side effects such as sleep disturbances or memory problems that often occur with antidepressants such as fluoxetine, the generic drug Eli Lilly & Co. sells as Prozac, the researchers said.

The compound is still undergoing animal testing at the company's European laboratories. If successful, SSR149415 could one day enter a global depression drug market worth about $13.4 billion in 2000, according to data compiled by IMS Health Inc.

``The present findings indicate that SSR149415 has antidepressant-like properties that are comparable in terms of efficacy of the effects to those of a classical antidepressant," Sanofi-Synthelabo researcher Guy Griebel wrote in the study.

According to the study, the drug helped animals in experiments designed to create symptoms of depression but wasn't as effective as older medications SSR149415 appeared more promising in tests designed to create anxiety and trauma, the researchers said. The drug seemed generally free of side effects in the rodent studies.

Shares in Sanofi-Synthelabo, France's second-biggest drugmaker, fell 40 cents to 69.1 euros. Bristol-Myers Squibb Co. markets two of Sanofi's best-selling drugs, the heart treatments Plavix and Avapro, in the U.S.

Nom de code SSR149415: une nouvelle classe d?antidépresseur à venir ? - *Article complet*

- 16/04/2002 - Des chercheurs de Sanofi-Synthelabo relatent dans les comptes-rendus de l? académie des sciences américaine, l?essai chez le rat et la souris, d?une nouvelle molécule visant à traiter les troubles de l?émotion comme le stress et l?anxiété. Cette molécule cible les récepteurs de la vasopressine V1b impliquée dans l?émotivité et permet de réduire l?anxiété parmi des animaux soumis à un stress psychosocial. La molécule, dénommée SSR149415, prise oralement, semble aussi efficace que la fluoxétine pour réduire le stress chronique sans avoir les effets secondaires indésirables des antidépresseurs traditionnels.

L'arginine vasopressine (AVG) est un neurotransmetteur cyclique non peptidique synthétisé dans l'hippothalamus et retrouvé sous les formes V1a et V1b dans le système nerveux central, notamment dans les zones associées à l'anxiété et à la dépression, où leurs récepteurs sont présents.

Récemment, un antagoniste des récepteurs de la forme V1b de l'arginine vasopressine (SSR149415) a été mis au point dans les laboratoires du groupe pharmaceutique, et Guy Griebel (Bagneux, France) et ses collaborateurs ont décidé de le tester sur des modèles animaux de troubles du comportement liés à l'anxiété et à la dépression, induits par différents facteurs externes.

SSR149415 a produit, sur les modèles animaux classiques d'anxiété, des effets anxiolytiques à partir d'une dose de 1 mg/kg (administré per os ou en ip), mais moins importants que ceux du diazépam (une benzodiazépine) utilisé comme contrôle positif.

En revanche, dans les modèles de stress traumatiques, SSR49415 a montré des effets anxiolytiques nets et efficaces, avec une amélioration de l'anxiété, de l'état physique et du comportement stressé.

SSR49415, de plus, semble montrer moins d'effets indésirables que les antidépresseurs et anxiolytiques classiques, comme la perturbation du sommeil, la perte de mémoire et l'activité locomotrice réduite.

Source : *Proc Natl Acad Sci of the USA* 16 avril 2002; publication électronique avancée, DOI:10.1073/pnas092012099

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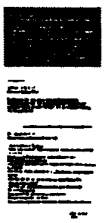
2002-04-16 09:36:46
Sanofi-Synthélabo SA/Wegelin: Neues Medikament gegen Angst

Zürich (awp 22) - Die Forscher des französischen Pharmaunternehmens Sanofi-Synthélabo haben vielversprechende Ergebnisse in der Entwicklung eines Medikamentes gegen Angstzustände erzielt. Das Präparat wurde bei Mäusen erfolgreich getestet und die Schlussfolgerungen sollen in der am Mittwoch dieser Woche stattfindenden Sitzung der National Academy of Sciences vorgelegt werden. Das Mittel mit dem Testnamen SSR149415 könnte in ferner Zukunft womöglich das Antidepressivum von Ely Lilly, Prozac, konkurrenzieren, schreibt Wegelin im heutigen "Früh - Sttick".

LieferscheinNr.:1399715,MedienNr.:6557;MedienausgabeNr.:620595;ObjektNr.:7208567;SubobjektNr.:1;LeserinNr.:12;AboNr.:757032;InsertNr.:10190891

(page 3)
Nouveau medicament contre la peur
Les chercheurs de Sanofi-Synthélabo ont atteint des résultats prometteurs dans le développement d'un médicament agissant dans les états anxieux. La molécule (SSR 149415) a donné des résultats positifs chez les souris et les résultats devraient être présentés ce mercredi à la réunion de l'académie nationale des sciences. Elle pourrait concurrencer éventuellement un jour le prozac



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Experimentan en Francia cun novo fármaco destinado a combate-lo estrés

Un novo medicamento, que se dirixe ó receptor da vasopresina, pode ofrecer unha nova forma de tratar alteracións emocionais, segundo informan os autores dun novo estudio publicado na última edición da revista *Proceedings.* O composto, coñecido como SSR149415, bloquea un subtipo de receptor que se atopa en áreas cerebrais asociadas coa ansiedade e a depresión. Nunha serie de experimentos que expuxeron a ratas e ratos a formas agudas e crónicas de estrés, científicos de Sanofi-Synthelabo, en Francia, amosaron que os animais ós que se lles administrou medicamento tiñan menos ansiedade e estaban menos deprimidos que os animais non tratados.

Comparado cos fármacos tradicionais contra a ansiedade, o novo composto era menos eficaz á hora de reduci-la ansiedade causada por situacións perigosas ou a estímulos que producen aversión ou rexeitamento, pero igual de eficaz á hora de reduci-lo estrés debido a encontros sociais traumáticos.

Francia.- Se desarrolla un nuevo fármaco que podría combatir el estrés

4/15/2002 11:36:37 AM
((Noticia embargada hasta las once de la noche))

MADRID 15 (EUROPA PRESS)

Un nuevo medicamento que se dirige al receptor de la vasopresina puede ofrecer una nueva forma de tratar alteraciones emocionales según informan los autores de un nuevo estudio publicado en la última edición de la revista Proceedings. El compuesto conocido como SSR149415 bloquea un subtipo de receptor que se encuentra en áreas cerebrales asociadas con la ansiedad y la depresión.

En una serie de experimentos que expusieron a ratas y ratones a formas agudas y crónicas de estrés científicos de Sanofi-Synthelabo en Francia mostraron que los animales a los que se administró el medicamento tenían menos ansiedad y estaban menos deprimidos que los animales no tratados.

Comparado con los fármacos tradicionales contra la ansiedad el nuevo compuesto era menos eficaz a la hora de reducir la ansiedad causada por situaciones peligrosas o a estímulos que producen aversión o rechazo pero igual de eficaz a la hora de reducir el estrés debido a encuentros sociales traumáticos. En un test que duró mes para medir la capacidad del nuevo medicamento de reducir los efectos del estrés crónico se vio que SSR149415 era igual de eficaz que la fluoxetina un antidepresivo común.

Sin embargo a diferencia de los ansiolíticos y antidepresivos tradicionales que alteran el sueño limitan la memoria y reducen la actividad locomotriz el nuevo fármaco posee escasos efectos secundarios. Los autores concluyen que SSR149415 puede ser útil para tratar la depresión y ciertas clases de ansiedad alteraciones que a menudo se producen al mismo tiempo en un mismo paciente.

Más noticias