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

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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

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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)

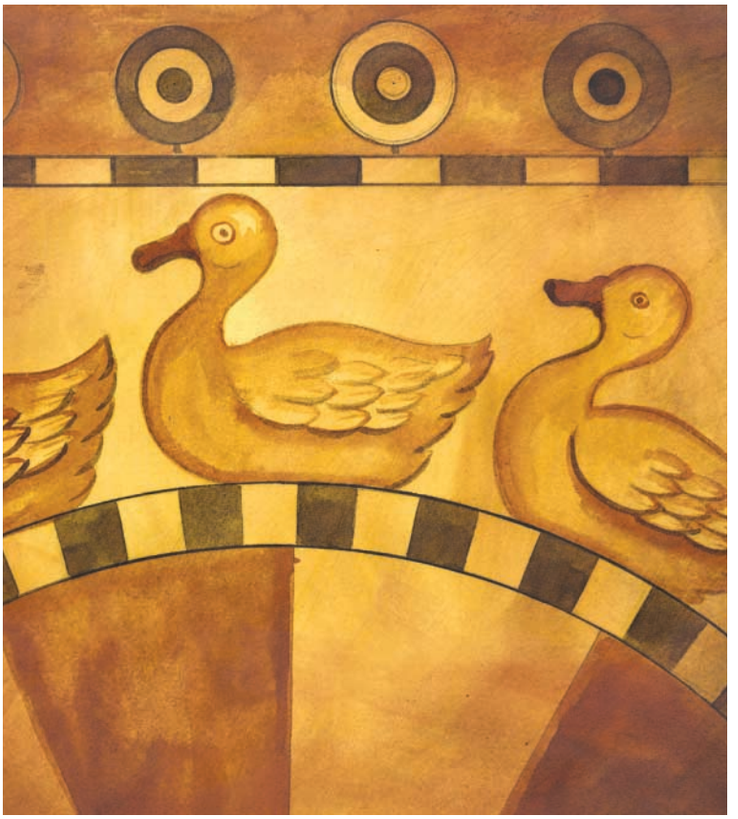
Lock *et al.* compared the gene expression profiles of 'active' and 'silent' multiple sclerosis (MS) lesions to identify genes that are expressed at different stages of the disease. Several genes that were differentially expressed had not previously been associated with MS. By modulating the expression 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.



ANTICANCER DRUGS

Next in line?

The success of the kinase inhibitor Gleevec in the treatment of chronic myelogenous leukaemia — which is caused by the aberrant activity of the BCR–ABL tyrosine kinase — has given much encouragement for the development of other molecularly targeted therapies. As two reports in *Cancer Cell* now indicate, inhibitors of the FLT3 kinase, which is mutated in ~30% of patients with acute myelogenous leukaemia (AML), could be promising candidates for targeted treatment of this disease.

The first study involved the kinase inhibitor CT53518, which is selective for FLT3 and two other kinases, platelet-derived-growth-factor receptor (PDGFR) and KIT, *in vitro*. CT53518 was found to inhibit several different constitutively active *FLT3* mutants that were cloned from patients with AML and expressed in Ba/F3 cells, and also to induce apoptotic cell death in human AML cell lines with mutations in *FLT3*. Encouraged by these observations, Kelly *et al.* tested CT53518 *in vivo* in two mouse models of mutant-FLT3-mediated AML, and found that CT53518 resulted in a significant decrease in disease progression, as assessed by spleen weight and white blood cell (WBC) count, and an increase in survival. Furthermore, CT53518 was shown to have suitable pharmacokinetic and toxicity profiles for clinical use.

The second study, by Weisberg *et al.*, assessed the activity of the kinase inhibitor PKC412 — which targets FLT3, and also the kinases KDR, PDGFR, KIT and protein kinase C — and found it to be highly toxic to Ba/F3 cells that expressed mutant FLT3 receptors from AML patients. And in a

STRESS-RELATED DISORDERS

Controlling emotion

The process of proving that a promising compound can have a viable therapeutic application is more often than not a case of having the right tools for the task.

Take, for example, stress-related disorders. It is widely accepted that arginine vasopressin (AVP) is involved in various behavioural processes. It has also been shown that chronic immobilization stress increases levels of vasopressin V_{1b} receptor in the brain, and that this receptor is involved mainly in modulating the effect of AVP on corticotropin secretion — a crucial component in the response to stress or emotional situations. But, without the existence of a V_{1b} receptor antagonist, the role of the V_{1b} receptor in controlling emotional processes could not be proved.

Now, two papers from the same laboratory report the characterization of SSR149415, a selective, non-peptide, orally active V_{1b} receptor antagonist, which they hope will be an innovative approach for the treatment of stress-related disorders.

In the first paper, published in *The Journal of Pharmacology and Experimental Therapeutics*, Serradeil-Le Gal and colleagues showed that SSR149415 has high affinities for both native and recombinant human and rat V_{1b} receptors, has a much lower affinity for other vasopressin receptors, and was inactive in >90 binding assays for neurotransmitters and peptides. They also showed that SSR149415 is a potent antagonist, as it inhibited both AVP-induced Ca^{2+} increase in Chinese hamster ovary cells that expressed the human or rat V_{1b} receptor, and AVP-induced corticotropin secretion in rats.

The second report, published in the *Proceedings of the National Academy of Sciences*, looked at the effects of SSR149415 in animal models of anxiety and depression. When Griebel and colleagues tested SSR149415 in classical models of anxiety (such as the light/dark, the elevated plus-maze and the punished drinking tests), it produced anxiolytic (reduced anxiety) effects, although the magnitude of these effects were less than that of the benzodiazepine diazepam. However, the authors found that SSR149415 produced a clear anxiolytic effect in models of traumatic stress exposure (the social defeat paradigm and the defence test battery).

When Griebel and colleagues looked at classical models for depression (forced swimming and chronic mild stress tests), they found that SSR149415 showed a dose-dependent antidepressant-like activity, which was comparable to those that were observed with the antidepressants fluoxetine and imipramine.

So, it seems that V_{1b} receptor antagonists could provide a new strategy for the treatment of some depressive and anxiety disorders. And although the site of action of SSR149415 is uncertain, it should serve as a useful tool for investigating the functional importance of the brain AVP in emotional processes.

Simon Frantz

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Serradeil-Le Gal, C. *et al.* Characterization of (2*S*,4*R*)-1-[5-Chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-*N*,*N*-dimethyl-2-pyrrolidine carboxamide (SSR149415), a selective and orally active vasopressin V_{1b} receptor antagonist. *J. Pharmacol. Exp. Ther.* **3**, 1122–1130 (2002) | 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* **9**, 6370–6375 (2002)

mouse model of mutant-FLT3-mediated leukaemia, PKC412 treatment completely blocked the development of leukaemia, whereas all of the mice in the placebo group developed fatal disease. Moreover, spleen weights and WBC counts were also significantly lower in the treated mice.

Both of these studies strongly support the idea that FLT3 is potentially a good drug target in AML. PKC412 and CT53518 are now being evaluated in clinical trials for AML, and it seems likely that several other FLT3 inhibitors will also be clinically tested. It will be of considerable interest to compare their efficacies and toxicities, as these are likely to be influenced by the non-FLT3 targets of each drug, which might differ significantly.

Peter Kirkpatrick

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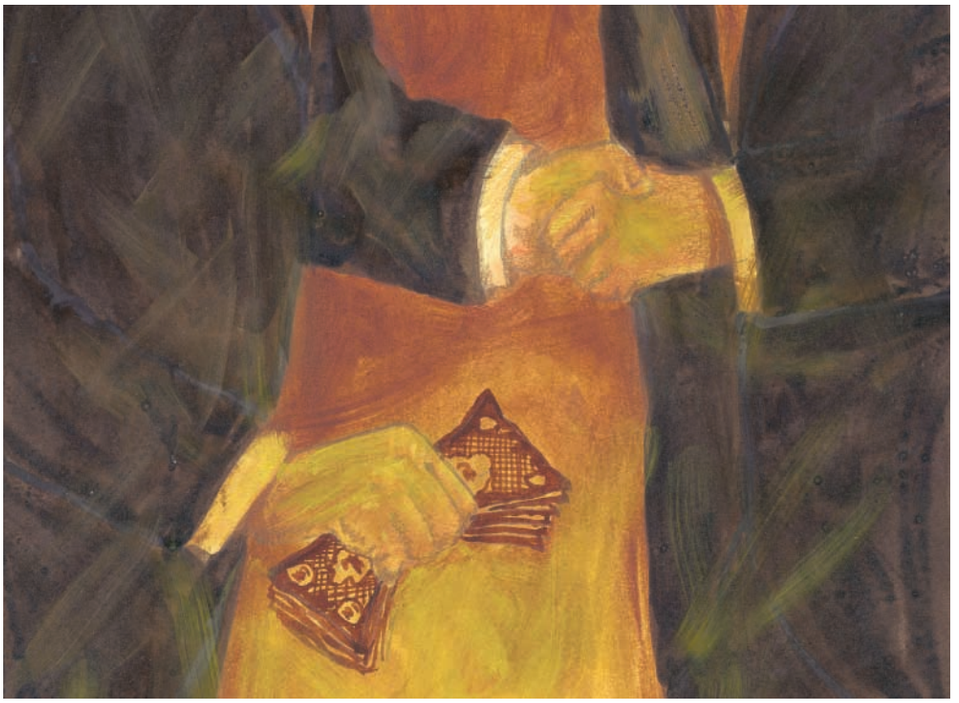

VIRAL INFECTIONS

Exchange control

Exchange is a fundamental process of life. In one type of cellular exchange process, the enzyme thioredoxin and the tripeptide glutathione mediate reduction–oxidation reactions between molecules. Disulphide exchange in one of the molecular domains of the CD4 molecule is required for entry of HIV-1 into T cells, according to new research in the August issue of *Nature Immunology*. This redox change could represent new potential targets for HIV-entry inhibitors.

HIV infection of helper T cells requires the receptor CD4, as well as a chemokine co-receptor. Although co-receptor use varies between virus strains, the use of the CD4 receptor is an almost universal feature of HIV-1 strains. CD4 is a surface membrane protein that is expressed at high levels on helper T cells. The molecule contains four immunoglobulin-like domains — D1 to D4 — of which D1, D2 and D4 each contains an intramolecular disulphide bond. These are formed when the sulphydryl group of one cysteine residue reacts with that of another cysteine in an oxidation reaction to form a disulphide bridge. An unusual feature of the D2 disulphide bond is its relatively high strain energy compared with the other disulphide bonds, which makes it more prone to reduction to the free sulphydryl groups.

Hogg and colleagues showed that a fraction of the cell-surface CD4 molecules contained one or more free thiols, and this was due to redox activity of the D2 disulphide bond. Regulation of the D2 redox state seems to be controlled by thioredoxin, which is secreted by T cells. The authors tested whether the redox state of the CD4 D2 domain was important for HIV-1 entry. To prevent the exchange between the oxidized and reduced forms, the authors used glutathionearsenoxide, which consists of a trivalent arsenical attached to the cysteine thiol of glutathione. Trivalent arsenicals form high-affinity ring structures with closely spaced dithiols, but not with monothiols or dithiols that are spaced far apart. Fixing the D2 thiols in the reduced state by labelling with this agent blocked HIV entry. It seems, therefore, that conformational changes in the D2 domain after reduction/oxidation and/or disulphide-dependent dimerization of CD4 molecules are important for HIV-1 infection of T cells.

Binding of the envelope protein of HIV-1 to CD4, which occurs through the D1 domain, is not affected by the redox state of the D2 disulphide. HIV-1 entry, however, occurs preferentially by means of receptors that are in the oxidized state. Detailed quantification of binding kinetics and avidity of HIV for the different redox forms of CD4 might reveal the explanation for the authors' observations. As well as having potential therapeutic applications for HIV-1 infections, this strategy could be a general approach for other molecules that contain redox-active structures.

Melanie Brazil

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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.

more Biotech/Pharmaceutical

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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.

Des cellules souches cérébrales adultes deviennent des neurones

Des chercheurs ont isolé des cellules souches de l'hippocampe de rats adultes et les ont mises en culture avec des cellules de soutien, des astrocytes. Les neurones développés à partir de ces cellules souches adultes ont qualitativement les mêmes propriétés que les neurones du SNC.

« Il est tout à fait clair que les cellules souches embryonnaires peuvent produire des neurones parfaits, sinon, il n'y aurait pas de développement du cerveau », souligne dans un communiqué le Dr Charles Stevens, du Salk Institute (La Jolla), qui a codirigé l'équipe. *« Mais personne n'avait démontré auparavant que les cellules souches adultes peuvent produire des neurones pleinement fonctionnels, au-delà du simple fait de présenter des marqueurs protéiques neuronaux. »*

Dans le cerveau adulte, il n'y a pas de production de nouveaux neurones, à l'exception d'une ou de deux régions, dont l'hippocampe. Là, les cellules souches peuvent donner naissance aux trois types majeurs de cellules du SNC – les neurones, les astrocytes et les oligodendrocytes. On ignore toutefois si ces cellules souches adultes peuvent donner naissance à des neurones pleinement fonctionnels. Il n'est pas sûr non plus que les signaux responsables de la maturation neuronale et de la formation des synapses durant le développement soient encore présents chez l'adulte.

Song, Stevens et coll. ont étudié ces questions en utilisant un système de coculture *in vitro*. Ils ont isolé des cellules souches à partir de l'hippocampe de rats adultes et les ont mises en culture. Ces cellules ont été marquées par transfection avec le gène d'une protéine fluorescente, afin de ne pas les perdre de vue au cours de leur différenciation.

Dans une première expérience, les chercheurs ont cultivé ces cellules souches adultes avec des neurones adultes et des astrocytes d'hippocampe néonatal. Ces dernières cellules de soutien sont connues pour produire les signaux chimiques qui déclenchent la croissance neuronale. Les neurones adultes ont été ajoutés à la culture, afin de voir si les neurones dérivés des cellules souches sont capables de s'intégrer dans le circuit neuronal établi par les neurones adultes.

Résultat, les cellules souches de l'hippocampe adulte se développent en neurones dotés de toutes les caractéristiques des neurones du SNC : ils ne se divisent pas et présentent un axone et des dendrites, ils sont actifs électriquement et envoient des potentiels d'action en réponse à la stimulation synaptique, ils forment des synapses capables de transmission et sont fonctionnellement intégrés dans le réseau neuronal. Enfin, ils peuvent libérer les neurotransmetteurs classiques en réponse aux potentiels d'action.

Il existe toutefois une différence quantitative, les neurones ne forment pas autant de synapses que les neurones normaux, mais cette différence s'estompe à l'ajout du BDNF (Brain-Derived Neurotrophic Factor).

Dans une deuxième et une troisième expérience, les chercheurs ont cocultivé les cellules souches adultes de l'hippocampe avec, cette fois-ci, uniquement les astrocytes dérivés de l'hippocampe néonatal ou de l'hippocampe adulte. Ils ont, là encore, observé le développement de neurones tout à fait fonctionnels, alors que, en l'absence d'astrocytes, les neurones dérivés des cellules souches adultes de l'hippocampe restent immatures, morphologiquement et fonctionnellement.

Des implications cliniques potentielles

Cela pourrait avoir des implications cliniques. *« Il y a eu beaucoup de discussions sur la question de savoir si les cellules souches nerveuses adultes, ainsi que les cellules souches embryonnaires, pourraient être utilisées pour régénérer le tissu cérébral lésé »*, explique le Dr Stevens, dans un communiqué. *« Ces résultats semblent indiquer que si l'on arrive un jour à ce que la thérapie par cellules souches soit possible pour traiter de telles maladies, on peut espérer que les cellules souches adultes puissent marcher. »*

Le chercheur souligne toutefois que des études comparatives approfondies entre cellules souches embryonnaires et cellules souches nerveuses adultes seront nécessaires, avant que leurs avantages et inconvénients respectifs puissent être déterminés. *« Il est absolument vital de poursuivre la recherche sur les cellules souches nerveuses embryonnaires*, affirme-t-il. *Il se pourrait que, pour des raisons que nous ne comprenons pas encore, les cellules souches adultes ne soient jamais utiles en thérapie et que nous ayons toujours besoin des cellules embryonnaires. Ou cela pourrait être l'inverse. Nous n'en savons rien. »*

Dr Véronique NGUYEN

« Nature Neuroscience » du 15 avril, DOI : 10.1038/nn844.

Art 50 peut être désormais prescrit sans limitation de durée

ECHODIAH, essai mené sur trois ans dans la coxarthrose, montre que la diacerhéine (Art 50) en ralentit la progression radiologique. Un symposium des Laboratoires Negma-Lerads a permis de faire le point.

Le traitement symptomatique de l'arthrose fait appel à des médicaments : antalgiques, anti-inflammatoires non stéroïdiens (AINS), et plus récemment inhibiteurs sélectifs de COX-2, qui soulagent la douleur à court terme, souligne le Dr T. Pham (Marseille).

Les notions de tolérance et de coût entrent en ligne de compte dans le choix, poursuit-elle. On accorde aussi un grand intérêt aux mesures non pharmacologiques, qui devraient être associées en première intention aux médicaments : perte de poids (pas seulement en cas d'obésité sévère), exercice physique adapté, semelles viscoélastiques, orthèses…

L'évaluation des traitements de fond de l'arthrose évolue. C'est le cas pour la diacerhéine, inhibiteur de l'interleukine 1, dont l'effet structuro-modulateur sur le cartilage (100 mg par jour) est mis en évidence par ECHODIAH (Evaluation de l'effet CHOndromodulateur de la DIacerhéine dans l'Arthrose de Hanche). Art 50 est indiqué dans le traitement symptomatique des signes fonctionnels de l'arthrose. De nombreuses études ont montré son efficacité sur la douleur et les indices algo-fonctionnels. Ces effets, différés de trente à quarante cinq jours après le début du traitement, sont aussi rémanents, persistant plusieurs mois après arrêt. Le bénéfice se traduit aussi par une réduction du handicap fonctionnel, un moindre recours aux soins, une amélioration de la qualité de vie, une réduction de consommation d'AINS et d'antalgiques.

ECHODIAH est une étude randomisée en double aveugle *versus* placebo chez 507 patients ayant une coxarthrose, menée sur trois ans. Elle montre que le pourcentage de patients ayant une aggravation radiologique définie par un pincement articulaire supérieur ou égal à 0,5 mm est significativement moins important dans le groupe diacerhéine (47,3 % contre 62,3 % avec le placebo) après trois ans chez les patients ayant terminé l'étude.

Allongement du délai de survenue du pincement

Le délai médian de survenue du pincement est allongé (« épargne » de 350 jours sur les trois ans d'observation).

Le recours à une prothèse de hanche est diminué dans le groupe diacerhéine sans que les résultats soient significatifs. Des études complémentaires sont nécessaires.

ECHODIAH a confirmé la bonne tolérance (notamment gastrique) du produit à long terme. Ces données d'efficacité et de tolérance à trois ans ont conduit une modification d'AMM en France, Art 50 peut désormais être prescrit sans limitation de durée. **Dr Janine DEFRANCE**

Symposium « Recherche et thérapeutiques dans l'arthrose. La voie des inhibiteurs de l'IL 1 », organisé par les Laboratoires Negma-Lerads.

Une nouvelle voie de recherche sur les troubles affectifs

Le blocage du récepteur de la vasopressine pourrait représenter un nouveau moyen de traiter les troubles affectifs. Cela représente d'ores et déjà une voie de recherche sur laquelle une équipe française s'est engagée. Ses résultats obtenus chez l'animal sont publiés dans les « Proceedings » de l'Académie des sciences américaine.

C'est la localisation en situation limbique du récepteur V1b de la vasopressine qui a fait soupçonner un rôle du récepteur dans le contrôle émotionnel. Guy Griebel et coll. (Sanofi-Synthélabo, France) ont alors étudié sur des modèles murins de l'anxiété et de la dépression les effets d'un composé mis au point par la firme, le SSR149415, qui est le premier antagoniste des récepteurs V1b actif par voie orale.

Dans les essais sur des tests classiques d'anxiété, le composé induit une activité anxiolytique-like, qui demeure moins importante toutefois que celle du diazépam, utilisé comme produit contrôle.

En revanche, sur des modèles de stress traumatique, le SSR149415 produit un effet clairement anxiolytique. Il exerce aussi des effets antidépresseurs chez des rats normaux et hypophysectomisés.

Et sur le modèle de stress léger chronique, l'administration répétée de SSR149415 pendant trente-neuf jours empêche la dégradation de l'état physique, ainsi que l'anxiété et la perte des capacités d'adaptation qui sont habituellement observés dans cette situation.

Il reste à déterminer précisément le site d'action du SSR149415. Il implique probablement des récepteurs V1b situés au niveau de l'amygdale, l'hippocampe ou l'hypothalamus, régions associées à la transduction et à l'intégration du stimulus induit par le stress. **Dr B. V.**

« Proc Natl Acad Sci USA » on line : www.pnas.org/cgi/doi/10.1073/pnas092012099

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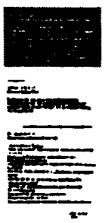
2002-04-16 09:36:46
Sanofi-Synthélabo SA/Wegelin: Neues Medikament gegen Angst

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