

Fédération Huntington Espoir



Nouvelles de la Recherche Octobre 2006

PRIX NOBEL DE MÉDECINE ET PHYSIOLOGIE 2006

Andrew Fire et Craig Mello, chercheurs en biologie moléculaire (USA), ont reçu le prix Nobel cette année pour leur découverte sur l'ARN interference (RNA interference)

L'ARN est un régulateur naturel de l'expression des gènes, et protège contre les infections virales. Les laboratoires l'utilisent pour étudier les fonctions des gènes et de nombreux chercheurs, dont Fire et Mello pensent qu'il renferme des promesses thérapeutiques.

Subject: **Noble Prize awarded to 2 Americans for RNAi**

Date: Mon, 2 Oct 2006 11:08 AM

RNAi could lead to a breakthrough in HD research.

RNAi pioneers win Nobel prize for medicine

02 October 2006

US molecular **biologists Andrew Fire and Craig Mello** have been awarded this year's Nobel prize in physiology or medicine for their discovery of RNA interference (RNAi).

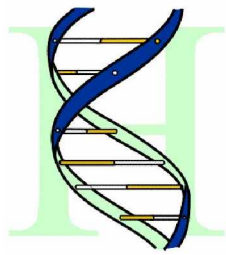
Fire, professor of genetics at Stanford University School of Medicine, and Mello, professor of molecular medicine at the University of Massachusetts Medical School, reported in 1998 that genes could be silenced by the mechanism of RNAi.

The prize is well deserved, said Muhammad Sohail, a biochemist at the University of Oxford, UK, and editor of the Journal of RNAi and Gene Silencing: 'These are the two pioneers in the field ... People will be very happy that this has been recognised so early.' About five years ago there were only 70 or 80 papers in the field, said Sohail: 'Now there's 70 or 80 every hour!'

RNAi is activated when RNA molecules occur as double-stranded pairs in the cell. Double-stranded RNA activates biochemical machinery that degrades messenger RNA molecules with a genetic code identical to that of the double-stranded RNA. (Messenger RNA is transcribed from a DNA template in the nucleus, and exported out of the nucleus where it becomes a template for protein synthesis in the cytoplasm.)

RNAi is a natural regulator of gene expression, and guards against viral infection. It is used in the lab to study gene function, and many researchers - including Fire and Mello - believe it holds therapeutic promise.

Bea Perks



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ESSAIS CLINIQUES

EFFICACITÉ ET SURETÉ DE LA MEMANTINE.

Les résultats du traitement par l'amantadine sont irréguliers.

La Memantine présente des avantages potentiels sur l'amantadine, mais des essais contrôlés supplémentaires doivent être pratiqués pour affirmer la valeur de la mémantine pour le traitement des symptômes et la modification de la maladie. (étude menée sur 12 patients, Baylor college)

(W.G.Ondo, Nicté I.Mejia, C.B.Hunter, Parkinson's disease center, Baylor college, Huston, TX))

A pilot study of the clinical efficacy and safety of memantine for Huntington's disease

Parkinsonism & Related In Press, Corrected Proof, Available online 13 October 2006

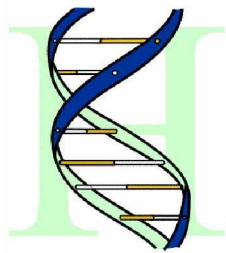
William G. Ondo, Nicté I. Mejia and Christine B. Hunter

Although amantadine has been advocated for HD chorea, results are inconsistent.

Potential advantages of memantine over amantadine include: (1) it has a much longer half life, allowing for once daily dosing, (2) it does not stimulate dopamine release, which could worsen chorea [5], and (3) it has less anti-cholinergic properties, which could worsen cognition and chorea. To date, memantine has not been associated with livido reticularis, which is very common with chronic amantadine exposure.

The design and short duration of the trial cannot differentiate an acute symptomatic effect from any neuroprotective effect, but the relatively rapid change suggests a direct biochemical effect on chorea. Numerous other limitations are inherent to an open label study of this size. There was no follow-up data on the three drop-outs, but reasons for dropping varied, and given the intentionally inclusive nature of the enrollment criteria, there was considerable variability of subject's ability to complete the cognitive assessments.

Based on our results, however, we do feel that larger controlled trials are justified to assess the value of memantine for both symptomatic treatment and disease modification in HD.



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UN ANTIDÉPRESSEUR RALENTIT LA MALADIE DE HUNTINGTON CHEZ LES SOURIS

Les souris qui ont des gènes mutés, traitées avec la sertraline (Zoloft), ont de meilleures performances motrices, vivent plus longtemps et leur cerveau présente moins de morts cellulaires que les souris non traitées. Des expériences antérieures ont montré que la paroxétine (Paxil) protégeait les cellules du cerveau et augmentait la durée de vie des souris mutées en augmentant le niveau de BDNF (brain derived neurotrophic factor).

La protéine stimule la croissance cellulaire du cerveau, la survie et les fonctions pendant la croissance et la phase adulte. L'équipe Johns Hopkins pense que sertraline a le même effet.

Classe de ces antidépresseurs: SSRIs (selective serotonin reuptake inhibitors).

(Johns Hopkins Neuroscience oct2006 Atlanta,GA)

Antidepressant [Paxil] slows HD in mice & other neuroscience news(Med 2006-110) and other tidbits from John Hopkins!

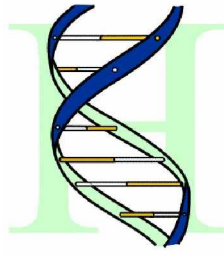
ANTIDEPRESSANT SLOWS HUNTINGTON DISEASE IN MICE

Johns Hopkins scientists have shown that along with the antidepressant paroxetine (Paxil), a close relative called sertraline (Zoloft) slows brain shrinkage in mice that have genetically engineered models of human Huntington's disease (HD). HD is an inherited disease that kills brain cells and causes loss of motor control.

When the mice, which contain altered genes that produce HD-like symptoms, were treated with **sertraline**, they had better motor skills, lived longer and sustained less brain cell death compared with untreated littermates. Previous studies showed that **paroxetine** helped protect brain cells from dying and increased survival of the same mutant mice by increasing levels of a brain chemical called brain-derived neurotrophic factor, or **BDNF**. The protein enhances brain cell growth, survival and function during development and adulthood and the Johns Hopkins researchers suspect sertraline does the same.

Studies are planned to determine safe equivalent doses for clinical trials of both drugs, which are among a class of compounds known as SSRIs, or **selective serotonin reuptake inhibitors**.

"Many SSRIs are FDA-approved and widely used with few side effects, making them especially attractive for other research" say Christopher Ross, M.D., Ph.D., professor of psychiatry, neurology and neuroscience at Johns Hopkins, and his colleague Wenzhen Duan, M.D., Ph.D, an assistant professor of psychiatry. "Now that we've shown these two to be effective in treating mice with HD, we're interested in further pursuing their use for treating people with HD."



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THÉRAPEUTIQUES EXPÉRIMENTALES

GREFFE DE CELLULES SOUCHES HUMAINES SUR DES RATS

Des cellules souches d'embryon humain transplantées dans le cerveau des rats ne prennent pas seulement l'identité des cellules nerveuses qui les entourent, mais semblent faire des connections avec d'autres cellules nerveuses. Quinze semaines après la transplantation, 70% des cellules transplantées s'étaient transformées en gène spécifique neural, assumant ainsi leur rôle; de plus, en observant leur environnement, les chercheurs John Hopkins ont eu la preuve que les cellules transplantées ont commencé à se connecter à d'autres cellules nerveuses du cerveau.

(Johns Hopkins Neuroscience oct2006 Atlanta,GA)

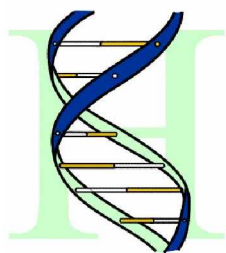
HUMAN EMBRYONIC STEM CELLS TAKE ON BRAIN IDENTITY IN RATS

Human embryonic stem cells transplanted into rat brains not only took on the identity of the nerve cells around them but also appeared to make connections with other nerve cells, experiments at Johns Hopkins have shown.

Fifteen weeks after transplanting ES cells that were first chemically coaxed along the path to nerve cell development, more than 70 percent of the transplanted cells turned on a nerve-specific gene, indicating that the cells had indeed assumed their rightful roles.

Studying the area around the transplants, the Johns Hopkins researchers found extra nerve endings, a hint that the transplanted cells had begun connecting to existing nerve cells in the rat brain.

"We're encouraged that stem cells seem to make connections when grafted directly into the brain," says Vassilis Koliatsos, M.D., an associate professor of pathology at Johns Hopkins. "It's a first step in bringing hope to millions affected by neurodegenerative disease."



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PEROSPIRONE POUR LE TRAITEMENT DE LA MH

Etude menée sur 1 patient.

C'est un antipsychotique de deuxième génération qui a des effets antagonistes sur les récepteurs de serotonine 5-HT(2A) et dopamine D(2), et un effet positif unique sur les récepteurs de serotonine 5-HT(1A). Le fait que la perospirone s'oppose aux récepteurs D(2) peut expliquer ses effets sur les syndromes d'hyperkinésie, alors que ses effets positifs sur les récepteurs HT(1A) peuvent expliquer l'amélioration des symptômes psychiatriques (peur et anxiété).

Des études futures permettront d'élucider l'utilité de la perospirone pour le traitement des mouvements involontaires et des symptômes psychiatriques dans HD.

(prog neuropsychopharmacol, Biol, Psychiatry 2006 jul31; Tomohide Roppongi, Takashi Togo, Shinichi Nakamura..., Japan)

Apparently perospirone is in the category of atypical antipsychotic drugs like risperidone, olanzapine, and quetiapine. Other abstracts show it also may help with aggressive behaviors in those with dementia, helping psychiatric patients eat who refused to eat, etc.. The downside is one case report of NMS in a patient with MS from this drug from Japan.

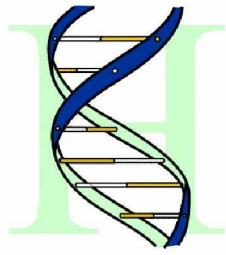
Prog Neuropsychopharmacol Biol Psychiatry. 2006 Jul 31

PEROSPIRONE in treatment of Huntington's disease: A first case report.

<http://lib.bioinfo.pl/meid:159746> [can anyone get this full study?]

Tomohide Roppongi, Takashi Togo, Shinichi Nakamura, Takeshi Asami, Asuka Yoshimi, Kazumasa Shiozaki, Daiji Kato, Chiaki Kawanishi, Yoshio Hirayasu

Huntington's disease (HD) is a hereditary disorder clinically characterized by involuntary movements, cognitive decline and psychiatric symptoms. We report on a patient with HD, whose involuntary movements and psychiatric symptoms were clinically improved with perospirone, a second-generation antipsychotic agent with antagonistic effects on serotonin 5-HT(2A) and dopamine D(2) (D(2)) receptors, as well as a unique agonistic effect on serotonin 5-HT(1A) (5-HT(1A)) receptors. The fact that perospirone antagonizes D(2) receptors could explain its effects on the hyperkinetic syndrome, while its agonistic effects on 5-HT(1A) receptors may explain the amelioration of psychiatric symptoms (fear and anxiety) in this patient. Future studies would be valuable to elucidate the utility of perospirone for the treatment of involuntary movements and psychiatric symptoms in HD.



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COLLABORATION PSYCHOGENICS - HIGH Q - CHDI

PsychoGenics développe sa recherche sur HD en collaboration avec High Q Foundation et CHDI, inc. sur les phénotypes de modèles de souris transgéniques HD et évalue le potentiel thérapeutique de médicaments sur ces modèles.

Dans le cadre de cette collaboration, PsychoGenics a développé des protocoles standardisés et validés qui comprennent une évaluation des comportements moteurs et cognitifs au cours de la progression de la maladie, dans des modèles de souris transgéniques HD.

CHDI, inc et la High Q foundation, inc sont des organisations sans profit qui partagent la mission de fournir aux universités, industries, agences gouvernementales et autres fondations, les résultats de leur recherche sur les traitements de la maladie de Huntington.

CHDI,inc poursuit une recherche en biotechnologie, pour découvrir rapidement et développer des médicaments qui empêchent ou ralentissent HD.

HIGH Q soutient la recherche sur HD, avec l'objectif de l'identification et la validation de cibles, le développement et l'utilisation de modèles animaux, les médicaments et la recherche de marqueurs de l'évolution de la maladie.

PSYCHOGENICS est leader sur l'étude du comportement neurobiologique préclinique et fournit des solutions personnalisées et innovantes pour la recherche de médicaments du système nerveux central (CNS).

"As part of this collaboration PsychoGenics has developed standardized and validated protocols that include assessment of motor and cognitive behavior during disease progression in established transgenic mouse models of HD."
"PsychoGenics' ability to rapidly screen drug candidates for HD through established high quality behavioral tests has enabled us to expand the relationship and increase the number of potential therapeutics to be evaluated"

PsychoGenics expands Huntington disease research collaboration with High Q Foundation and CHDI
CHDI Press Release in PDF format: <http://www.chdi-inc.org/press-releases/20060922-PsychoGenics.pdf>

September 22, 2006 - PsychoGenics Inc. Tarrytown, New York has expanded its research collaboration with the High Q Foundation and CHDI, Inc. to phenotype transgenic mouse models of Huntington disease (HD) and evaluate potential therapeutics in those models.

HD is a devastating, hereditary, and ultimately fatal neurological condition for which no treatment currently exists. HD gradually and progressively impacts an individual's capacity to function, affecting their physical and cognitive abilities. The transgenic HD models provide a

valuable discovery tool to aid in the development of much needed drugs. "We are delighted about expanding our work with CHDI and High Q. Combining transgenic models with our behavioral expertise will aid in the discovery of new therapies for HD," said Dr Daniela Brunner, PsychoGenics' VP of Behavioral Research and Development.

As part of this collaboration PsychoGenics has developed standardized and validated protocols that include assessment of motor and cognitive behavior during disease progression in established transgenic mouse models of HD. Using these mouse models and an adaptive allocation approach to experiment design, whereby compounds are screened and actives are rescreened to increase the statistical power, PsychoGenics has developed a high throughput approach to compound screening allowing the company to profile the effects of compounds on multiple behavioral domains.

"PsychoGenics' ability to rapidly screen drug candidates for HD through established high quality behavioral tests has enabled us to expand the relationship and increase the number of potential therapeutics to be evaluated", explained Dr Larry Park, CHDI Director of Preclinical Research.

About CHDI and High Q Foundation:

CHDI, Inc. and the High Q Foundation, Inc. (High Q) are non-profit organizations that share the mission of bringing together academia, industry, governmental agencies, and other funding organizations in the search for Huntington disease (HD) treatments. CHDI, Inc. is pursuing a biotech approach to rapidly discover and develop drugs that prevent or slow HD. Through collaborations with industrial and academic partners, CHDI, Inc., participates in all aspects of drug discovery and development from high throughput screening to preclinical development.

High Q supports HD research aimed at target identification and validation, the development and use of animal models, drug delivery, and the search for markers of disease progression. For more information about CHDI, Inc. and the High Q Foundation please contact:

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About PsychoGenics

PsychoGenics is a leader in preclinical behavioral neurobiology and a provider of customized and innovative solutions for central nervous system (CNS) drug discovery. PsychoGenics works with pharmaceutical and biotechnology companies, academic institutions and not-for-profit research foundations to address such major neurological disorders as: ALS, Huntington's Disease, anxiety, cognitive impairment, depression, psychosis/schizophrenia and SMA.

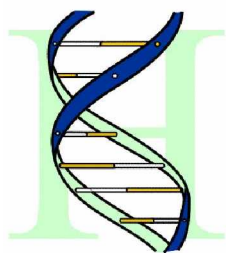
PsychoGenics supports the understanding and treatment of CNS disorders = by offering an extensive range of established and customized solutions, = including validated in vivo behavioral tests, genotyping, behavioral = pharmacology, phenotyping, neuromorphology, bioinformatics, = microdialysis and radiotelemetry.

For more information on PsychoGenics Inc. and its services contact:

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MARQUEURS CLINIQUES

ANALYSE ADN DANS LA POPULATION BRÉSILIEUNE

La MH est liée à l'expansion des répétitions de trinuécléotides CAG dans le gène MH. Des mesures précises de la répétition des séquences CAG effectuées sur 92 sujets brésiliens sans MH, 44 sujets présentant des aspects cliniques suggérant la MH et 40 sujets venant de 6 familles touchées par la MH, montrent une gamme de 7 à 33 répétitions chez les sujets normaux et 39 à 88 chez les sujets affectés.

On a mis en évidence une tendance entre la précocité de l'âge de l'apparition des premiers symptômes et le nombre de répétitions.

On a observé une augmentation des répétitions plus grande dans la transmission paternelle que maternelle.

Les données générées par cette étude peuvent avoir des implications significatives pour l'étiologie, la connaissance et l'incidence, le diagnostic, le pronostic, le conseil génétique et le traitement des malades MH brésiliens.

"It has been showed that there is a relation between incidence of HD and the median size of normal CAG repeat in different populations."

HUNTINGTON DISEASE DNA ANALYSIS IN BRAZILIAN POPULATION

Full PDF study available here:

http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-282X2000000600001&tlng=en&lmg=en&nrm=iso

ABSTRACT

Huntington disease (HD) is associated with expansions of a CAG trinucleotide repeat in the HD gene. Accurate measurement of a specific CAG repeat sequence in the HD gene in 92 Brazilian controls without HD, 44 Brazilian subjects with clinical findings suggestive of HD and 40 individuals from 6 putative HD families, showed a range from 7 to 33 repeats in normal subjects and 39 to 88 repeats in affected subjects. A trend between early age at onset of first symptoms and increasing number of repeats was seen. Major increase of repeat size through paternal inheritance than through maternal inheritance was observed. Data generated from this study may have significant implications for the etiology, knowledge of the incidence, diagnosis, prognosis, genetic counseling and treatment of HD Brazilian patients.

It is difficult to define the smallest size of the CAG repeat expansion, which leads to the disorder.

- In most studies 37 repeats were reported as the lowest CAG repeat associated with HD on European descendant. The absence of HD pathology has not been documented in any individual with a HD allele size larger than 40 repeats.
- The CAG length has a significant impact on age of onset, defined as the first time at which a patient had either neurological or psychiatric symptoms that represented a permanent change from the normal state. The mean age of onset is 35 to 44 years, the median survival time is 15 to 18 years and the average age at death is 54-55 years.
- About 10% of patients with HD have juvenile onset before age 20 years and 5% before 14 years old, whereas late onset (at >50 years of age) occurs in 20%. The CAG trinucleotide expansion is unstable during transmission from parents to offspring and it has been shown that the repeat length can expand during spermatogenesis. HD anticipation (offspring having symptoms at earlier ages of onset than their affected parents) is more intense in paternal transmission, that is, offspring of affected fathers on average have both longer repeat lengths and earlier ages of onset than offspring of affected mothers.
- HD occurs with variable prevalence rates in different parts of the world with most countries having rates between 5-10 affected persons per 100,000.
- In Japan and Africa however, there is remarkably, a 10 times reduced prevalence rate. The lowest frequencies have been found in South African Blacks, with 0.01 affected person per 100,000, that is, 500-1,000 times lower than the worldwide prevalence, but this is probably an underestimate, because the authors used only 11 documented African cases to calculate it. A study in blacks from North America showed a prevalence of 0.97 per 100,000 persons, about one-fifth the prevalence for Caucasoid patients with HD in the same population.
- It has been shown that there is a relation between incidence of HD and the median size of normal CAG repeat in different populations. The larger the median size of normal CAG repeats, the higher is the incidence of HD. The incidence as well as the genetic basis of HD in Brazil is unknown. Therefore we decided to use direct Polymerase Chain Reaction (PCR) from whole blood to genotype three groups of individuals: a) 92 healthy subjects older than 50 years old from the normal Brazilian population with no family history of HD, b) 44 unrelated HD subjects and c) 40 persons of 6 HD families.

RESULTS

The normal CAG repeat spectrum in the Brazilian population sample studied, as determined by the study of 184 chromosomes from 50 Caucasoids and 42 African-Brazilians normal control subjects, ranges from 7 to 33 trinucleotides in the Caucasoid sample and from 13 to 30 in the African-Brazilian sample (Table 1). Repeats with 17 triplets (37%) and 15 triplets (28.6%) were found at a peak frequency, while the mean was 17,7 and 17,9 CAG repeats in the Caucasoid and African-Brazilian samples respectively,