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Gene therapy for psychiatric disorders

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Abstract

There is no indication that gene therapy can be applied in psychiatric patients any time soon. However, there are several promising developments on the level of experimental neuroscience indicating that gene therapy approaches have an effect in animal models of several psychiatric disorders including drug addiction, affective disorders, psychoses and dementia, modifying behavioural parameters via interventions on the molecular and cellular level. However, before gene therapy in psychiatric disorders can be considered on the human level, not only neurobiological and technical problems need to be overcome, but also important ethical questions answered.

Keywords

Addiction; alzheimer disease; depression; ethics; gene transfer; molecular neuroscience; psychiatry; psychiatric treatment; psychopharmacology; psychosis; schizophrenia

Introduction

In recent years, several genes contributing to psychiatric disorders have been successfully identified (Burmeister et al. 2008). Although some psychiatric conditions have an important hereditary component, they are no genetic disorders *sui generis* with a defined Mendelian inheritance. Therefore, it is unrealistic to expect a psychiatric gene therapy to emerge soon enabling doctors to “cure” psychiatric disorders by simply “exchanging” a “disease gene” by a “healthy one”. Interestingly, for logical reasons, it cannot be excluded that some mental health conditions are monogenetic. However, it is the nemesis of psychiatry not to be able to establish proper diagnoses as so-called “nosological entities”. Instead, psychiatric “diagnoses” are based on international consensus criteria of specific clinical phenomenologies which most likely subsume different pathophysiologies with similar clinical presentations under one diagnostic label.

Nevertheless, with gene-transfer techniques it is possible in experimental settings using animal models to alter CNS gene expression and thereby the intrinsic generation of

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Statement of Interest

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molecules involved in neural plasticity and neural regeneration, and thereby modifying ultimately behaviour.

As early as 1998, Carlezon et al. were able to show that viral-gene transfer techniques can be used to significantly modify drug-seeking behaviour in a rat model of cocaine addiction.

Such groundbreaking work on the experimental level fostered a discussion whether such gene-transfer strategies, which were originally mainly used to better understand brain function, could emerge in the future as a promising therapeutic option for psychiatric patients (Lesch 1999; Sapolsky 2003). A key issue, of course, remains the question whether gene delivery can be safely managed in humans. In animal models, mostly quite invasive methods such as the stereotactic intracerebral injection of genetically modified viruses are used. Translating this methodology into the clinical sphere of human medicine does not only pose several technical problems, but also raises a plethora of ethical questions, especially given the fact that psychiatric symptoms often change considerably during life time, cause very different levels of functional disruption in different individuals and exhibit great differences regarding their impact on quality of life when comparing individuals with the same psychiatric diagnosis. Furthermore, there are effective treatment strategies such as pharmacotherapy and psychotherapy already available, although they are usually not reliable regarding treatment outcome, and in most cases not free of side effects.

Nevertheless, it is worthwhile to review the progress in gene-therapy research made in different areas of psychiatry.

Addiction

As early as in the 1990s, studies were conducted as proof of principle that gene-transfer techniques can be successfully used to alter addictive behaviour in rodents, for example regarding appetite or aversion to cocaine (Carlezon et al. 1998). In recent years, it was possible to use similar methods to modify ethanol intake in animal models. Specifically targeting the expression of the aldehyde dehydrogenase gene (ALDH2), led to a significantly altered alcohol-drinking behaviour (Ocaranza et al. 2008).

Affective disorders

While animal models of addiction can be relatively easily established, it is difficult to model human affective disorders in animals. For example, it is next to impossible to model in animals psychotic symptoms such as delusional feelings of guilt often observed in patients suffering from severe depression. Nevertheless, some aspect of depression such as anhedonia (loss of interest) and reduced motor activity (psychomotor retardation) can be modelled.

Recently, it was reported that reduction of p11, a serotonin receptor binding protein, in the nucleus accumbens led to depression-like behaviour in rodents, while restoration of the p11 gene expression in this anatomical area reversed this behaviour (Alexander et al. 2010). It was pointed out that “gene therapies aimed at enhancing p11 in the NAcc” may be a future strategy for depression treatment, however it was also noted that “a large number of clinical and regulatory issues must be overcome before such therapies can be implemented” (Chen et al. 2010).

Psychoses

Even more difficult than modelling human depression in animals on a behavioural level, is the modelling of psychotic/schizophrenic symptoms. Nevertheless, even for this most

complex and enigmatic of psychiatric conditions, gene-transfer approaches have been suggested. However, at the present time, research in this area is still at a very early stage and the proposed strategies are rather intended to elucidate fundamental pathophysiological mechanisms involved in the genesis of psychotic disorders, than “curing” psychoses (Seshadri and Hayashi-Takagi 2009).

Dementia

Most of the published gene-therapy studies in experimental psychiatry focus on conditions affecting cognitive abilities such as dementia. This is not surprising because cognition can be relatively easily and reliably modelled in animals and neuropsychiatric disorders such as Alzheimer’s dementia are among the few psychiatric conditions which exhibit well defined neuropathological features such as amyloid plaques and neurofibrillary tangles.

Recently, it was shown that the gene transfer of CBP (CREB (c-AMP response element binding protein) binding protein) improves cognitive deficits in an animal model of Alzheimer’s dementia via increasing the expression of BDNF (brain-derived neurotrophic factor) (Caccamo et al. 2010). The same authors were also able to show in this study that accumulation of amyloid- β (A β) interfered with CREB activity which is physiologically involved in memory formation.

In another study, it was shown that A β deposition and plaque formation can be reduced by sustained expression of the neprilysin (an endopeptidase) gene which also led to improvements on the behavioural (i.e. cognitive) level (Spencer et al. 2008).

Similarly, the intracerebral gene transfer of ECE (endothelin-converting enzyme) via a virus vector stereotactically injected in the right anterior cortex and hippocampus, has also shown to reduce A β deposits in a transgenic mouse model of Alzheimer’s dementia (Carty et al. 2008).

Discussion

The complexity and heterogeneity of psychiatric disorders as well as the still unsolved problem of identifying genuine psychiatric nosological entities pose a major problem for the treatment of these conditions. On the other hand, future life planning and quality of life can be severely affected in a negative way by psychiatric disorders. Therefore, innovative treatment strategies with better efficacy and less side effects than the presently available conventional methods (mainly psychopharmacotherapy and psychotherapy) are urgently needed. However, the application of a new technique such as gene therapy, poses significant risks (Neumaier 2003, Russo 2008). Even if all technical problems were mastered, significant ethical questions would remain to be answered. For example, it will remain difficult to conduct a risk–benefit analysis, when it comes to use a very invasive technique such as injecting genetically modified viruses in specific brain areas or using human neural stem and progenitor cells (Martinez-Serrano et al. 2001), in order to treat psychiatric conditions. Another moral problem is the potential use of this methodology for enhancing normal brain functioning (Lesch 1999).

In summary, gene therapy for psychiatric disorders has not yet reached the point of translating findings in animal models to the human sphere. However, it is important to note that CNS gene therapy is already undergoing clinical trials, for example in patients with malignant brain tumours (Barzon et al. 2006; Kaplitt 2009). Should gene therapy prove to be useful and safe in severe and life-threatening neurological conditions, its use in psychiatry might come sooner than presently imagined.

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