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GENERAL REVIEW

In search of innovative therapeutics for neuropsychiatric disorders: The case of neurodegenerative diseases

À la recherche de thérapeutique innovante pour les pathologies neuropsychiatriques : le cas des maladies neurodégénératives

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Summary The recent medical literature highlights the lack of new drugs able to prevent or treat neurodegenerative diseases such as Alzheimer disease or Parkinson disease. Yet, the prevalence of these diseases is growing, related to increasing life expectancy, and is leading to a rise in their economic and social cost. At the same time, pharmaceutical companies are reducing or halting their investment in neuropharmacological research. Why have advances in basic neuroscience and our understanding of these diseases not allowed innovative discoveries in drug research? This review will try to explain this failure and suggest possible solutions: develop basic and clinical research but with the emphasis on translational and truly collaborative research; improve preclinical studies by developing more appropriate animal models, using new biomarkers and methodologies such as imaging suitable for clinical trials, providing worthwhile information on the ability of the drug to reach its intended target and induce significant pharmacological changes; build a new system of research management, based on stronger interdisciplinary relations between preclinical and clinical research and including the introduction of international precompetitive research between academic teams, start-up companies

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and pharmaceutical laboratories; hold early discussions with the regulatory authorities during preclinical studies and at the beginning of clinical trials in order to validate the methodological approaches; involve patients' associations in this new organization of research. These changes should help to ensure the discovery of effective treatments for these pathologies.

MOTS CLÉS
Maladies neuropsychiatriques ;
Développement préclinique et clinique ;
Modèles animaux ;
Collaboration précompétitive ;
Organisation de recherche pharmaceutique

Résumé La littérature médico-scientifique récente a souligné l'absence de médicaments innovants pour les pathologies neurodégénératives comme la maladie de Parkinson ou d'Alzheimer. Or la forte prévalence de ces pathologies, revers de l'allongement de l'espérance de vie, entraîne un coût économique et social considérable. Malgré cela, les grandes firmes pharmaceutiques réduisent leurs activités de recherche en neuropharmacologie. Pourquoi la progression indiscutable des connaissances en neurosciences et sur la physiopathologie de ces maladies ne s'est pas traduite en innovations ? Cette revue propose quelques explications sur l'origine possible de cette impasse et expose quelques solutions envisageables pour accélérer l'identification de médicaments innovants : poursuivre l'effort des recherches fondamentales et cliniques mais avec une approche translationelle et réellement collaborative ; améliorer considérablement les études précliniques en construisant de meilleurs modèles animaux de ces pathologies, en introduisant l'emploi de nouveaux marqueurs et méthodologies donnant l'assurance que la molécule testée atteint bien sa cible et avec efficacité ; instaurer une nouvelle organisation de recherche renforçant les interactions entre recherche préclinique et clinique avec une ouverture transdisciplinaire, la mise en place de structures de recherche précompétitives dépassant le niveau national et associant équipes de recherche académiques à celles des start-up et des laboratoires pharmaceutiques ; renforcer l'ouverture de relations avec les autorités réglementaires dès le stade préclinique et surtout au moment du passage vers des études cliniques ; reconnaître la place des associations de patients dans cette nouvelle organisation. Ces nouvelles dispositions devraient assurer la découverte de médicaments efficaces pour lutter contre ces pathologies.

A few years ago, in January 2008, a special session was held at the French Academy of Pharmacy to review perspectives on Alzheimer disease. A lecture was given by Frédéric Checler and Luc Buée [1] concerning new therapeutic avenues at the late preclinical stage and during clinical development of the disease. They emphasized strategies such as the inhibition of α-secretase or β-secretase in order to reduce the production of β-amyloid. These targets, as well as the reduction of Tau protein, were also highlighted in a set of reports [2—4] that had been published two years before in a commemorative tribute to the first anatomopathological report on this disease by Alois Alzheimer. Unfortunately, none of these drugs successfully completed phase III clinical studies [5,6]. This was not the first failure in a long list of drugs developed to slow down the course of the disease. However, these failures must be seen in light of the fact that ''studies of solanezumab for Alzheimer's disease have shown that there is a 36% rate of false diagnosis of Alzheimer's disease in clinical trials that were made in expert centers but based only on clinical criteria'' [7].

A quite similar situation arose in the case of another major neurodegenerative pathology, namely Parkinson disease. For this disease, a symptomatic strategy consists in correcting the behavioral disturbances caused by the degeneration of nigral dopaminergic neurons ending in the associative and motor striatal territories. This was first achieved using DOPA therapy, which remains the gold standard treatment, and is only mildly challenged by the use of dopaminergic agonists. Indeed, dyskinesia, one of the main undesirable adverse effects of DOPA therapy, is only moderately reduced by using dopaminergic agonists. Moreover, some behavioral effects, such as excessive gambling [8], are also observed with the use of dopaminergic agonists. Another strategy, the use of neuroprotective agents in Parkinson's disease, also remains unsuccessful.

The development of new pharmacological treatments remains a major difficulty, whatever the brain pathology, acute or chronic. A recent report [9] for brain injuries such as stroke states that ''In the past 10—15 years, dozens of clinical trials for stroke neuroprotection — involving thousands of patients — have failed''. A similar issue has arisen in the case of translational studies in neuropsychiatric pathologies. For example, a large, comparative, multicenter clinical study, including 1432 patients treated either by perphenazine, olanzapine, quetiapine, risperidone, or ziprasidone, led to the conclusion that medication with perphenazine, a first generation antipsychotic, or olanzapine, a second generation medication or ''atypical'' antipsychotic, did not bring significant improvement, whereas the patients treated with the other drugs discontinued their treatment, a consequence of an insufficient efficacy/tolerance ratio [10]. As reviewed by Alison Abbott [11], such results provoked shock wave when the codes used to mask the name of the drugs

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