Cell. Mol. Life Sci. (2016) 73:1383–1385
DOI 10.1007/s00018-016-2141-1

Cellular and Molecular Life Sciences

LETTERS AND COMMENTS

Parkinson's disease: towards better preclinical models and personalized treatments

Dan Lindholm[1,2] · Johanna Mäkelä[1,2] · Valentina Di Liberto[3] · Giuseppa Mudò[3] · Natale Belluardo[3] · Ove Eriksson[1] · Mart Saarma[4]

Received: 7 January 2016 / Revised: 13 January 2016 / Accepted: 14 January 2016 / Published online: 3 February 2016

We thank Dr. Segura-Aguilar, Paris and Muñoz for their interesting letter "The need of a new and more physiological preclinical model for Parkinson's disease" [1] that as such nicely complement issues raised in our recent review on Parkinson's disease (PD) [2]. The letter by Segura et al. brings forward some very important problems in the field particularly related to the use of toxin models in preclinical PD research and their value for our understanding the human disease and for the development of better treatment strategies for PD patients. To clarify these issues we would like to highlight the following points further.

Despite great efforts made during the last 50 years by many skilled and devoted scientists we still lack rational disease-modifying treatments of (PD) [2–4]. As discussed by Segura-Aguilar et al. [1] at least two major problems and obstacles do exist that have hampered progress in this field. One is the lack of understanding of the pathogenic mechanisms underlying PD and its progression, and the second concerns with the limitations of the current animal models used to study PD.

Recent progress made in the field of molecular genetics has led to the discovery of more than dozen genes regulating different signaling pathways and cellular processes responsible for the familial forms of PD [2–4]. These insights have stimulated research and raised high expectations that similar mechanisms would prevail in sporadic PD representing the majority of PD patients. Unfortunately the progress has so far been rather modest. Even in the case of α-synuclein that was identified as the first PD causing gene almost 20 years ago, we do not still know the precise function of this protein in brain neurons. The funding for PD research has no doubt increased in recent years, but we think that one reason for the slow progress to unravel the pathogenesis of PD are the still insufficient research resources. There is a genuine concern about funding for other brain diseases as well and research devoted to PD makes no exception. The situation becomes more clear when one considers how much resources have been assigned to the study for example of AIDS and for the development of drugs to prevent HIV replication. Even with these significant resources we still lack effective vaccines to HIV.

Segura-Aguilar et al. [1] correctly mention that the current neurotoxin models have serious limitations. However, we should still remind that many drugs that efficiently work in the symptomatic treatment of PD, such as catechol-*o*-methyltransferase inhibitors, MAO-B inhibitors, rasagiline, etc. have been developed using the MPTP and 6-OHDA animal models of PD [3]. We suggest that there is another very important point that has not considered with sufficient attention, as PD is a disease of aging people. However, the vast majority of studies on rodent models of

✉ Dan Lindholm
dan.lindholm@helsinki.fi

[1] Medicum, Department of Biochemistry and Developmental Biology, Medical Faculty, University of Helsinlki, POB 63, 00014 Helsinki, Finland

[2] Minerva Medical Research Institute, Biomedicum-2 Helsinki, Tukholmankatu 8, 00290 Helsinki, Finland

[3] Division of Human Physiology, Department of Experimental Biomedicine and Clinical Neuroscience, University of Palermo, Corso Tukory 129, 90134 Palermo, Italy

[4] Institute of Biotechnology, University of Helsinki, P.O.Box 56, Viikinkaari 9, 00014 Helsinki, Finland

PD have not been performed with aged animals. There is increasing evidence that fundamental differences in the efficacy of neuronal signaling and capacity for neuroprotection do exist between young and aged animals [5]. It would therefore be important to use also aged animals in PD studies although this may raise the price tag of the experiments. In this view the study of mechanisms of PD will take the same path as that of other brain diseases such as Alzheimer's disease in which age, comorbidity, and the interplay between genetic and environmental factors are considered of utmost importance.

Regarding preclinical animal models for PD, experiments based upon the use of mutated or over-expressed genes causing familial forms of PD have largely resulted in disappointing results [2, 3]. Thus studies of the mutant α-synuclein, the LRRK2, and the DJ-1 and Parkin over-expressing mice showed little or no neurodegeneration in the nigrostriatal system [6]. Recently, Wade-Martins and colleagues reported of a new mouse line for that may prove more useful for the study PD [7]. These mice generated by the use of bacterial artificial chromosome that express wild-type α-synuclein from the complete human SNCA locus, display an age-dependent loss of nigrostriatal dopamine neurons and show motor impairments characteristic of PD [7]. In addition in this mouse line the deficits in dopaminergic transmission precedes neuronal loss as most probably occurs in clinical PD. These mice will in the coming years be very useful to study the mechanisms and the role of α-synuclein in the pathogenesis of PD.

Another transgenic mouse line that is relevant for the studies of PD has been generated by Larsson's and Olson's groups [8]. They have used a reverse genetic approach and conditionally disrupted the gene for mitochondrial transcription factor A (Tfam) in dopamine neurons. The knockout mice have reduced mtDNA expression and respiratory chain deficiency in midbrain DA neurons, leading to a parkinsonism phenotype with adult onset of slowly progressive impairment of motor function accompanied by formation of intraneuronal inclusions and dopamine nerve cell death [8].

Concerning the suitability of other experimental models, there has been a recent interest in the use of proteasome inhibitors to induce protein aggregation and degeneration of dopaminergic neurons causing progressive parkinsonism in mice [9, 10]. This strategy when combined with the study of the role of autophagy in PD can give valuable insight into specific disease processes in PD. Likewise the aminochrome model proposed and studied by Segura-Aguilar et al. [1] has merits in focusing on the role of dopamine and its metabolites in the function of degenerating dopamine neurons. It would be important to study further the role and the accumulation of aminochrome in the substantia nigra in vivo as well as in human sporadic PD.

Segura-Aquilar et al. [1] also rightly point out that the pathogenic mechanisms in PD include different cellular processes such as dysfunction in protein degradation, formation of protein aggregates, mitochondrial dysfunctions, oxidative stress, neuroinflammation and ER stress. The precise interplay between the different pathways are, however, not fully understood nor do we know the event(s) or environmental factors that can trigger the disease [2–4]. In our review we stressed the potential importance of ER and associated pathways in the pathogenesis of PD [2]. With regard to treatments use of neurotropic factors has been often mentioned, but little data is available on these, especially from patient material. Although the first four phase 2 clinical trials with neurotrophic factors GDNF and NRTN have either failed or produced very modest results [5, 11] one should also realize that intracranial delivery of proteins and viral vectors is a completely new therapeutic avenue that by itself has so many unknown aspects and potential hurdles. In view of this it would be premature to conclude that neurotropic factors do not work in human PD patients. Encouraged by the good results obtained with the treatments of rodent and non-human primate models of disease with trophic factors we should rather try to understand how to use this knowledge to improve the efficacy in the clinical settings and in treatment of human PD patients.

Given the complex etiology of genetic and environmental risk factors in PD it is possible that multiple events may underlie the different forms of the disease. To understand these in more detail more studies devoted to detection of novel biomarkers using clinical material as well as the generation of relevant preclinical models better mimicking the human disease are required. With the increased knowledge of the pathophysiological mechanisms and of the neurotropic factors governing dopamine neuron survival we may hopefully in the future arrive at a rational treatment of the neurodegeneration in PD. In this view it may in the long-run be able to treat individual patients afflicted by PD with tailor-made therapies targeting the underlying cause and defect as done in personalized medicine and as exemplified by modern treatments of specific cancer subtypes.

References

1. Segura-Aguilar J, Paris I, Muñoz P (2015) The need of a new and more physiological preclinical model for Parkinsońs disease. Cell Mol Life Sci
2. Lindholm D, Mäkelä J, Di Liberto V, Mudò G, Belluardo N, Eriksson O, Saarma M (2015) Current disease modifying approaches to treat Parkinson's disease. Cell Mol Life Sci. 2015 Nov 30 (**epub ahead of print**)

3. Fahn S (2010) Parkinson's disease: 10 years of progress, 1997–2007. Mov Disord 25:S2–S14
4. Kalia LV, Kalia SK, Lang AE (2015) Disease-modifying strategies for Parkinson's disease. Mov Disord 30:1442–1450
5. Domanskyi A, Saarma M, Airavaara M (2015) Prospects of neurotrophic factors for parkinson's disease: comparison of protein and gene therapy. Hum Gene Ther 26:550–559
6. Aron L, Klein R (2011) Repairing the parkinsonian brain with neurotrophic factors. Trends Neurosci 34:88–100
7. Janezic S, Threlfell S, Dodson PD, Dowie MJ, Taylor TN, Potgieter D, Parkkinen L, Senior SL, Anwar S, Ryan B, Deltheil T, Kosillo P, Cioroch M, Wagner K, Ansorge O, Bannerman DM, Bolam JP, Magill PJ, Cragg SJ, Wade-Martins R (2013) Deficits in dopaminergic transmission precede neuron loss and dysfunction in a new Parkinson model. Proc Natl Acad Sci 110:E4016–E4025
8. Ekstrand MI, Terzioglu M, Galter D, Zhu S, Hofstetter C, Lindqvist E, Thams S, Bergstrand A, Hansson FS, Trifunovic A, Hoffer B, Cullheim S, Mohammed AH, Olson L, Larsson NG (2007) Progressive parkinsonism in mice with respiratory-chain-deficient dopamine neurons. Proc Natl Acad Sci 104:1325–1330
9. Bentea E, Van der Perren A, Van Liefferinge J, El Arfani A, Albertini G et al (2015) Nigral proteasome inhibition in mice leads to motor and non-motor deficits and increased expression of Ser129 phosphorylated alpha-synuclein. Front Behav Neurosci 9:68. doi:10.3389/fnbeh.2015.00068 **(pmid: 25873870)**
10. Kumar A, Kopra J, Varendi K, Porokuokka LL, Panhelainen A, Kuure S, Marshall P, Karalija N, Härma MA, Vilenius C, Lilleväli K, Tekko T, Mijatovic J, Pulkkinen N, Jakobson M, Jakobson M, Ola R, Palm E, Lindahl M, Strömberg I, Võikar V, Piepponen TP, Saarma M, Andressoo JO (2015) GDNF overexpression from the native locus reveals its role in the nigrostriatal dopaminergic system function. PLoS Genet 11(12):e1005710. doi:10.1371/journal.pgen.1005710
11. Bespalov M, Saarma M (2007) GDNF receptor complex is an emerging drug target. Trends Pharmacol Sci 28:68–74