ARE ANIMAL MODELS USEFUL FOR DRUG DEVELOPMENT IN DISEASES WITH RELATIVELY UNEXPLORED ETIOPATHOGENESIS?
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It is a fact that many new compounds and treatment strategies for Alzheimer's disease which showed favourable outcome in animal models have later on failed to show efficacy in human clinical trials. This certainly raises the question if it makes sense at all to use animal models which are based on an incomplete understanding of the etiopathogenesis of a disease.
The selection of an appropriate animal model for proof of concept studies is certainly complicated by the fact that no animal shows something like sporadic Alzheimer's disease or familial Alzheimer's disease. It is true that to some extent dogs and also non-human primates develop brain pathology which is similar to Alzheimer's disease, but there are still remarkable differences on one hand and on the other hand these models are not widely accessible for drug testing. Therefore most of the animal models which are used for screening of the efficacy of new compounds are based on the key pathological hallmarks of Alzheimer's disease and over expression of amyloid or tau protein is used in tg models to drive pathology and functional changes. In spite that the majority of scientists believe in the amyloid cascade theory behind Alzheimer's disease it still is a theory, and the same is true for the role of tau hyperphosphorylation or aggregation. But animal models which are specifically targeting some of these pathways are useful to explore consequences of the over expression of one of these target proteins in terms of the effects on brain morphology and animal behaviour. It is no doubt that many of the models have been disappointing because they did not clearly support the prevailing theories on one hand and on the other hand drug testing in these animals often resulted in a too optimistic interpretation. But at least these models provide tools to study consequences of the accumulation and aggregation of pathogenetically important proteins, ideally these models will also provide some insight into a better understanding of the theories which have been developed based on findings from the human disease and hopefully if they are used in the right way they might also be supportive for drug development. We should also not forget that a few important recent discoveries were based on animal experiments, like the role of amyloid oligomers in synaptic failure and neurodegeneration. Findings which are also important for understanding of the human disease which might even open new pathways for successful treatment. On the other hand many findings in animal models were disappointing because they were not supporting expectations, e.g. even high overexpression of amyloid did not cause neurodegeneration, it did not trigger tau pathology, and in fact also consequences on behaviour have been modest. On the other way around also tau overexpression and tau pathology did not trigger amyloid pathology, but at least showed more pronounced behavioural deficits. Highly complex animal models have their limitations because they are forming quite artificial systems by combination of multiple mutations and the use of unregulated promoters which are quite different from naturally occurring sporadic Alzheimer's disease.
But all of these tools helped to develop compounds addressing some of the mentioned pathways, they have proven similar effects even in patients, but these effects did not result in expected functional changes. One of the examples is the immunotherapy of Alzheimer's disease where in animal models as well as in clinical trials significant reduction of amyloid pathology was achieved, in animals this resulted in subtle cognitive improvements, in patients at least so far such an improvement has not been shown. But we learned that based on this data that most likely in human disease treatment starts too late which was guiding the research into new criteria for early diagnoses of Alzheimer's disease and start of new clinical studies in this disease population. Unfortunately so far no data have been finished. Also tau tg models helped to identify interesting treatment approaches, in this case unfortunately proof from clinical trials is missing because only few compounds made it into early stage of clinical trial. So even in uncompleted understanding of etiopathogenesis these animal models can help to explore several pathways and to verify or falsify theories which were based on the clinical findings, they are also helpful to explore potential safety issues of some treatments (e.g. micro oedema and micro haemorrhages in Abeta lowering treatments). But what is certainly most important is the appropriate use of animal models, what means the right selection of the model depending on the proposed mechanism of action of the drug, the right time point of onset of treatment as well as relevant treatment duration, and of course also following best scientific practice, preventing biased results. This can be summarised in the way that animal studies should also strictly be performed in blinded way, pilot data should be used for appropriate power calculation to determine the right number of animals per group to get robust data, interpretation of data must be done with care and reconfirmation of the findings in a second model should be done. This would already reduce a lot of over optimistic findings in animal research and would narrow down the number of compounds entering clinical trials. Early failure determined in animal experiments could also help to accelerate drug development into new directions. Of course we all should be constantly aware that model systems have to be improved based on new findings from clinical research, new findings in animal research should be used to improve the theories behind the etiopathogenesis of such a complex disease like Alzheimer's disease.