

The Future of Antidepressant Drug Discovery and Development

Professor Holsboer presented a keynote lecture at the Annual Meeting of the American Psychiatric Society in Toronto, May 17, 2015

Situation

1. Diagnoses based exclusively on verbally transmitted information and patients appearance are not helpful for studies of causality and R&D of new drugs.
2. The absence of valid diagnoses must spur us to develop laboratory tests that objectify underlying pathologies.
3. As we do not treat diagnoses but symptoms, a transdiagnostic approach seems more fruitful for discovery and development of innovative drugs.
4. Dr. Holsboer highlighted that despite there is much room improvement for treatment of depression and anxiety the last century has seen a medical revolution since Roland Kuhn and Jules Angst from Switzerland had discovered the first antidepressant imipramine.
5. As depression gets increasingly accepted market grows, prescriptions increase, but revenues decrease because market gets saturated with generics that are not replaced by innovative drugs.
6. Dr. Holsboer argued the lack of innovation has many reasons:
 - Industry got spoiled by phenomenal returns of investment in the past, resulting in risk aversiveness.
 - Industry is reluctant to depart from blockbuster philosophy (“one-size-fits-all”).
 - Researchers overemphasis poor preclinical predictors which results in unreasonably delayed exposure to humans.

Solution

The CRH/CRHR1-system as a case in point

7. Dr. Holsboer was the first (1984) to report the hormonal response to peripherally administered human CRH in depression, the first who report that CRHR1 knock-out mice have decreased anxiety- like behavior (2005), while CRH overproducing transgenic mice have higher stress responses (2008) and the first (2000) who reported on clinical effects of a CRHR1-antagonist in depression. He analyzed in his talk why up to now no CRHR1-antagonist has made it to the market.
8. Using transgenic CRH-overexpressing mice, Dr. Holsboer's team showed that these animals have disinhibited REM-activity (the segment of sleep where eyes move and muscle tonus is low), which disappeared after treatment with CRHR1-antagonists. Also many patients with depression have that REM-disinhibition. And those patients are particularly benefitting from CRHR1-antagonists.
9. Dr. Holsboer suggested that sleep-EEG measurements in combination gene-based laboratory tests are useful to stratify patient populations and to identify those that will respond well to CRHR1-antagonists.

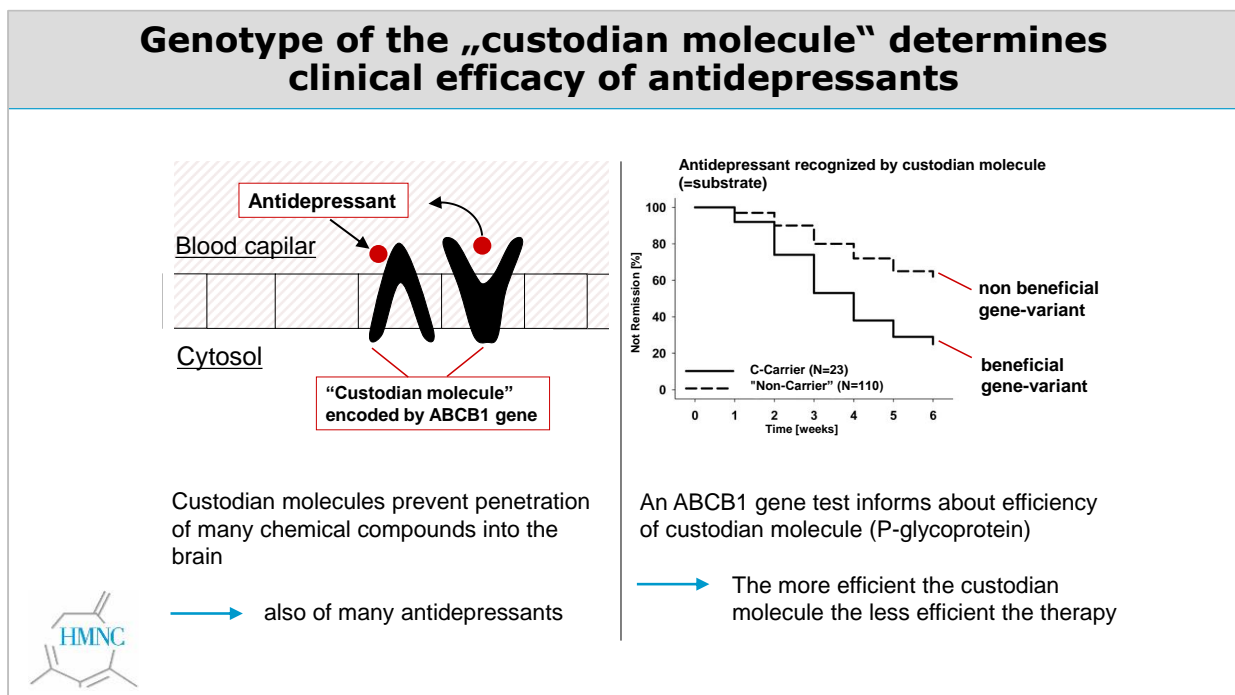
The vasopressin/V1B-System – another promising target

10. Dr. Holsboer told that 35 years ago he had published the results of a neuroendocrine challenge test where he showed that neither intravenously administered CRH nor vasopressin can overcome dexamethasone suppressed corticotropin synthesis and release. Only when both neuropeptides are administered concurrently ACTH levels increase. That study was conducted with healthy controls. In contrast, among dexamethasone pretreated depressives CRH injections result in a substantial increase of plasma ACTH concentration. That led Dr. Holsboer to conclude that in a subgroup of depressives increased central vasopressin plays a key role in stress hormone dysregulation. Vasopressin exerts also anxiety-like behavioral effects in animals and is supposedly a depressiogenic transmitter in the human brain.
11. According to the corticosteroid receptor hypothesis of depression published by Holsboer in 2000 the receptors to which cortisol binds are incapable to fully exert the negative feedback effect on CRH, vasopressin and ACTH. Antidepressants restore that impairment by activating the synthesis of corticosteroid receptors. That is why normalization in neuroendocrine tests assessing the stress hormone axis is a prerequisite for clinical recovery.
12. Dr. Holsboer propagated that only those patients having a "vasopressin-problem" will respond to V1B-antagonist and therefore such next-generation antidepressants have to be combined with companion tests that identify potential V1B-antagonist responders.

Personalized treatment of depression – the future is now

13. A frequently discussed issue relates to the costs of personalized medicine (after President Obama's speech now renamed "precision medicine"). Dr. Holsboer explained that the R&D-costs for drugs with specific mechanisms are not higher as the clinical development costs are much cheaper, because less patients are needed for trials.

14. Personalized depression therapy is not in remote future, the first steps are done. That is exemplified for a gene test that allows to predict if a prescribed drug is indeed penetrating in an adequate quantity into the brain tissue. Researchers have found that in the walls of blood capillaries in the brain “custodian molecules” termed P-glycoproteins are located that prevent the passage from blood into the brain tissue. The gene encoding the “custodian molecule” is named ABCB1-gene. In humans it has many variants that determine whether the blood brain barrier can be easily passed by an antidepressant or not.
15. The ABCB1 genotype has profound clinical consequences: Patients with a certain genotype may not respond well to a given antidepressant. But that holds only true if the drug is recognized by the P-glycoprotein. Thus patients with such an unfavorable genotype benefit from higher dosages, or combination with other drugs (antidepressant, antipsychotics) augmentation (anticonvulsant) or an antidepressant that is not recognized by the P-glycoprotein. In any case psychotherapy is recommended, in case of the unfavorable genotype psychotherapy needs to be enforced. Those with favorable genotype will benefit from an antidepressant that is a substrate (i.e. recognized by the P-glycoprotein) and given at recommended dosage, ideally monitored by measurement of plasma concentration. For the first time we can offer a laboratory test that informs the doctor about adequacy of treatment.



Reengineering the R&D process

16. The previous decades have seen an impressive multiplication of neuroscience knowledge that contrasts with little innovations in drug discovery. While there are promising signals for treatment of psychotic depression with mifepristone (formally used as abortion pill) and for major depression with botox® (botulinum, a neurotoxin used for cosmetics effects) and with NMDA-antagonists (e.g. Ketamin, also used as party drug) fundamentally new drugs have not entered clinical practice.

17. The key problem is that we do not have a valid preclinical model for screening new drug candidates that have a different mode of action. The forced swim test, where rats or mice are put in a beaker half filled with water are observed and the time is measured until they stop struggling and start floating is still popular. The test claims that a drug works clinically as antidepressant if it prolongs the struggling time. But this test was validated for monoamine based antidepressants. Drugs with other mechanisms of action will be missed. And the comparison of the floating with the struggling time of rodents has nothing to do with clinical depression.
18. The key question Dr. Holsboer raised: Do animals have depression? In the light of the big difference in brain size and number of neurons between mice and men he argues that a huge number of brain cells and their connections is needed to create depression. Mice have too little of such connections. Brain imaging studies on the human connectome underscore that connectivity impairments play a causal role in development and course of depression.
19. There are data from Alzheimer's research where many drugs were found to work in animal models that overexpress β -amyloid, a peptide believed to play a key role in that devastating disease. So far not one single drug that works in animal models also works in human. Maybe our brain is too unique to allow extrapolation from rodents not only in Alzheimer's but also in depression. Recent genetic findings on a human-specific gene that promotes neocortex expansion may explain that we learn much less from worm, fish, flies, rats and mice for clinical psychiatry than we originally thought.
20. We have to keep in mind that the discovery of the first antidepressant made by Kuhn and Angst in the 1950ies was enabled by careful clinical observation. These pioneers did not know anything about neurotransmitters, signaling pathways, genomics and imaging. In the future, the most important step will be the rapid implementation of discoveries in human research. This is a big challenge but research institutes, public or private, need to engage in experimental medicine that works with patients.
21. Dr. Holsboer concluded that future efforts should remember the Greek philosopher Protagoras "Man is the measure of all means". If we follow that statement, we will pave the way for a more successful drug discovery than in the past.

Literature

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