Extended Abstract International Research Journal of Pharmacy and Pharmacology 2020
Vol.8 No.3

Pharma Europe 2020: Pharmaco-omics of Selective Serotonin Reuptake Inhibitor (SSRI) Response - Richard Weinshilboum - Mayo Clinic Rochester

Richard Weinshilboum
Mayo Clinic Rochester, MN, USA

ABSTRACT
Pharmacogenetics involves the study of the role of inheritance in individual variation in drug response phenotypes. In the 21st century "pharmacogenetics" has evolved to become "pharmacogenomics" with our ability to scan agnostically across the genome and then to become "pharmaco-omics" with the merger of other "omics" techniques with genomics. We have applied a metabolomics-informed genomics research strategy to study the pharmaco-omics of SSRIs, the class of drugs that is the worldwide standard of care for the pharmacotherapy of the number one psychiatric disease, Major Depressive Disorder (MDD, depression). Specifically, we identified metabolites assayed with an LCECA platform that were associated with measures of outcomes (HAMD and QUIDS) in response to the SSRI therapy of MDD patients enrolled in the 803 patient Mayo Clinic PGRN-AMPS SSRI clinical trial. The assayed metabolite that was most highly associated with outcomes (remission and response) was plasma serotonin (5-HT) and the metabolite most highly associated with symptom severity was plasma kynurenine. GWAS for plasma 5-HT identified two genome-wide significant SNP signals near or across the TSPAN5 and ERICH3 genes, while GWAS for plasma kynurenine identified SNPs in the DEFB1 and AHR genes. Subsequent functional genomic studies showed that knockdown of TSPAN5 and ERICH3 in CNS-derived cells resulted in decreased 5-HT in the culture media, that ERICH3 played a role in monoamine vesicular function and that DEFB1 and AHR were both associated with inflammation, a process that contributes to MDD pathophysiology. Finally, a machine-learning based predictive algorithm was developed that incorporated these SNPs which could predict SSRI response with approximately 75% accuracy as compared with 55% using only clinical information. In summary, the application of a "pharmaco-omic" research strategy identified novel genes that contribute to individual variation in SSRI therapeutic response and also, perhaps, to mechanisms involved in MDD pathophysiology.

Introduction:

Selective serotonin reuptake inhibitors (SSRIs) are amongst the most widely prescribed class of antidepressants worldwide. Their extensive use is due to their better safety and effectiveness profile when compared to other classes of antidepressants. Several differences in pharmacology of the various SSRI drugs may affect the treatment choice in individual patients. This article summarises the role of selective serotonin reuptake inhibitors in the management of depression, anxiety, panic disorder and other psychiatric disorders.

Selective serotonin reuptake inhibitors (SSRIs) are amongst the most prescribed antidepressants globally because of their effectiveness in treating many psychiatric disorders.1,2 Drugs in this class are used for the treatment of depression, anxiety, and certain behavioural disorders such as obsessive compulsive disorder, panic disorder and bulimia nervosa.3,4 SSRIs are considered to be safer and more tolerable alternatives to older antidepressant generations such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).2,5 They are also considered to be safer and generally cost-effective when compared to some newer antidepressant classes such as noradrenergic and specific serotonergic antidepressant (NaSSAs), norepinephrine reuptake inhibitors (NRIs), reversible inhibitors of monoamine oxidase A (RIMAs), serotonin–norepinephrine reuptake inhibitors (SNRIs), serotonin modulators and stimulators (SMSs), serotonin antagonists and reuptake inhibitors (SARIs), tetracyclic antidepressants (TeCAs).6,7 Fluoxetine was discovered in 1972 and later other SSRIs, namely sertraline, paroxetine, fluvoxamine, citalopram and escitalopram (which is the S-enantiomer of citalopram) became available on the market.

The introduction of selective serotonin (5-HT) reuptake inhibitors (SSRIs) has significantly improved the pharmacological treatment of a range of psychiatric disorders. Nevertheless, despite the undoubted advantages of antidepressant treatment in terms of improved tolerability to therapy while maintaining a high level of efficacy, not all patients benefit from it; an appreciable proportion do not respond adequately, while others may show adverse reactions. The necessary change of the initial treatment choice often requires extended periods for the remission of symptomatology. Such difficulties could be avoided if it should be possible to determine more quickly the most suitable drug. Several factors have been thought to influence the outcome of antidepressant therapy. Among the factors influencing the interindividual variability in response to treatment with SSRI, differences in genetic features may play a significant role. Several genetic polymorphisms have been associated with therapeutic SSRI response, including genetic variants of the 5-HT transporter, 5-HT-2A-receptor, tryptophan hydroxylase, brain-derived neurotrophic factor, G-protein beta3 subunit,

This Work is Partly Presented at 30th Annual European Pharma Congress scheduled During May 18,19-2020 at Berlin,Germany

interleukin-1beta and angiotensin-converting enzyme, although with conflicting results; also cytochrome P450 drug-metabolising enzymes may bear a particular importance, although further corroboration of the findings is necessary, and further key participating genes remain to be identified. The hope is that the identification of these genetic components will eventually facilitate the development of a customised SSRI treatment.

During the last decade selective serotonin (5-HT) reuptake inhibitors (SSRIs) have revolutionised the treatment of depression, the most prevalent psychiatric disorder.1 These drugs show high efficacy, and relatively few adverse reactions compared with the previously used tricyclic antidepressants, even though their mechanism of action is not entirely understood yet. However, these drugs are effective in only about two-thirds of depressed patients.2 The necessary change of the initial treatment choice often requires extended periods for the remission of symptomatology. Such difficulties could be avoided if it would be possible to determine more quickly the most suitable drug for each subject. Several factors have been thought to influence the outcome of antidepressant therapy and efficient clinical predictors have not been yet identified, but there is some evidence suggesting that genetic factors play a substantial role. Polymorphisms of drug target genes, reflected in the protein amino-acid sequence, could influence drug responsiveness. In other instances, protein expression level, or tissue distribution, could be affected by polymorphisms in a gene promoter, influencing its transcriptional control. Genes coding for proteins somewhat involved in monoaminergic pathways and other possible targets of antidepressant action could present functional polymorphisms, altering their constitutive activity, and furthermore, many of the drug-metabolising genes exhibit functional polymorphism that contributes to the interindividual variability in drug efficacy and toxicity. For example, the polymorphic cytochrome P450 (CYP) CYP2D6 metabolises several drugs implicated in common toxic reactions in individuals with low enzyme activity, such as tricyclic antidepressants. Collectively, these aspects of drug response variability belong to the emerging field of pharmacogenomics

Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs: it examines how genetic makeup affects this response. Pharmacogenomics combines traditional pharmaceutical sciences, like biochemistry, with annotated knowledge of genes, proteins, and single-nucleotide polymorphisms (SNPs). Some authors had differentiated it from pharmacogenetics: the former should refer to the general study of all of the many different genes that determine drug behaviour, while the latter should refer to the study of inherited differences (variations) in drug metabolism and response. For other authors, pharmacogenetics is more focused in scope than pharmacogenomics, which would encompass factors beyond those that are inherited, and is viewed as a subset of it. For other authors, the distinction between the two terms is considered arbitrary and the two terms could be used interchangeably.

The emerging field of pharmacogenetics/pharmacogenomics holds great potential, particularly in psychiatry, for refining psychopharmacology, given the lack of biologically based treatment guidelines.8, 9, 10 This field gained increasing attention and holds great promise for clinical medicine in the latest years.11, 12, 13, 14 A major obstacle to the advance of pharmacogenomics is the difficulty in finding candidate polymorphisms. SNPs, in fact, occur every 1000 bases; therefore, millions of SNPs must be identified and analysed to determine their involvement (if any) in drug response. Further complicating the method is our limited knowledge of which genes are involved each drug response. Since many genes are likely to influence responses, obtaining the large picture on the impact of gene variations is very time-consuming and Sophisticated . For this reason, candidate genes should be chosen according to their possible implications with pharmacological action and pathogenic mechanisms.

The foremost theory for explaining the biological basis of antidepressant action is their ability to improve monoaminergic transmission. Antidepressant drugs are therefore classified according to their properties in improving monoaminergic transmission in the different biogenic monoamine systems: 5-HT, noradrenaline (NA), and dopamine (DA). Since this first theory, other explanations based on the ability of antidepressants to act on the abnormal function of monoamine receptors or some impaired signalling pathways have been suggested. Behavioural, electrophysiological, and micro dialysis studies have shown that 5-HT receptors, mainly 5-HT1A, 5-HT1B, and 5-HT2C subtypes, exert a key role in modulating antidepressant activity. Indirect activation of neurotransmitter receptors by antidepressants may also lead, via increases in endogenous levels of 5-HT in synapses in specific brain regions to the activation of various G protein-coupled receptors, signal transduction, transcription factors, and neurotrophic factors such as brain-derived neurotrophic factor. These hypotheses need to be clarified by molecular biology.

Pharmacogenetic studies in mood disorder were performed only in recent years for a review see Serretti et al.16 Polymorphisms of some genes have been studied to date to

This Work is Partly Presented at 30th Annual European Pharma Congress scheduled During May 18,19-2020 at Berlin,Germany

test their association with antidepressant response. The choice of candidate genes has taken into account the possible involvement of each gene in the pathophysiology of the disease and in the mechanism of action of the analysed drugs.

Brief Biography

Dr. Weinshilboum received B.A. and M.D. degrees from the University of Kansas, followed by Internal Medicine residency at the Massachusetts General Hospital, a Harvard Hospital. He was also a Pharmacology Research Associate at the US NIH in the laboratory of Nobel Laureate Dr. Julius Axelrod. He is presently Professor of Pharmacology and Medicine at the Mayo Medical School. Dr. Weinshilboum's research has focused on pharmacogenomics, with over 475 published manuscripts. Dr. Weinshilboum has been the recipient of many awards including a Burroughs Wellcome Scholar Award in Clinical Pharmacology, the ASCPT Oscar B. Hunter Award, the ASPET Harry Gold Award and an honorary Doctor of Science degree from the University of Kansas. He has also served as a member of the Advisory Councils for two US NIH Institutes, NIGMS—the NIH Institute within which Pharmacology is based--and NHGRI, the NIH Institute that sponsored the Human Genome Project

This Work is Partly Presented at 30th Annual European Pharma Congress scheduled During May 18,19-2020 at Berlin,Germany