7. PHARMACOGENETICS OF DRUG RECEPTORS

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7.1 Introduction

Drug treatment is in many cases ineffective. Besides patients who do not respond to the treatment can develop so called adverse drug reactions (ADRs) as a consequence of the treatment (cause over 100 000 deaths per year in USA). Pharmacogenetics is the discipline, which takes the patient's genetic information of drug transporters, drug metabolising enzymes and drug receptors into account leading to optimal choice and dose of the drugs in question. It represents a kind of patient-oriented medicine or personalized medicine. It is believed that a lot of costs for the society can be saved by so called individualized drug therapy mainly based on pharmacogenetic data.

Genetic variations (mostly single nucleotide polymorphisms, SNPs and micro satellites) can be present in drug transporters, in majority of phase I and phase II drug metabolizing enzymes or in drug receptors. SNPs in drug transporters could alter the absorption, distribution and the elimination of the drug from the body. The polymorphisms in drug metabolising enzymes can cause abolished, quantitatively or qualitatively altered or enhanced drug metabolism. Several examples exist where subjects carrying certain alleles suffer from a lack of drug efficacy because of ultrarapid metabolism caused by multiple genes or by induction of gene expression. On opposite site, adverse effects can develop in slow metabolisers as a result of the accumulation of drug in presence of defective alleles. Finally, certain polymorph genes can be used as markers for optimisation of the drug therapy. It is likely that predictive genotyping is of benefit in 10–20% of drug treatment and thereby allows for prevention the appearance of ADRs and thus improves the health for this part of the patients.

7.2 Drug receptors

Receptor is a macromolecule in the membrane or inside the cell that specifically (chemically) bind a ligand (drug). The binding of a drug to receptor depends on types of chemical bounds that can be established between drug and receptor. The strength of this chemical bonds (covalent, ionic, hydrogen, hydrophobic) determine the degree of affinity of ligand to receptor. Ligands (drugs) that attracted the receptors may be classified as agonists or antagonists. Agonists produce the biological response as a results of receptor –ligand interactions therefore agonists posses efficacy. On the contrary antagonists did not provoke any biological activity after binding to its receptor.

There are different types of receptors (1):

1. Transmembrane ion-channels receptors
2. Transmembrane G-protein-coupled receptors
3. Transmembrane receptors with cytosolic domain
4. Intracellular (cytoplasm or nucleus) receptors

7.2.1   Transmembrane ion-channels receptors

The most rapid cellular responses to receptor activation are mediated via ligand-gated ion channels. These kind of transmembrane receptors composed of multiple peptide subunits and each of it contains four membrane-spanning domains (Figure 7.1.).
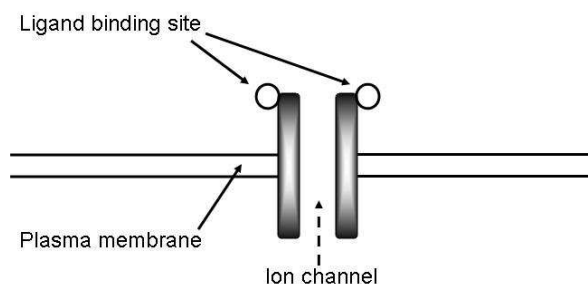

Figure 7.1. Ion-channel receptors (1)

The ligand binding causes the conformational changes of receptor and ion channel forming. The binding of Ach to each of four subunits of AchR induces change in receptor and opening the sodium selective channel through the centre of the receptor protein. It causes the depolarisation of surrounding membrane. In this type of receptors belong nicotinic acetylcholine receptors and receptors for GABA, serotonine and some other neurotransmitters.

7.2.2   Transmembrane G-protein-coupled receptors

The most abundant type of drug receptors are G-protein coupled receptors (GPCR). This are family of (over 100 different) transmembrane receptors which share a well conserved structure and transduce their signals via activation of intracellular guanidine nucleotide binding protein (G-protein) (Figure 7.2.). A variety of ligands for this receptors include biogenic amines (Ach, noradrenalin, serotonin), amino acid neurotransmitters (glutamat, glycine) and peptide hormones (angiotensinII, somatostatin). There are multiple GPCR types for a single ligand. The result is the possibility that single ligand can activate a variety of transduction pathways. Thus receptor is defined not only just by which ligands binds to it but also by second messenger systems (cAMP, PLC, Na/H exchange) and signal transduction pathway, which is activated by receptor activation.
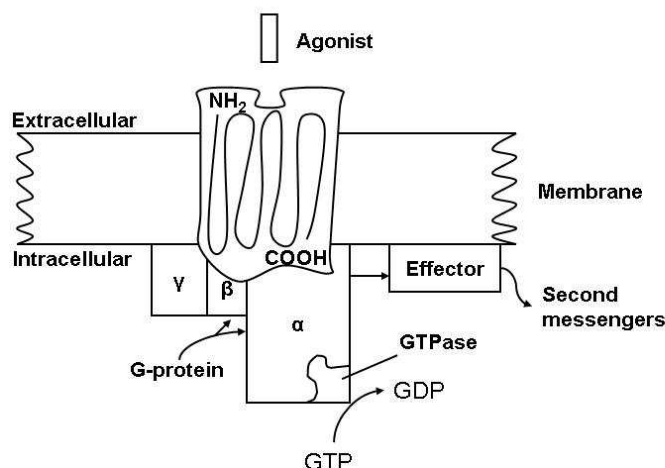

Figure 7.2. G-protein coupled receptors (1)

7.2.3   Transmembrane receptors with cytosolic domain

The intracellular domain of this transmembrane receptor is either enzymatic active (catalytic receptors) or is bound to specific enzyme(s) in cytosol (enzyme coupled receptors). The catalytic receptors are activated predominantly by peptide hormones (insulin, growth factors, etc). Catalytic part of receptors has the protein kinase activity. Mostly dimerisation of catalytic as well as enzyme-coupled receptors is necessary for kinase activity. Phosphorilation of intracellular proteins by these receptors results in effects such as opening the ion channels, initiation of gene expression or as in the case of enzyme coupled receptors activation of signal transducers and activators like JAKs and STATs.

7.2.4   Intracellular (cytoplasm or nucleus) receptors

Those receptors are not associated with cell membrane. In general their protein molecule consists from three main domains: Hsp-90 and DNA and ligand binding domains. Ligands are mostly lipid soluble and passively pass cell memmbrane. Agonists include nitric oxide, steroid hormones and vitamin D. Ligand binding activates receptor and initiates the dissociation from Hsp-90. The complex then translocates to nucleus and bind to specific DNA sequences mostly located in gene promoter region (Figure 7.3.). This kind of signal tranduction is slow, but duration of response can last long.
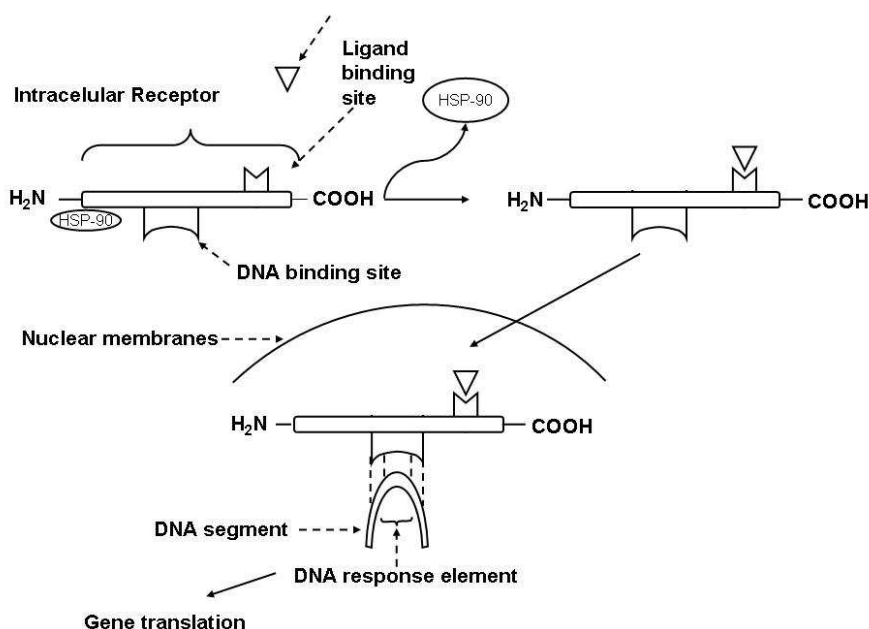

Figure 7.3. Schemes of nuclear receptors function (1)

7.3   Pharmacogenetics of human beta adrenergic receptors

Beta adrenergic receptors (ADRBs) are transmembrane G-protein-coupled receptors that bind adrenalin or noradrenaline in sympathetic nervous system. There are three types of ADRBs: ADRB1, ADRB2 and ADRB3. ADRB3 has been least studied to date and the role of ADRB3 in cardiovascular disease is not known. ADRB1 are the predominant type expressed in the hearth. ADRB2 are abundantly expressed in bronchial smooth cells and activation of them results in bronchodilatation.

ADRB1 and ADRB2 are intronless genes encoding 477 and 413 amino-acid proteins, respectively. They share a common structure with an extra cellular amino terminus domain,

seven transmembrane spanning domains and a cytoplasmic carboxyl terminus. Binding of ligand (adrenalin or noradrenalin or other agonists) to these receptors coupled to G- protein lead to conversion of ATP to cAMP. Increased cAMP stimulates a chain of events that culminates with removal of calcium from contractile protein and increase the activation of contraction through greater calcium cycling. The global effect is improved systolic and diastolic function (2).

7.3.1   ADRB1 polymorphisms

23 polymorphisms have been described and 13 of these change amino-acid sequence. As ADRB1 has not a recognised role in asthma, the majority of association and pharmacogenetic studies were done by cardiovascular phenotypes. Ser49Gly and Arg389Gly have been widely studied owing to studies supporting the functional effects on ADRB1 activity and phenotypes.

The Gly49 allel showed altered glycosilation and a more pronounced agonist-induced receptor down regulation in a fibroblast model what could explain the resistance to chronic beta-adrenergic stimulation through diseases or medication. The Arg 489 alleles showing higher basal levels of cAMP. Thus, the Arg389 may have inherently coupling to Gs and increase the signal transduction. Population association studies show Ser49 homozygotes have higher mean heart rates and are associated with reduced 5-year survival. However different studies gave divergent results. The Arg389 variant is associated with elevated diastolic blood pressure and higher resting heart rate. This finding was strengthened by similar conclusions of different studies. Furthermore Arg389Gly polymorphism appears to interact with 4-amino-acid deletion in the alpha-2-adrenergic receptor gene. Homozygotes with both polymorphisms have increased risk for heart failure (odd was 10,1). However it is approved in black population, the number of double homozygotes in Caucasians was too small (2).

7.3.2   ADRB2 polymorphisms

From 12 SNP identified only 5 of these predict the change of amino-acid sequence. The most studied SNPs are Arg16Gly, Gln27Glu and Thr164Ile. Functional analyses showed that the first two SNPs down regulate ADRB2 in fibroblasts and enhanced isoproterenol-mediated desensitisation in humans carrying the Arg16. The Ile164 allele has increased binding affinity for endogenous ligands. SNPs in ADRB2 have been studied in patients with asthma, obesity and diabetes. Recent studies concluded that Gly16 alleles predisposes to nocturnal asthma and asthma severity as well as to response to beta-agonist therapy (albuterol) in asthmatics. Association studies of ADRB2 gene variations with hypertensive phenotype yielded mixed results. In healthy individuals ADRB1 is far more abundant than ADRB2. However in the heart failure diseases proportion of ADRB2 is increased (to 40%). This data could be interpreted to mean that ADRB2 SNPs might have great effects on heart failure.

7.3.3   Pharmacogenetic studies of ADRBs

As the ADRBs are the major target for pharmacological therapy (beta receptor agonists and antagonists) some of pharmacogenetis studies were published. Studies showed that Arg389 homozygotes have increased effects of ADRB1 agonist dobutamine and ADRB1 antagonist metoprolol as compared to Gly 389 homozygotes. SNPs in ADRB2 influence the response to methacholine and albuterol therapy of asthma. In conclusion for ADRB1 the Gly49 and Arg389 alleles seem to be variants that perform more favourably in heart failure patients given beta-blockers, in case of ADRB2 the data suggest a negative effect of Arg 16 alleles on short term beta agonist therapy (2).

7.4 Pharmacogenetics of estrogen receptors

7.4.1 Type and function of estrogen receptors

Estrogen receptors (ERs) are intracellular nuclear receptors that belong to steroid hormone receptor family. There are two types of ER; ER alpha (ER 1) and ER beta (ER 2) encoded by two different genes ESR1 and ESR2, respectively. ESR1 and ESR2 are expressed mostly bones, breasts, ovaries, cardiovascular system and central-neural system, but ESR2 mRNA was also found in kidney, lung, colon and testis tissues. ERs function as transcription factors activated by a ligand. Ligands bind to ERs are endogenous estrogen hormones (estradiol) or estrogens administered at hormone replacement therapy (HRT). A new group of drugs, "selective estrogen receptor modulators" (SERMs) act as ER-agonist in a specific tissue (like raloxifen in bone) but as an ER-antagonist in other tissue (like tamoxifen in breast). Irrespective of ligand, ligand binding to ER results in activation and translocation of ERs to nucleus, where the complexes bind to specific DNA sequences (estrogen responsive element). In association with other coactivators and represors alters the expression of target genes. For example binding of ER1-ligand complex to fos/jun complex facilitate the binding of fos/jun heterodimer to AP-1 site and activation of many genes including IGF-1. On the contrary, ESRs inhibit binding of NF-kB to IL-6 promoter.

7.4.2 Pharmacogenetics of ERs

Pharmacogenetics of ERs was mostly studied regarding the role of ERs genes polymorphisms in determine the response to estrogen and SERM therapy and the risk of cardiovascular events. Clinical data of hormone replacement therapy (HRT) for maintain the health of postmenopausal women showed an increase in cardiovascular complications as the adverse drug reactions. However our data at raloxifen (SERM) treatment showed opposite effect with lowering of cholesterol level. Both, estrogens and SERMs activity could be modified with genetic polymorphisms of ER alpha gene. In this regard 10 different SNPs or microsatelite polymorphisms over regulatory, coding and uncoding regions were analysed. Cluster of four SNPs located at the 3' end of intron 1 were significantly associated with higher increase of HDL level at HRT treatment. Among these SNPs the IVS1-401T>C was most strongly related to HDL increase (3). Our data approve positive effects of exonic but not intronic SNPs on total cholesterol level at postmenopausal osteoporotic women treated with raloxifen (4).

Several other studies have also examined the effects of ER1 IVS1-401T>C polymorphism on response to HRT or bisphosphonates treatment of osteoporosis. IVS1-401C allele was associated with greater effects of estrogen on bone mineral density. Our data on nearly 60 postmenopausal women treated with raloxifen didn't show any influence of ER1 SNPs on SERM effect.

7.5   Conclusion

The information about the role of polymorph drug receptors for efficiency of drug therapy are more scarce, although promising examples are seen in drug treatment of asthma where the efficiency can be severely enhanced by predictive genotyping of the drug targets. To move the field to clinical practice, future studies should be larger and have to consider the complexity of drug response (receptor protein with proteins in signal transduction). Finally, for those drugs with multiple pharmacological effects or effects in different organs, the genetic contributions have to be considered separately (5). Discovering highly predictive genotype-phenotype associations during drug development and demonstrating their clinical validity and utility in well-designed prospective clinical trials will no doubt better define the role of pharmacogenetics in future clinical practice.

Recommended literature:

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