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PHYSIOPATHOLOGICAL IMPLICATIONS OF 7TM RECEPTORS

Abstract: Seven-transmembrane (7TM) receptors are one of the most important proteins involved in perception of extracellular stimuli and regulation of variety of intracellular signaling pathways. Divergence of receptor types, their ligands and signaling pathways makes 7TM receptors important factors in pathology of many diseases. This review focused on the main diseases in which involvement of 7TM receptors was established e.g., retinitis pigmentosa, severe obesity, and dwarfism. Recent findings of aberrant expression of 7TM receptors in development of cancer were also summarized.

Key words: Seven-transmembrane receptors, G protein coupled receptors, pathology, cancer

1. 7TM RECEPTORS AS UNIVERSAL SIGNAL MEDIATORS

During evolution an extremely diverse family of heptahelical receptor proteins emerged. These proteins are called seven-transmembrane receptors (7TMRs) or G-protein coupled receptors (GPCRs) due to the fact of signal transmission via heterotrimeric G-proteins. The superfamily of 7TM receptors is the largest class of cell membrane receptor found in metazoans. The completion of the human genome project revealed over 800 genes encoding 7TM receptors (LAGERSTROM, SCHIOTH 2008). In view of existence of alternative splice variants and editing isoforms of 7TM receptors (CADET *et al.* 2003; HIRASAWA *et al.* 1995; NELSON, CHALLISS 2007) it is anticipated that true number of functional receptors is

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much higher. Sequence of these receptors is highly variable and the only homology between all 7TM receptors is the presence of seven α-helical transmembrane segments joined by intra- and extracellular loops with N-terminal chain located in the extracellular space and C-terminal chain located in cytoplasm. 7TM receptors react in response to a varied range of stimuli e.g., light, ions, peptides, lipids, and odorants. Upon ligand binding 7TM receptors constrain conformational change in α subunit of trimeric G-protein complex. This leads to exchange of GDP molecule for GTP and dissociation of G-protein and activation of subsequent intracellular responses (BOURNE *et al.* 1991).

Biological significance of 7TM receptors was consolidated after reports showing that heterotrimeric G-proteins are common, although not exclusive, mediators of cellular response after activation of these molecules (PIERCE *et al.* 2001; PIERCE *et al.* 2002). Unusual diversity among 7TM receptors allow them to play an important role in wide spectrum of biological processes ranging from neurotransmission and hormonal control to perception of taste, smell, light and pain.

Divergence of stimuli and rich pattern of intracellular signaling pathways governed by 7TM receptors makes this group of proteins undoubtedly prone to be involved in many pathological processes. In most cases mutation will exhibit as gain/loss of function phenotype of 7TM receptor. As a result of inherited mutations aberrant receptor will be present in every cell expressing particular gene while in somatic mutations even in the case of ubiquitous gene the expression of mutated gene will be limited to the cells derived from the progenitor of mutation (SPIEGEL 1997).

Mutations in nearly every part of the receptor may cause improper protein expression, folding, endoplasmic reticulum retention, or inability to interact with other proteins of the signalosome. Such abnormalities will exhibit loss of function phenotype and its presence will lead to ligand resistance. Mutations which lead to loss of function mutations are usually recessive and unveil their presence in homozygotes. Gain of function mutations will in most cases cause constitutive activation of the receptors and in case of hormonal signaling cause endocrine

hyperfunction. Since such mutations are dominant, heterozygotes are developing symptoms of the disease (SPIEGEL 2000).

At present several separate disease entities caused by mutations in 7TM receptors have been described. However, this number is likely to grow fast given to the fact, that over 160 7TM receptors are targeted in mice for homology with human diseases (SCHONEBERG *et al.* 2004).

2. DISEASES CAUSED BY INACTIVATION MUTATIONS IN 7TM RECEPTORS

The chances of mutational inactivation of the receptor are high. Amino acid substitution, deletion or insertion may cause loss or prematurely terminated transcription, improper protein folding or its inability to reach cell surface. Moreover, disruption of ligand binding pocket or receptor inability to bind with downstream signaling molecules, all result in loss of function phenotype (SPIEGEL 2000; SPIEGEL, WEINSTEIN 2004).

Diseases linked with inactivating mutations in 7TM receptors include: retinitis pigmentosa (RP) caused by mutations in rhodopsin; hypothyroidism and resistance to thyroid-stimulating hormone (TSH) caused by mutations in TSH receptor; nephrogenic diabetes insipidus (NDI) characterised by polyuria, polydipsia and hyposthenuria as a effect of mutations in vasopressin type 2 (V2) receptor (BARAK *et al.* 2001); Blomstrand chondrodysplasia in which mutations in parathyroid hormone/parathyroid hormone – related peptide (PTH/PTH-related peptide type 1) receptor; rare disease of familial hypocalciuric hypocalcaemia and potentially lethal neonatal severe hyperparathyroidism are linked with inactivating mutations in calcium-sensing receptor. Human red-hair color phenotype characterized by red hair, fair skin and poor ability to tan associated with loss of brown/black pigment eumelanin production, and susceptibility to development of skin cancers, have been linked with more than 60 variants of melanocortin type 1 (MC1R) receptor (SANCHEZ-LAORDEN *et al.* 2007; TAO 2006). Interestingly, inactivating mutations of CCR5 chemokine receptor, especially CCR5Δ32 are

associated with strong resistance to HIV infections, and slower progression of the disease (BALISTRERI *et al.* 2007).

2.1 Rhodopsin mutations and retinitis pigmentosa

A growing list of over 150 mutations, most of them missense or small in frame deletions, are primary causes of retinitis pigmentosa. Patients carrying this phenotypically and genetically diverse disease suffer from retinal dystrophy with symptoms ranging from night blindness to progressive loss of visual field (SCHONEBERG *et al.* 2004; TAO 2006).The first ever described mutation that causes this disease in humans was P23H substitution in rhodopsin. Mutated rhodopsin is retained in endoplasmic reticulum due to misfolding and aggregation. Although many single nucleotide mutations which causes retinitis pigmentosa can be found throughout the rhodopsin, cytoplasmatic part of the receptor and regions surrounding disulfide bridge connecting second extracellular loop with top of transmembrane three are more prone to hold retinitis pigmentosa mutations (STOJANOVIC, HWA 2002). The mechanism of retinal cells entering apoptotic pathway remains elusive, however, growing evidence suggest that aberrant formation of multimeric receptors complexes may contribute to this phenomena (ABDULAEV 2003).

2.2 Leptin/Melanocortin circuit; melanocortin receptor and severe obesity

Circulating leptin levels give the brain a reading of energy storage for the purposes of regulating appetite and metabolism. Leptin works by inhibiting the activity of neurons that contain neuropeptide Y (NPY) and agouti-related peptide (AgRP), and by increasing the activity of neurons expressing melanocyte-stimulating hormone (MSH).

Melanocortins are an important mediator of satiety. Leptin is produced in the adipocytes and mutations in the gene for the melanocortin receptors (MCRs) are linked to obesity in humans (TAO 2005). MC3R seems to exert its function in fat depository processes, rather than regulation of food intake. Inactivation of MC3R in mice results in elevated amount of fat mass while total body weight remains

unchanged (BUTLER *et al.* 2000; CHEN *et al.* 2000). Only recently first mutations of MC3R in obese patients were identified (LEE *et al.* 2002; RACHED *et al.* 2004; TAO, SEGALOFF 2004), confirming the importance of MC3R receptor in maintaining energy balance in the body. Heterozygous MC4 receptor mutations are found in 1–6% of severe cases of human obesity. More than 50 mutations in MC4 receptor gene, many of which were identified as heterozygous missense mutations, linked to obesity have been described in adults with morbid obesity or children with early onset obesity (GOVAERTS *et al.* 2005). The exact mechanism of observed dominant-negative effect of mutated MC4R is still far being clear, however recent reports suggest that altered sequence of MC4R may contribute to aberrant formation of multimeric complexes (BIEBERMANN *et al.* 2003).

2.3 7TM receptors mutations and reproductive physiology

Gonadothropin releasing hormone (GnRH) plays pivotal role in neuroendocrine regulation of reproduction. Hypogonadotropic hypogonadism occurs in patients with lack of GnRH receptor function. Characteristic for this disease is absence or decreased function of male testes or the female ovaries. Follitropin (FSH) receptor inefficiency is responsible for female infertility due to ovarian dysgenesis. At least 22 mutations in lutropin (LH) receptor responsible for production of testosterone have been reported to cause pseudohermaphroditis in males and hypergonadotropic hypogonadism, and primary amenorrhea in females (TAO 2006).

2.4 Growth hormone releasing hormone receptors and dwarfism

Growth hormone releasing hormone (GHRH) is synthesized and secreted by the arcuate nucleus of the hypothalamus. GHRH stimulates synthesis and secretion of growth hormone. Defective signaling in GHRH axis results in somatotroph hypoplasia and growth deficiency. GHRH receptor mutation was first identified in *little* mouse strain. Mutated murine GHRH receptor is unable to bind its ligand properly. In humans mutant receptors show aberrant signaling (TAO 2006). Inactivating mutations of growth hormone releasing hormone receptor lead to isolated growth hormone (GH) deficiency (LIN-SU, WAJNRAJCH 2002). At the same

time overexpression of GHRH was found to be an important factor in development of pituitary adenomas in mice (MAYO *et al.* 1988).

3. DISEASES CAUSED BY ACTIVATING MUTATIONS IN 7TM RECEPTORS

Gain of function mutations of 7TM receptors are in most cases missense mutations, however due to the fact that most of them are lethal during embryogenesis and thus undetectable, only 13% of diseases caused by mutated 7TM receptors are characterized by induction of agonist independent signaling. Constitutive activation of luteinizing hormone and thyrotropin receptors are cause of familial male precocious puberty characterized by accelerated sexual development at the age of 2 – 5 years. Familial hypocalcaemia is caused by calcium receptor hypersensivity to circulating Ca^{2+} and thus excessive hypercalcuria (SCHONEBERG *et al.* 2004; SPIEGEL, WEINSTEIN 2004).

Since many agonists for 7TM receptors exhibit mitogenic activity, many somatic gain of function mutations in 7TMRs are linked to development of adenomas and malignant tumors. In approximately 80% of thyroid adenomas activating mutations in thyrotropin receptors are reported. Smoothened, a member of frizzled family of 7TMRs that signals through hedgehog pathway is supposed cause of basal cell carcinoma (SCHONEBERG *et al.* 2004). Tumorigenic activity has been demonstrated for constitutively active receptors encoded by Kaposi's sarcoma associated virus and human cytomegalovirus (SODHI *et al.* 2004; VISCHER *et al.* 2006)

4. ABERRANT 7TM RECEPTORS EXPRESSION IN NEOPLASMS

Alterations in expression of different 7TM receptors have been reported in numerous human both benign and malignant neoplasms. It has been showed that aberrant expression of gastric inhibitory polypeptide and luteinizing hormone receptors is a sufficient event to trigger hyperplastic growth of adrenogortical cells (MAZZUCO *et al.* 2007). Systematic study of data from microarray analysis of primary lung, breast, prostate, gastric and melanoma cancers has revealed that

expression of multiple e.g., chemokine, PAR, neuropeptide, adenosine, purine and calcium receptors are significantly upregulated in human neoplasms (LI *et al.* 2005). Summary of latest findings on changes in 7TM receptors expression changes in various human neoplasms is presented in Tables 1a and 1b.

Table 1a. Abberations in 7TM receptors expression in neoplastic cells

Receptor	Ligand	Expression	Neoplasm		Reference
AXOR12	KiSS-1 peptide	↓	high grade epithelial ovarian cancer		HATA *et al.* 2007
Cb2	cannabinoids	↑	acute myelogenous leukemia	overexpressed in human myeloid leukemia cell lines	JORDA *et al.* 2004
CRH-R	corticotropin-releasing hormone	↑	corticotroph tumours		DE KEYZER *et al.* 1998
CysLT2R	leukotriene C4	↑	colorectal adenocarcinoma	subsequent downregulation causes poor prognosis	MAGNUSSON *et al.* 2007
D-GPCR	odorants	↑	malignant prostate	upregulation correlated with advancement of tumor	FUESSEL *et al.* 2006
FZD7	Wnt proteins	↑	hepatic cancers	subsequent activation of Wnt/beta catenin pathway	MERLE *et al.* 2005
Ghrelin 1a	ghrelin	↓	adenoid cystic carcinoma	parallel overexpression of 1b isoform	BARZON *et al.* 2005
GnRH	gonadotropin-releasing hormone	↑	multiple		EAVERI *et al.* 2004
GPR30	estrogen	↑	breast cancer	upregulation correlated with tumor size, invasiveness, Her2/neu expression	FILARDO *et al.* 2006
		↓	infiltrating ductal carcinoma	correlation in ER+ cells	KUO *et al.* 2007

Table 1b. Abberations in 7TM receptors expression in neoplastic cells (continued)

Receptor	Ligand	Expression	Neoplasm		Reference
GPR48	orphan	↑	multiple	downregulation of p27(Kip1) is associated with increased tumor malignancy and poor prognosis	GAO *et al.* 2006
GPR49	orphan	↑	colon, primary ovarian		MCCLANAHAN *et al.* 2006
GPR54	Kisspeptin	↑	bladder, thyroid		NICOLLE et al. 2007
GPR56	orphan	↓	pancreas	in vitro study	HUANG *et al.* 2007
		↑	gliomas		SHASHIDHAR *et al.* 2005
GPR87	lysophosphatidic acid	↑	lung squamous cell carcinoma		GUGGER *et al.* 2008
LPA2/3	lysophosphatidic acid	↑	colon	in vitro study; LPA induced proliferation mediated by beta catenin pathway	YANG *et al.* 2005
LPA2	lysophosphatidic acid	↑	invasive ductal carcinoma		KITAYAMA *et al.* 2004
Metastin	KiSS-1 peptide	↑	thyroid papillary carcinoma		RINGEL *et al.* 2002
Orphan BTR	orphan	↑	prostate		PARMIGIANI *et al.* 2004
PAR1	thrombin	↑	colon, prostate, aggressive melanoma, invasive breast		ARORA *et al.* 2007
			high grade endometrial cancer	no expression in benign tumors	GRANOVSKY-GRISARU *et al.* 2006
SCTR	secretin	↓	pancreas	dominant negative effect of truncated secretin receptor	KORNER *et al.* 2005
V3	vasopressin	↑	corticotroph tumors		DE KEYZER *et al.* 1998

5. COMMERCIAL POTENTIAL OF 7TM RECEPTORS

7TM receptors are one of the most studied targets for present and future therapy targets. More than 30% of all drugs on the market are believed to exert their

clinical action through one of the 7TM receptors family members (HOPKINS, GROOM 2002). About half of the commercially exploited 7TMRs are activated by polypeptide/protein ligands, further over 25% with biogenic amine ligands. But still less than 30% of 7TMRs which are identified in human genome are currently targeted by pharmacological therapies (LAGERSTROM, SCHIOTH 2008).

7TMRs make a very good drug targets, however pharmacological profiling of still existing, orphan receptors and searching for new drug candidates for receptors with established natural ligands have forced scientists and pharmacological industry to come up with highly efficient systems able to efficiently screen 7TMRs of interest against vast compound libraries. The general strategy that enables resourceful characterization of orphan is termed "reverse pharmacology" approach. It employs studied receptor as a bait to fish out its ligand at first step, usually out of biologically active tissue or organ extracts (WILSON *et al.* 1998).

Out of top 20 drug best sellers in the U.S. in 2003, 35% were 7TMR related, and have brought over 16 billion $ of income (SCHLYER, HORUK 2006).

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