"ROLE OF TYROSINE KINASE INHIBITORS IN TYPE 2 DIABETES MELLITUS"

A PROJECT SUBMITTED TO

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In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

BY

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Semester VIII

UNDER THE GUIDANCE OF

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2019-2020

CERTIFICATE

This is to certify that ***"ROLE OF TYROSINE KINASE INHIBITORS IN TYPE 2 DIABETES MELLITUS"*** *is the bonafide work carried out by* ***PATEL SHREYA HIMANSHUBHAI (16BPH091)****, B.Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction.*

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CERTIFICATE OF SIMILARITY OF WORK

*This is to undertake that the B.Pharm. Project work entitled "**ROLE OF TYROSINE KINASE INHIBITORS IN TYPE 2 DIABETES MELLITUS**" Submitted by **PATEL SHREYA HIMANSHUBHAI (16BPH091)**, B.Pharm. Semester VIII is a bonafide review/research work carried out by me at the Institute of Pharmacy, Nirma University under the guidance of "Snehal Patel and Palak Parikh". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, the review/research work carried out by me is not reported anywhere as per best of my Knowledge.*

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DECLARATION

I, PATEL SHREYA HIMANSHUBHAI (16BPH091), student of VIII[th] Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled "ROLE OF TYROSINE KINASE INHIBITORS IN TYPE 2 DIABETES MELLITUS" is a result of culmination of my sincere efforts. I declare that the submitted project is done solely by me and to the best of my knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.

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1. INTRODUCTION

1.1 Diabetes mellitus

It is also known as diabetes. It is one term which includes how our body turns food into energy by using different pathways in our body. When we take carbohydrate, our body turns it into a sugar which is known as glucose which leads to our bloodstream. After this, insulin is released by pancreas. Insulin is hormone which helps to move glucose into our cells from our blood, which use it for energy. There is possibility of high glucose level in blood which is known as high blood sugar which may be occurred by non-treatment diabetes. (Mealey et al ,2006)

1.1.1 Types of diabetes mellitus

There are mainly two types of diabetes mellitus known. One of which is type 1 diabetes and another one is type 2 diabetes. Major difference between these two types of diabetes are type 1 is called insulin dependent or juvenile onset diabetes and type 2 is called noninsulin dependent or adult onset diabetes.

Type 1 diabetes: It is a kind of autoimmune condition. It occurs when your pancreas is attacked by your body with antibodies. Our body is not able to make insulin. This kind of diabetes might be caused by your genes. If any problem is there in cells of pancreas then also it will lead to problem. Too many problems can come with this kind of diabetes like diabetic retinopathy which occurs in eyes, diabetic neuropathy which occurs in nerves, diabetic nephropathy which occurs in kidney. people may high risk of heart disease and stroke. For the treatment of type 1 diabetes insulin is given by transdermal route by using syringes, insulin pen, jet injectors and pumps. Non pharmacological treatment like frequent testing of your blood sugar levels, meal planning, exercise on daily basis and other medicine as well as insulin. Body is not able to make insulin. The cells of pancreas are being attacked and destroyed by immune system. Diabetes mellitus is a kind of metabolic disorder which is characterized by chronic hyper glycemia because of the defects in secretion of insulin and its action. It is triggered by auto immune obliteration of pancreatic beta cells. Infiltration T cell, convoyed thru cytokine besides “reactive oxygen species(ROS)” production, which ultimately results in beta cell dysfunction and apoptosis (Fountas et al, 2015).

Type 2 diabetes: In this kind of diabetes insulin is generated by pancreas but doesn't used properly by body receptors. Sometimes cells do not act against insulin and this kind of problem occurs in fat liver and muscle cells. Body cannot make insulin or not use insulin well. It can cause such major health complications like tiny vessels in your kidneys, nose, eyes. It is also act as a risk factor of heart disease and stroke. Obese person have more chances for suffering from type 2 diabetes. Generally, obesity causes resistance of insulin hence, pancreas has to work harder for making much amount of more insulin. Treatment of this kind of diabetes includes healthy weight, eat right food and exercising also meditation. It is characterized by targeted tissues resistance of such metabolic insulin actions and pancreatic cells dysfunctions. (Fountas et al, 2015)

Gestational diabetes: This kind of diabetes is due to pregnancy. While pregnancy baby get each nutrition from her so it's important to control his mind of diabetes for the protection of baby's growth and its development. Furthermore, in this kind of diabetes baby may have much weight gain before birth, trouble in breathing at birth and having a higher risk obesity and diabetes in future. Its treatment is careful meal without much fat and calories daily exercise weight gain under control taking insulin regularly.

Other kind of diabetes are like monogenic diabetes that is inherited form of diabetes as well as cystic fibrosis related diabetes. (Mealey et al ,2006)

1.1.2 Risk factors

Age of 45 or older, any family history of diabetes, overweight, physically inactive, having health problems like blood pressure, heart disease, stroke

1.1.3 Prevention of type 2 diabetes

Lose weight,

move more,

eat healthy food

1.1.4 Following disease maybe occurred if they have diabetes*:* Disease related to heart, stock, disease related to kidney, eye problem, dental disease, damage in now foot problems.

1.1.5 Symptoms

Elevated thirst and urination, increased hunger, fatigue, blurred vision, numbness in the feet and hands, sores that do not heal, loss in weight

1.1.6 Causes

For type 1 diabetes: genes environmental factor

For type 2 diabetes: overweight, obesity and physical in activity insulin resistance genes, family history

For gestational diabetes: insulin resistance, genes, family history

Other causes: genetic mutation, hormonal disease like Cushing syndrome, hyperthyroidism, removal or damage of pancreas, such medicines like niacin, anti-seizure drugs, psychiatric drugs, glucocorticoid, diuretics.

1.1.7 Pathophysiology

Diabetes term lies the knowledge of the basics of carbohydrate metabolism and insulin action. Subsequently the feeding of food carbohydrates stay shattered down into primary glucose molecules. After that the primary glucose molecules are absorbed into the bloodstream and elevate blood glucose levels. This increase in glycemia stimulates the secretion of insulin from the beta cells present in pancreas. Insulin is necessary for most of the cells to permit glucose inside the wall. This insulin tends to bind to receptors which are specific in nature and it facilitates glucose entry into the cell which is used for the energy requirements. Basically, the improved secretion of insulin from the pancreas & simultaneous cellular glucose results in decreasing glucose level in blood. This low level of glucose results in reduced insulin secretion. As the manufacture and discharge of insulin are changed by any kind of illness then the undercurrents of blood glucose will alter. Uncertainty there is decreased manufacture of insulin then the entry of glucose into the cells will be inhibited which will result in hyperglycemia. This same kind of effect will be seen if insulin secreted from the pancreas is normal but it is not utilized properly by the target cells. If the secretion of insulin increases the level of blood glucose will go very low that suggest hypoglycemia because huge amounts of glucose arrive the cells & little amount remnants into bloodstream. Many hormones can disturb glycemia as in level

of glucose in the body. Insulin is main hormone which controls the blood glucose level. There are many other hormones present like catecholamines, glucagon, growth hormone, glucocorticoids, thyroid hormone and they all act to upsurge blood glucose level in adding to their physiological actions. (Mealey et al,2006)

1.1.8 Complications

Problems resulted from diabetes perform a major cause of disability low quality of life and death. Complications of diabetes can affect various parts of individual's body manifesting in in different ways for different people. It rises patient's risk for serious health problems. In men it causes erectile dysfunction, low testosterone levels and emotional factors like depression, anxiety and stress that can interfere with sexual feelings. In female diabetes may be especially hard. Even those women who do not have this disease pregnancy may bring the risk of gestational diabetes. According to data analysis from the American Diabetes Association had disease is now the leading cause of death in females with diabetes. In addition to this, women with diabetes are affected by depression, their sexual health is at risk and different kinds of eating disorders tend to occur more frequently.

Diabetes can affect mostly every part of the human body the feet, eyes, skin and other vital organs. Problems are become the initial sign like person having this disease. In all of these foot complications can get worse and may lead to serious complicated disorders like neuropathy, skin changes, foot ulcer and poor circulation. (Olokoba et al, 2012)

1.1.9 Risk factors

Controllable risk factors associated with diabetes are obesity and poor life style. But uncontrollable risk factors are also there which are ethnicity and genetics which contributes dramatic role. Type 1 diabetes has a primary risk factor of family history. Means family members having diabetes. In addition to this, some kind of injury or disease to the pancreas which may inhibit the production of insulin may lead to type 1 diabetes. Low production of insulin and obesity. Race and ethnicity include higher level of diabetes in some groups like Mexican Americans, Africans Americans, native Hawaiians, American Indians and Asian Americans. They are in more danger because of high blood pressure, obesity and diabetes. Race and ethnicity are not only determinants of developing diabetes. Major variations in diet and low bodily activity

because of technical growth and urbanization have controlled to very loud surges in diabetic patients.

1.1.10 Prevention

1) Regular measurement of bp

2) bp of 130-139 /80-89 mmHg should effort healthy routine & behavioural treatment for 3 month.

3) Annual lipid testing

4) Limit consumption of saturated fat, trans fat and cholesterol.

5) Diabetic patients should do an eye test and dilation within 3 to 5 years

6) Patients should control optimal glucose and bp to reduce the likelihood of developing retinopathy (Paterson et al ,2007)

7) Patients with peripheral neuropathy should take care of foot with special footwear to reduce the risk of ulceration. Quite smoking.

1.2 Old & new approaches towards treatment

1) pharmacological treatment: Alternative medicines and other treatments require careful and responsible environment. Moreover, diabetes is associated with cardiac and stroke related deaths, kidney failure, blindness and 60% of non-trauma lower limb amputation (National diabetes fact sheet, Atlanta 2004).

2) Insulin therapy: Insulin is a hormone resulting from pork (porcine) beef or is genetically made to identical to human insulin.

Rapid acting insulin: onset of action within few minutes.

Regular or short acting insulin: onset of action is 30 minutes and lasts for 6 hours.

Intermediate acting insulin: onset of action is 2 to 4 hours and lasts up to 18 hrs.

Long acting insulin: 6 to 10 hrs to range bloodstream and work entire day.

When insulin is prearranged under skin, it may typically taken that 2/3rd of the total daily dose is specified in the morning and 1/3 of the total daily dose is given in the evening.

3) Problems of the insulin therapy: Major complications associated with insulin therapy are hypoglycemia, hypertrophy and rash at the site of injection or over the entire body. The most common symptoms are, extreme fatigue, low blood sugar, irritability, trembling hands, cold sweats, anxiety and confusion. These are caused by insulin overdose (Gkaliagkousi,2007). There are other complications like diabetic ketoacidosis produced by stress, infections, trauma which may reason growth in insulin requirements . But with proper treatment abnormal blood sugar levels, ketone production, acidosis and dehydration can be cured and patient may recover well. Hyperosmolar hyperglycemic non kenotic syndrome is less common than ketoacidosis and happens in older obese patients with type 2 diabetes (Buysschaert,2000)

4) Non -insulin Diabetes Treatment: Also known as incretin mimetics. DPP -4 inhibitors are given along with these drugs.

5) Oral hypoglycemic agent: Sulphonylureas, Biguanides, Thiazolidindiones, Alpha glucosidase inhibitors and Incretins analogues. (Boulton, 2005).

6) Metabolic surgery for type 2 diabetes: Remission is pragmatic in the days near weeks afterwards surgery before any significant weight loss. Bariatric surgery has a blindingly safe operative profile and is allied with low death (Rubino et al, 2009).

7) Non pharmacological treatment: The micro and macro vascular complications were significantly increased in smokers compared to non-smokers (Buysschaert,2000).

Diet: Slow release carbs deliver lasting energy & assistance people to stay full longer (Gross, 2005).

Exercise: At least 30 minutes of physical exercise a day decreases the risk of emerging type 2 diabetes through 30- 50%. (Gkaliagkousi 2007). Exercise is the best way to reduce insulin resistance. (Goodpaster et al, 2010). Exercise can reduce hepatic insulin resistance. (Haus et al 2010). Physical exercises build stronger bones and muscles to stay flexible in all ages.

8) Organic drugs: Monoclonal antibodies (MABs)

CHAPTER 2. TYROSINE KINASE

Tyrosine kinase is the most important mediator signaling cascade is used to determine search roles and functions in biological process like growth differentiation metabolism and apoptosis as a result against external and internal stimuli. These kinds of kinases are essential in signal transduction process followed toward cell proliferation preparation migration metabolism and cell death. Tyrosine kinase is kind of enzyme that catalyzes phosphorylation process of tyrosine residue in the targeted proteins by utilization of ATP. This kind of covalent post translational modification important component of communication of cells homeostasis maintenance. (Paul and Mukhopadhyay, 2004)

2.1 Biochemical kind of mechanism of action of tyrosine kinase

Several kind of tyrosine residues in different substrates are phosphorylated by tyrosine kinase. this tyrosine kinase receptor is activated by using the mechanism of ligand binding to the extracellular part. Such extracellular signaling molecules quad ligands induce dimerization of the particular receptor. By using different kind of strategies different ligands achieve the stable dimeric conformation. there are two kind of ligand binding may be possible. One of which is ligand bind with two molecules of receptor and form 1:2 ligand: receptor complex. Another one is that ligands may bind simultaneously with 2 receptors and form 2:2 ligand-receptor complex to provide simple mechanism of dimerization of receptor. It is ligand binding process to extracellular domains helps to stabilize the formation of active dimers as well as simultaneously activation of protein tyrosine kinase. Oligomerization process also increase the concentration of receptor tyrosine kinase which leads to effective transphosphorylation of particular tyrosine residues in loop activation of catalytic domain. After tyrosine phosphorylation activation loop result in open confirmation which gives permission to ATP and substrates and also provide ATP transfer from MG-ATP to the residue of tyrosine on the receptor and in signal transduction such cellular proteins are involved. Intracellular catalytic domain of ATP binding site used to catalyze photophosphorylation of receptor which use highest level of conservation between receptor tyrosine kinases. Various kind of ATP binding site provide docking site specific binding of specific proteins and protein tyrosine binding domain. This assembly of complexes between activated receptors and membrane and activation of

intracellular signals results in activation of different kind of subsets of gene and known as biological response to signals. While the time of these activation process receptor transfer into the plasma membrane which block it and form endocytic vesicle. This kind of vesicles come in contact with lysosome and receptor as well as ligand might be created by this lysosomal enzyme. Through the process of internalization of receptor search ligand-receptor complex is dissociated which leads to termination of signaling reaction. (Paul and Mukhopadhyay, 2004)

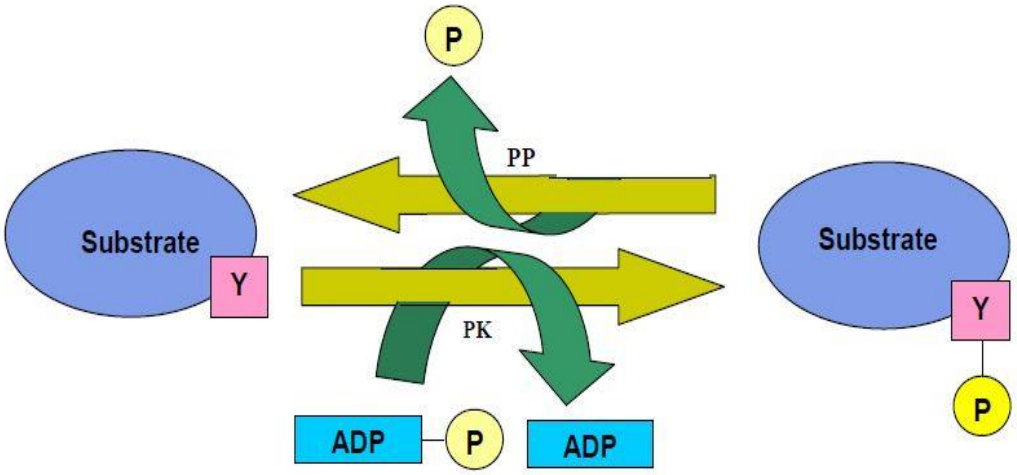


Figure:1 schematic representation of tyrosine kinase mode of action where PK is protein kinase and PP is protein phosphates.

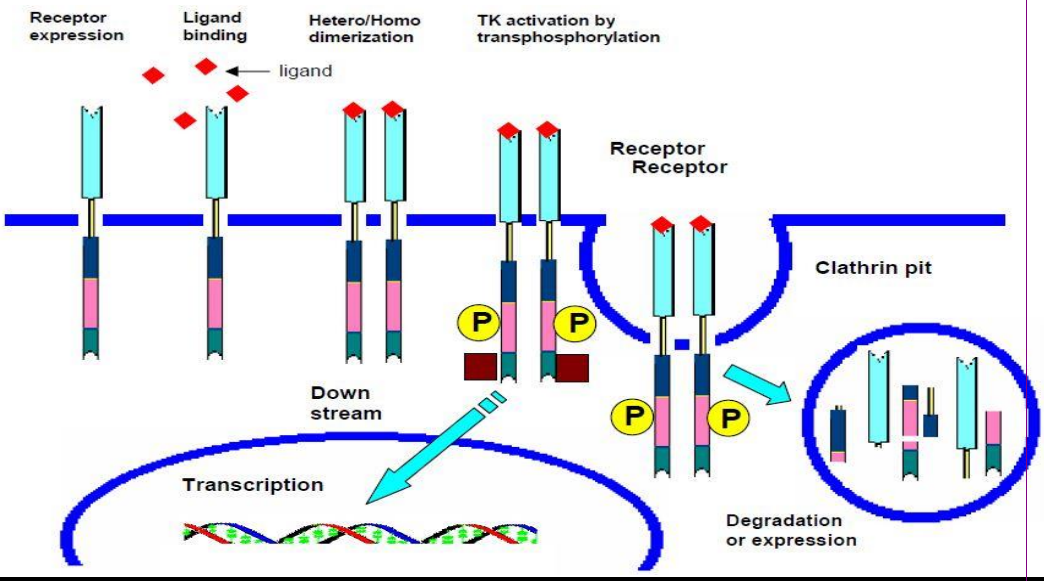


Figure: 2 mechanism of action of tyrosine kinase

2.2 Classification of tyrosine kinase

Generally, tyrosine kinase class divided in to two different types: Receptor tyrosine kinases (RTKs) & second is non-RTKs (NRTK).

Tyrosine kinase mainly classified is receptor tyrosine kinase example epithelial growth factor receptor, PDGFR, FGFR, IR. Second one is non receptor tyrosine kinase example SRC, FAK, ABL. Tyrosine kinase have both the activity of cell surface transmembrane process and kinase activity also. Tyrosine kinase receptor has multidomain extra cellular ligand to convey ligand specificity. Tyrosine kinase is present into the single pass transmembrane lipophilic helix as well as into a cytoplasmic portion. This domain always has sequence of both C and N terminal ends. (Hunter, 1995 and Schlessinger,2000)

RTKs are same as transmembrane glycoproteins which contains extracellular domain and hormone binding site, transmembrane area, as well as intracellular field thru intrinsic tyrosine kinase activity. (Fountas, 2015)

Non receptor tyrosine kinase is responsible for structural availability. They have kinase domain as well as other various protein-protein or signaling domain pathways. (Schenk, 1999) The tyrosine kinase domain extents around 300 residues and contains N terminal lobe contains one 5 stranded β sheet and one α helix. On the other hand, the C terminal domain is known as cytoplasmic domain which is of α helical. Aster the process of ATP binding two lobes and tyrosine which has sequence of protein substrates interrelates with C terminal lobe.

For the process of tyrosine kinase receptor ligand must have to bind with the extracellular space which process then followed by the dimerization process which further followed by the process of trans-phosphorylation in the cytoplasmic domains. (Heldin,1995) In contrast of the tyrosine kinase receptors, the nonreceptor tyrosine kinases activation process is done by various kinds of heterologous protein-protein interaction for trans phosphorylation. (Paul and Mukhopadhyay, 2004)

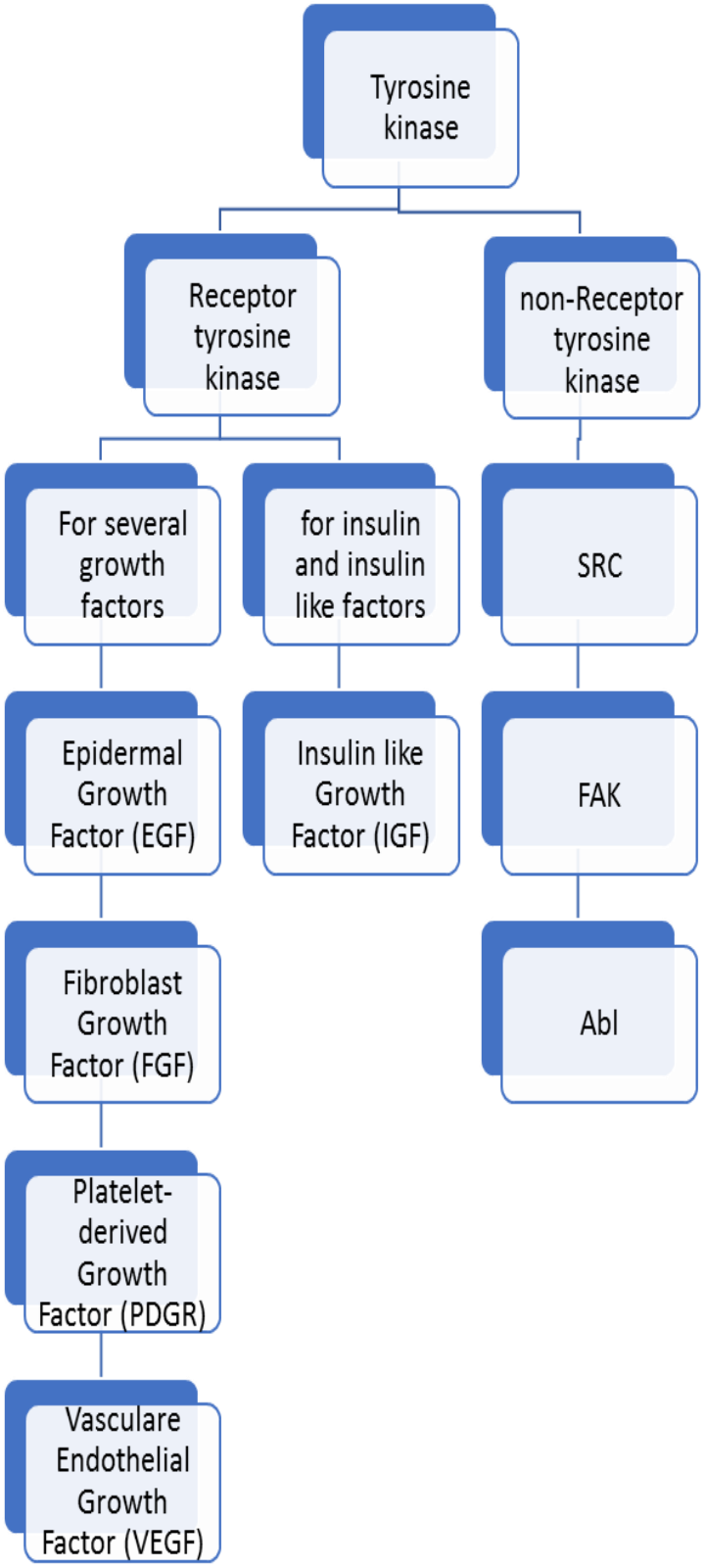


Figure: 3 classification of TKIs

2.3 Action of protein tyrosine kinase

Protein tyrosine kinase residue on targeted proteins and phosphorylate this tyrosine residue. Protein tyrosine kinase activity is regulated by such genetic or epigenetic alteration. Protein- tyrosine kinase activity is occupied in different kind of proliferative situations specially in neoplastic disease. Activated form of this kind of enzymes may cause elevation in dangerous cell growth, accelerate anti-apoptotic effect and increase angiogenesis. Growth-factor binding process promote receptor dimerization as well as tyrosine residues trans phosphorylation. This sector also generates phosphor-tyrosine shadowed by selection of connecter protein growth-factor receptor bound protein 2 (Grb-2). Insulin receptor is also act as receptor tyrosine kinase but shows some different activity from growth factor. Insulin receptor transduces metabolic as well as mitogenic signals. Hence, this with it's receptor accelerate transphosphorylation of cytoplasmic sphere which results in in selection and activation of insulin receptor substrate bi process of phosphorylation on tyrosine residues. Receptor tyrosine kinase consists of Src, Janus kinase (JAKs) and Abelson murine leukemia viral oncogene homolog 1(Abl 1). This is located in cytoplasm & give signal after membrane receptor to cytosol which reaches into nucleus. Non receptor tyrosine kinase shows the activity in in different kind of signalling process like mitogenesis, T & B cell activation and cytoskeleton rearrangement. (Fountas, 2015)

Chapter 3. TYROSINE KINASE RECEPTORS EFFECT ON DIABETES

The insulin receptor is same like transmembrane glycoprotein which consists of two alpha-subunits of 135 kilo Dalton and two beta-subunits of 95 kilo Dalton. Binding of insulin to alpha subunits leads to rapid phosphorylation of particular residue of tyrosine which is present om beta subunits. (Kahn and White, 1988). Various tyrosine containing site present on various receptors are responsible for activation of insulin receptor kinase to tyrosine residues of different protein substrates (Oshima et al, 1990). Diminished activity of insulin receptors for autophosphorylations or for activation of their kinases may cause insulin resistance. This kind of diminished activity also may lead to decreased effect of insulin on biological actions (Klein et al, 1991).

3.1 Signal transmission from insulin receptor:

All the process of signaling including glucose uptake is mediated by such particular cell surface receptors. Insulin signal is transmitted through the plasma membrane for which analysis of each molecular properties should be known.

3.2 Tyrosine kinase role in diabetes

Two efficient domains of tyrosine kinase receptors: - 1) Extracellular 2) Intracellular

1) Extra cellular:

α subunit which containing the majority or the totality of hormone binding site. The α subunit enclose the major insulin binding region of the receptor, and the proposed cDNA sequence for this subunit implies that it is totally extracellular.

2) Intra cellular:

β subunit which possess insulin stimulated tyrosine kinase activity. The β subunit encloses a tyrosine specific protein kinase as well as is auto phosphorylated. This subunit is a transmembrane protein. Concern within the insulin receptor has focused on the kinase purpose of the 3 subunits, either as the means for coupling insulin binding to insulin induced effects or as a parallel manifestation of the coupling process.

•Receptor enzymic function: For generation of metabolic and growth promoting effects of insulin.

•Mechanism: Interaction of insulin with α subunit leads to conformational change which leads to activation of β subunit and activation. This β subunit activation leads to phosphorylation of cellular protein substrates which leads to growth promoting effect and finally this phosphorylated and active substrate results to generate insulin effects. (Lane et al, 1990)

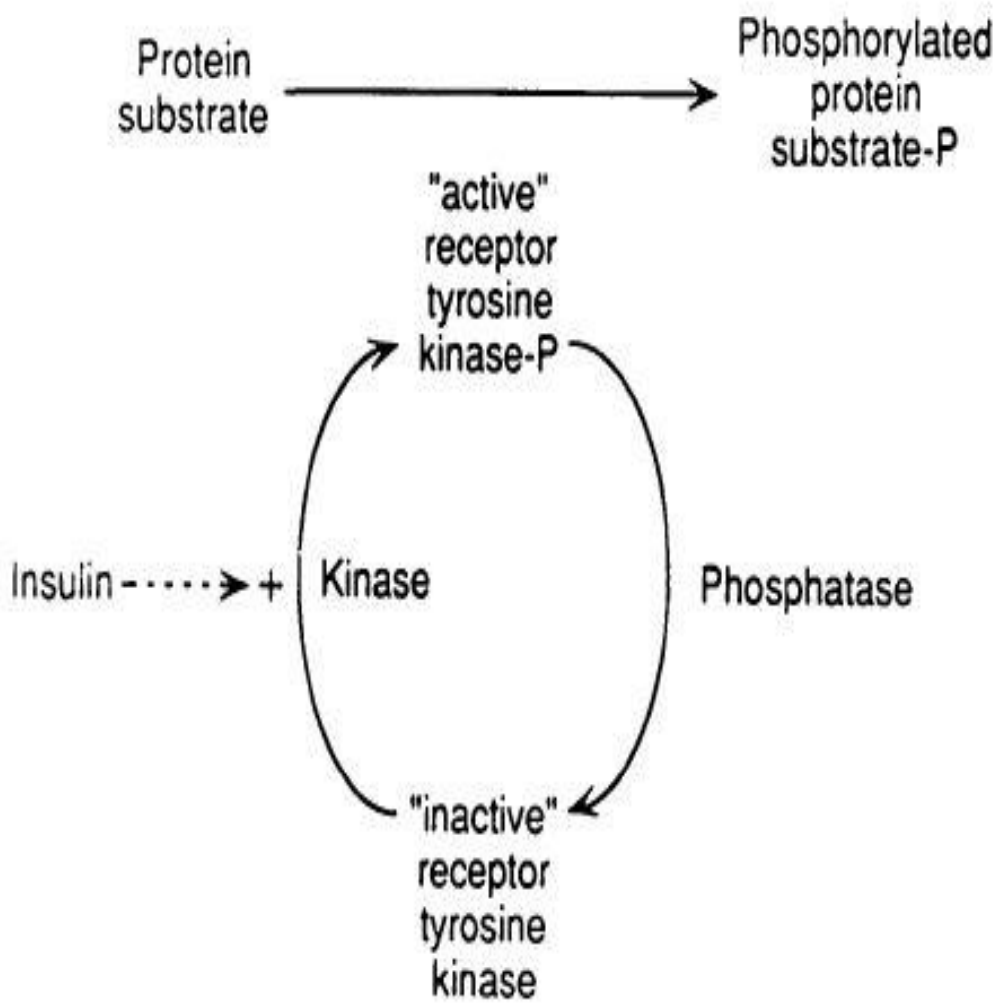


Figure: 4 Autophosphorylation stimulated by insulin stimulation and phosphorylation of protein substrates insulin receptor

CHAPTER 4. TYROSINE KINASE INHIBITORS

so many tyrosine kinase inhibitors which shows different kind of mechanism of action was being approved for so many scientific situations since 2001. Imatinib which is also known as 2 phenyl amino pyrimidine derivative. It is a selective tyrosine kinase inhibitor which mainly acts on c-Abl, PDGFR and SCF receptor c-Kit. Along with this on discoidal domain receptor 1 and 2 (DDR 1 and DDR 2). It is mainly used in chronic myeloid leukemia which is produced by chromosomal trans-location which leads to abandoned activity of divide bunch region Abelson murine leukemia viral oncogene homolog chimeric protein kinase (bcr-Abl) and in bcr-abl positive adult acute leukemia (AAL). In gastrointestinal part, it is secondhand to treat gastrointestinal stromal tumor (GIST) which is results of mutations of c-Kit and distortions. Dasatiinib used in action of ALL and CML specially for the patients who have resistance to imatinib. disturb targets c-Abl, PDGFR, Src. Sunitinib mainly targets c-Kit, PDGFR, VEGFR but not c-Abl and used to treat GIST, renal cell carcinoma (RCC) and neuroendocrine cancers. It is approved in 2006. Sorafenib targets PDGFR-B and FLT2 and 3 which is used to treat renal cell carcinoma. it also inhibits proton oncogene serine and threonine kinase. Erlotinib is used to treat non-small cell lung carcinoma and pancreatic cancer, which mainly targets EGFR mutation. district is approved in 2004.

Drug	Indications	Target
Imatinib	chronic myeloid leukemia, acute lymphoblastic leukemia	c-Abl
Dasatinib	chronic myeloid leukemia, acute lymphoblastic leukemia	c-Abl
Sunitinib	Metastatic renal cell carcinoma	PDGFR
Sorafenib	Renal cell carcinoma	PDGFR
Erlotinib	Pancreatic carcinoma	EGFR

Table 1. list of tyrosine kinase inhibitors

4.1 Adverse properties of TKIs:

TKI adverse effects affect various systems. Common side effects: cutaneous SE that are dose-dependent, rashes and hand foot syndrome. Moreover, cardiovascular actions, like heart failure, hypertension, QT prolongation, left ventricular systolic dysfunction, VEGFR inhibitor is connected to augmented risk of hemorrhage & thromboembolic actions, whereas EGFR inhibitor is drawn in advanced occurrence of pleural distillation, that is dose-dependent, pulmonary arterial hypertension. Gastro-intestinal side things are Mucosal inflammation and diarrhea. Cytopenia is also side effect of it. TKI therapy affect endocrine arrangement. Thyroid disturbances owing toward TKIs treatment. Augmented thyroid stimulating hormone (TSH). Condensed T4 levels. Bone and mineral metabolism Hypophosphatemia and hypocalcemia by associated hyperparathyroidism, disregulation of bone makeover owing towards condensed osteoclastic activity. Development impairment in child and adult, owing toward growth hormone lack, decrease in testosterone concentrations. Gonadal development,

4.2 Potential mechanism of tyrosine kinase inhibitors as antidiabetic

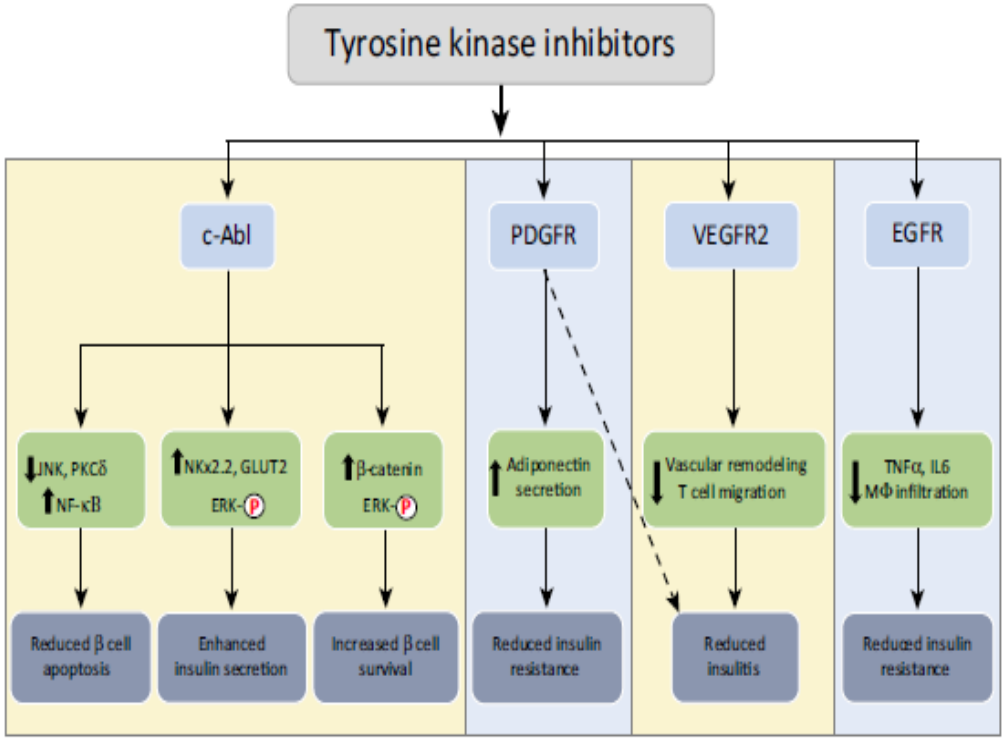


Figure: 5 mechanism of action of TKIs

4.3 c- Abl

c-Abl is type of tyrosine kinase which generally shows the activity of promoting beta cell death upon activation. c-Abl participate in switch of cytoskeleton function, in progression of cell cycle, migration. (Sirvent et al, 2008) Under the condition of cellular stress like oxidative-stress and ER-stress upon activation JNK, c-Abl is triggered which important to cell cycle capture as well as cell death and it inhibits NF-kB activation. Hence, imatinib inhibits activity which protect ourselves from apoptosis in diabetic patient. c-Abl inhibitor like GNF-2 and GNF-5 given with imatinib promotes survival of β cell in contradiction of STZ persuaded apoptosis. c-Abl is collaborated with decreased beginning to JNK & protein kinase δ, that is having a catalytic part in apoptosis of β cell. (Shan et al, 2000) Apart from this, c-Abl also act as a gatekeeper for secretion of beta cell insulin and appearance of the same. Production of beta cell insulin is either positive which means glucose stimulated or negative controlling (Halperin et al, 2012). Sometimes Abl performance as negative regulator for expression of beta cell insulin. This mechanism is regulated by gene expression of NKx2.2, which is a positive regulator for expression of insulin gene and glucose transporter type 2(GLUT2) (Xia et al, 2014). This regulatory mechanism acts on on the function of glucose stimulated β cells as well as latent β cells. Tyrosine kinase inhibitors inhibit these activities and results in increased production of insulin via the help of residual beta-cell. When imatinib is used it also encourage β cell propagation and endurance (Schroeder et al, 2006). This process is based on signaling pathway of insulin thru phosphatidyliinositol-4,5- biphosphate 3 kinase (PI3K), PKB/Akt, beta catenin pathway is responsible aimed at survival of β cell and propagation and purpose of the same. Beta catenin is the most significant go-between of Wnt and equity gesturing which augmented β catenin level and results in anti-apoptotic and proliferative effect in numerous cell types. (Kulkarni et al, 2012). PI3k promote signaling maybe antagonized by src homologous 2. Along with this activates SHIP2 wire phosphorylation which leads to regulation of PI3k pathway by the mechanism of reduction in production of beta catenin and impairs beta cells ability and potential of survival (Schroeder et al, 2006). Hence, by separation of tyrosine kinase receptor upon mechanism of relieving beta cells and activation of SHIP2, leads to beta cell survival by the use of tyrosine kinase inhibitor, imatinib. C-Abl inhibit secretion of low density lipoprotein receptor related protein 1(LRP 1) complex with

extracellular signal regulated kinase phosphorylation and LRP 1 is significant for functioning of beta cell and survival of it. LRP 1 interact with PDGFR results in increased cable for violation that may protect against beta cell death and dysfunction. Hence, act as antagonist by blocking PDGFR induced LRP1 phosphorylation and inhibits AVL which promote ERK phosphorylation (Fred et al, 2015). Abelson tyrosine kinase is targeted by various tyrosine kinase inhibitors. Abelson- tyrosine kinase known by means of Abl-1 and cAbl, transmembrane receptor tyrosine kinase, platelet deriived growth factor receptor (PDGFR), and ABL-related genes (Savage et al, 2002 and Mauro et al, 2002). It was assessed in two types, one of which is type1 and other is type2 diabetes for probable into organization of diabetes as it's distinguished that patients of CML(Chronic myelogenous leukemia) with diabetes whom took Imatinib to regulator CML similarly presented enhancement in his diabetes (Veneri et al, 2005 and Fitter et al, 2010). It is proved that CML patients with type2 diabetes have noticeably raised stages of adiponectin, associating a device for enhanced sensitivity of insulin in the peripheral tissues (Tsapas,2008). Beta cell insulin secretion is induced by Imatinib followed by amelioration of diabetes. Such kind of scientific comments shows that CML patient with type2 diabetes has greater stages of serum C peptide whereas taking c-Abl tyrosine inhibitor (Ono et al, 2012). Similarly, Imatinib treatment expands diabetes over various mechanisms works composed like as long as beta cell survival signals & simultaneously promoting insulin production (Zia et al, 2014).

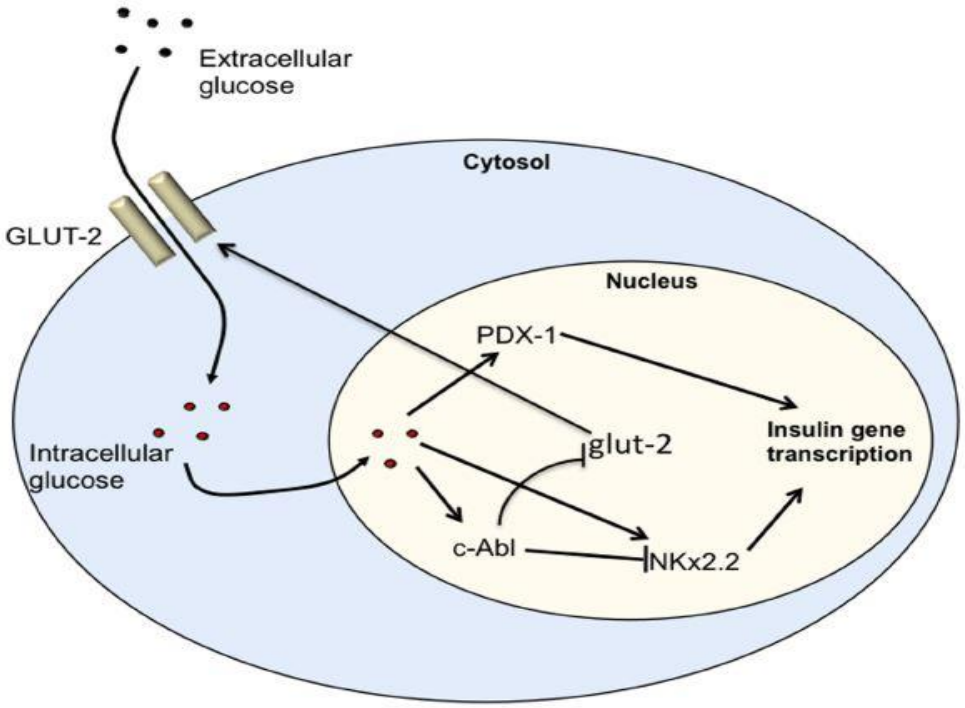


Figure:4 c-Abl regulating insulin gene expression; beta cell up taking signal of glucose upon glucose intra-cellular transport via GLUT 2 transporter regulate insulin gene +ve regulatory factors, like PDX1 and NKx2.2 to improve expression of insulin gene. Alternatively, negative regulatory pathway is initiated by beta cells through regulating cAbl expression, and cAbl in turn down regulates NKx2.2 genes expression and insulin genes, in addition to GLUT-2. beta cell apoptosis and islet inflammation are prevented by Imatinib.

4.4 Mechanism of how c-Abl act as negetive controller:

Insulin expressions in beta cell is controlled by cAbl tyrosine kinase like negative regulator. +ve and -ve regulator for beta cell insulin manufacture is correspondingly significant and are physiologicaly active & working in performance towards switch insulin-production with normal ranges. The effect of c-Abl is significant as a -ve regulator for beta cells insulin expressions. These mechanisms function in both glucoses stimulated beta cells as well as into beta cell at inactive state. c-Abl regulates the PDX-1 expression which is main factor for indorsing manufacture of insulin via presenting which reserve of cAbl by means of Imatinib is not alter the levels of PDX-1 expressions. Furthermore, c Abl tyrosine kinase is not straightly affect pdx1 promoter driven luciferase-reporter gene expressions in a gene transfections cell-

model. NKx2.2 that regulate insulin gene expression related transcriptional-factor, neuroD-1. C Abl overexpression into beta cell reduces genes expression for insulin as well as NKx 2.2 to similar degree. C Abl action has not any association by PDX-1. Inhibition process of c Abl via Imatinib evidently improves NKx2.2 level. Glucose act as the most significant stimulator for insulin secretion physiologically. Inhibition process of c-Abl via Imatinib work in collaboration by glucose inspiration to endorse production of insulin. Glucose stimulation intensely boosted the cAbl expression into beta cells. These reveal an imperative mechanism of insulin secretion, where glucose activate insulin +Ve regulator towards rise production of insulin and too accelerates -ve regulator like c-Abl towards prevention of insulin over-expression. Hence, a suitable level of insulin container be upheld. Therefore, c-Abl act like a significant gate-keeper intended for beta cells insulin expressions as well as emission. Another side by side of adaptable expressions of insulin by c Abl can accompanying with upsetting glucose transporter GLUT 2 on beta cell. Certainly, embarrassment by Imatinib significantly indorsed GLUT 2 expressions on beta cell, that will improve intra-cellular glucose transportation followed by enthused insulin-expressions. As revealed in above figure, glucose transporter GLUT 2 on beta cell transport glucose molecule inside cell, where glucose formerly triggers insulin gene transcriptional regulator, like PDX-1, NeuroD1 and MafA towards control insulin expressions. Alternatively, glucose similarly stimulates c Abl gene expressions as -ve response towards controlling insulin genes expressions and to bound heights of glucose transporters GLUT 2. The judgement of glucose starting these 2 opposite process is still indistinct. Glucose & c-Abl disturb expressions of insulin individualistically nonetheless co-operatively.

4.5 PDGFR

This target for tyrosine kinase inhibitor has mitogenic proliferating result on standard tissue and has frequent compulsive circumstances like lung and kidney fibrosis and arteriosclerosis. (Heldin and Westeermark, 1999) PDGFR signaling is increased in diabetes through hyper-glycemia and low peroxisome proliferator activated receptor Gama and low adipo-nectin and result in resistance of insulin and arteriosclerosis. The plasma level of positive regulator for insulin sensitivity which is called adiponectin

are increased by giving imatinib therapy. (Fitter et al,2010) Imatinib promotes adiponectin secretion by differentiation of human mesenchymal stem cells. (Fitter et al, 2012)

4.6 c-Kit

This tyrosine kinase is inhibited by imatinib, sunitinib and dasatinib. These drugs are implicated in survival of cell and endocrine proliferation as well as pancreatic islets. (Krishnamurthy et al, 2007). C Kit is a significant character in β cells inhibition through may unhelp in diabetes improvement.

4.7 VEGFR

These tyrosine kinases are mainly targeted through sunitinib. Angiogenesis and vasculogenesis is regulated by VEGF, Upon activation of VEGFR2. By the mechanism of increasing Iceland vascularity and imported migration of T cells and by reducing severity of insulitis, VEGFR2 shows their activity (Mukai et al, 2015)

4.8 EGFR

This receptor is collaborated with and initial diminish in TNF-alpha and IL-6 expressions, by decrease in M1 pro-inflammatory macrophages located into adipose tissue. These will result in in development in glucose open-mindedness diminution in resistance of insulin and diminish into IRS-serine phosphorylation into targeted insulin tissue. Erlotinib are the major target of EGFR (Fountas, 2015)

•EGFR shows signaling activity of receptor and normal growth and it affects cell migration, proliferation, motility and apoptosis. This is done by following processes:

1) Ligand binding

2) Trans phosphorylation

3) Ubiquitination: protein degradation

CHAPTER 5. STRUCTURAL MECHANISM OF INSULIN RESISTANCE IN T2DM:

Type 2 diabetes is multifaceted ailment portrayed thru mix of disabled insulin activity, expanded liver glucose creation, & secretory of insulin deformities. Longitudinally examinations propose which variations from the norm in both insulin activity and insulin emission happen right off the bat in the pathogenesis of type 2 diabetes. Hereditary components add towards the pathology of T2DM, the tall predominance in convinced cultural gatherings, & expanded pervasiveness into posterity influenced patients. An atomic stage, different deformities into insulin flagging was appeared towards adding of fringe insulin obstruction, remembering diminishes for insulin receptor no. & proclivity, modified insulin receptor kinases movement, diminishes into phosphorylations of intra-cellular substrate, & variations from the norm in glucose transporters translocation & enactment. Interestingly, guideline for insulin emission as of pancreatic β cell presently can't seem to be totally explained, as a result of its outrageous intricacy, and the atomic system hidden the general brokenness of β cell in type2 diabetes was as yet vague. Sympathetic hereditary qualities for type2 diabetes was muddled via way of which numerous qualities were probably going to associated with pheno-typically various subcategories of patient having type2 diabetes, furthermore in agreed patients having malady. As needs be, impressive exertion has been given to distinguishing qualities that add to this hereditary inclination. In one way to deal with this inquiry, a few gatherings of examiners have screened for the nearness of transformations in up-and-comer qualities whose items have significant capacities in the biochemical pathways managing insulin emission or insulin activity. To be sure, sub-atomic filtering of applicant qualities has brought about the clarification of the hereditary premise of uncommon monogenic types of diabetes with characterized methods of legacy. For example, changes in the insulin receptor quality have been recognized in uncommon disorders of extraordinary insulin obstruction, for example, Leprechaunism and Rabson-Mendenhall. Essential deformities in pancreatics β cell has been exhibited into development beginning diabetes of youthful (MODY), an uncommon types diabetes brought about thru transformations into qualities indoctrination glucokinase, hepatocyte atomic factor (HNF) 1 alpha, and HNF4alpha, HNF1beta, or IPF1. Notwithstanding extreme examination, the hereditary premise of the normal type of

T2DM have not been distinguished. Insulin applies it's different consequences for cells development & digestion via official towards it's cell superficial transmembrane receptors which has a place with the huge group of development factors receptors through characteristic tyrosine kinase movement. Insulin official to the insulin receptor extra-cellular alpha subunit invigorates auto-phosphorylation upon numerous tyrosine deposits of cytoplasmic bit for transmembrane beta subunits. These outcomes into initiation of inborn tyrosine kinase, that catalyze phosphorylation of an assortment of intra-cellular docking protein as well as insulin receptor substrate (IRS) proteins. A few littler connector particles, for example, the development factor receptor-restricting protein Grb-2, Crk, and Nck. The actuation of these SH2 space proteins starts flagging falls, prompting the initiation of various down streaming effector that at last convey insulin sign towards an expanding arrangement in intra-cellular pathway which manage cells digestion, endurance, development, & separation. Ongoing investigations have indicated that a few segments of the insulin flagging pathway assume a job in the development and secretory capacity of pancreatic b-cells. Rats with beta cells explicit disturbance of insulin receptors quality shows disabled insulins discharge because of glucose, and a dynamic glucose narrow mindedness. This information has raised the captivating chance that sub-atomic deformities in insulin flagging may add to fringe insulin obstruction & hindered insulins discharge, the 2 key parts into pathogenesis of T2diabetes. Insulin receptor has been viewed as conceivable competitor quality intended towards T2diabetes. These survey would concentrate upon basic & practical difference in insulin receptor, and will at that point talk about the pathogenetic job of insulin receptor variation structures and polymorphisms into advancement of the normal type of T2diabetes. (Sesti etal,2001)

CHAPTER 6. STRUCTURE OF INSULIN RECEPTOR

Insulin receptors quality are situated upon petite support of chromosomes-19 & covers 22-exons and 21-introns. The develop insulin receptor is a hetero tetrameric glycoprotein made out of two a subunit and two layers spreading over b-subunits connected by disulfide bonds. The insulin receptor is combined as a solitary high atomic weight proprioceptor (Mry180000) which is separated at tetra basic amino corrosive succession (Arg- Lys- Arg- Arg) situated to intersection and beta subunits for yielding a-b monomers. This monomer connection is guaranteed through disulfide bon interfacing Cys647 in alpha subunit with Cys872 in the beta subunits. 2 a-b monomers are associated composed thru interunit disulfide-bond among a Cys524 buildup & comparing buildup into contiguous alpha subunit. Cysteine was proposed shape disulfide connect coming about develop heterotetrametric alpha2beta2 arrangement. The a-subunit is totally extracellular and is answerable for high fondness insulin authoritative. The N-terminal & the cysteine rich spaces are required for high liking authoritative in blend with a COOHterminal area (buildups 704–719). Moreover, the nearness 12 amino corrosive arrangement encode via exon 11 adds adjustment to insulin restricting fondness, talked about beneath. Vacant alpha-subunit represses the inherent tyrosine kinases action of subunits and might see an administrates subunits synergist intracellulars subunits. Evacuation of the alpha subunits via proteolytic cleaving or via cancellation mutagenesis discharges inhibitory impact & initiates inborn kinase. Without ligand insulin receptor alpha subunit keeps up an auxiliary requirement simultaneously dynamic beta subunit kinase. The beta subunit insulin receptor makes out of petite extra-cellular space, transmembrane area, & cytoplasmic area, that was inborn tyrosine kinase movement. Unmistakable useful area has been characterized into intra-cellular part of beta subunit having ATP restricting space (Gly-X-Gly-X-X-Gly) & 3 autophosphorylation destinations situated intracellular juxta membrane locale (Tyr960), into intracellular area (Tyr1158-X-X-X-Tyr1162-Tyr1163), & to COOH-end (Tyr1328 and Tyr1334). Phosphorylation to site-960 into juxta membrane district makes a NPXpX acknowledgment theme for the PTB area of IRS protein, & likewise significant for receptor disguise. Process of tyrosine autophosphorylation buildups in the YXXXXYY of kinase administrative area fundamental of insulin-animated kinases movement & natural activities. What's more, the enacted kinase administrative circle official (KRLB) space is required for

collaboration between a one of a kind districts of IRS2 containing amino acids 591-786 & insulin receptor. (Sesti, 2006)

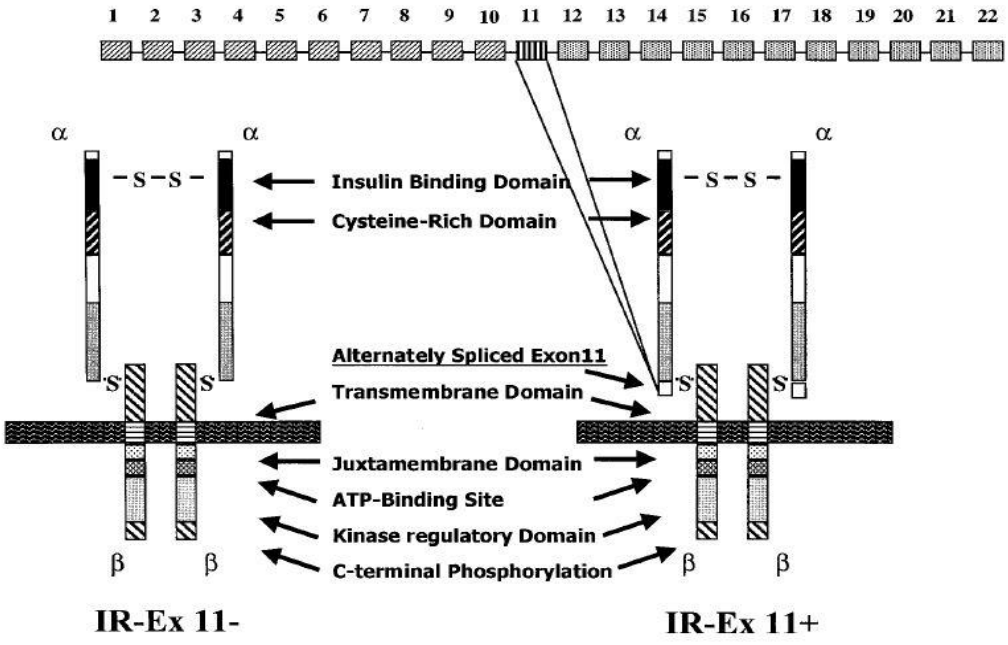
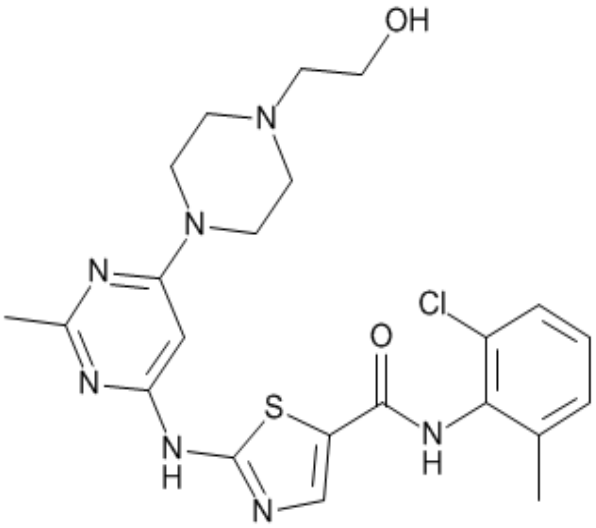


Figure: 6 Insulin receptor structure

CHAPTER 7. DASATINIB

Dasatinib is a drug approved for treatment of chronic myeloid leukemia (CML). It is physiologically a tyrosine kinase inhibitor. It potentially induces PGC-1alfa mRNA so increases protein content up to 6-fold in 3T3 -F442A adipocytes. But dasatinib has treatment had adverse effects on glucose tolerance in Ob/Ob and DIO mice. It is somehow correlated with high hepatic PGC-1 expression and gluconeogenesis genes PEPCK and glucose -6-phosphatase. One of the major players in maintaining glucose metabolism is the transcriptional coactivator PPAR gamma coactivator 1 alfa (PGC -1 alfa. Which regulates program of mitochondrial biogenesis and adaptive thermogenesis. Dasatinib is identified as a potent inducer of PGC-1 alfa , but the normal regulation of PGC-1 alfa in adipose tissue and liver is essential in regulating glucose homeostasis , dasatinib may influence glucose homeostasis. In DIO and Ob/Ob mice this treatment of dasatinib worsened the already impaired glucose intolerance, which is correlated with upregulation of PGC-1alfa mRNA liver expression and induction of gluconeogenesis enzymes such as PEPCK and G6Pase. In humans, the TKI s approved to treat CML have been associated with the metabolic syndrome X and impaired fasting glucose. But according to other study done in 7 CML patients the effect of dasatinib on liver in nonobese patients is less detrimental so in conclusion dasatinib only impairs glucose tolerance in obese mice. So, obese CML patients who are prescribed high dose of dasatinib should be monitored for glucose intolerance.



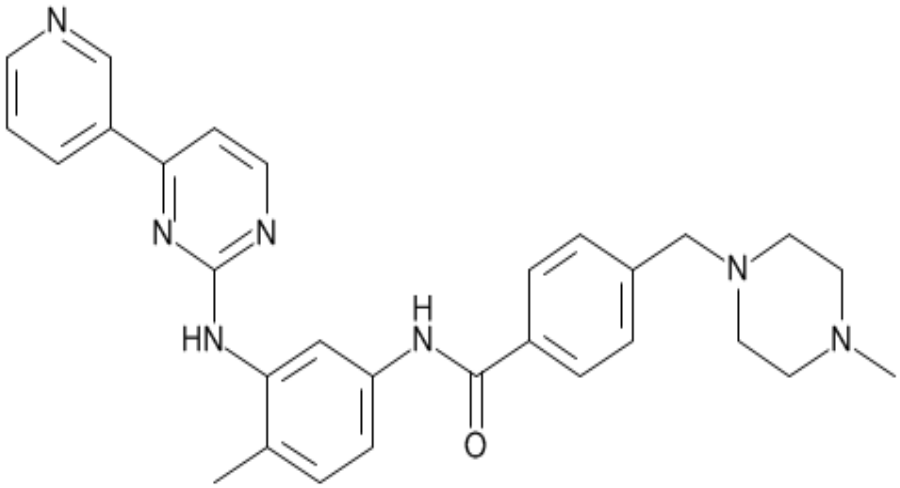
CHAPTER 8. IMATINIB

Mechanism of action:

Imatinib, 2-phenyl amino pyrimidine derivative which functions like precise inhibitor of a number of tyrosine kinase enzymes. It resides in the tyrosine kinase active site, followed by reduction in activity. There are numerous tyrosine kinase enzymes present in the body, as well as the insulin receptor. Imatinib is definite for the tyrosine kinase domain in Abl (the Abelson proto-oncogene), c-kit and PDGF-R (platelet-derived growth factor receptor). In chronic myelogenous leukemia, the Philadelphia chromosome mains to a fusion protein of Abl with bcr (breakpoint cluster region), known as bcr-abl. bcr-abl activity is decreased by imatinib. Each of the active sites of tyrosine kinases having binding site for ATP. The enzymatic activity is catalyzed by tyrosine kinase is the transmission of the terminal phosphate from ATP to tyrosine residues on its substrates, a process called protein tyrosine phosphorylation. Imatinib acts thru binding close to the ATP binding site of bcr-abl, fix it in a closed or self-inhibited conformation, as well as, inhibiting the enzyme activity of the protein semi-competitively.

Side effects:

Nausea, vomiting, diarrhea, Headaches, Leg aches, Cramps in leg/ hands, Retention of fluid, Visual disturbance, Rashes, Bleeding/brushing, Appetite loss, Increase in weight, Less blood cells- anemia, thrombocytopenia, neutropenia, Edema, Restoration of hair color, Cardiac failure



CHAPTER 9. SUNITINIB

Mechanism of action:

Sunitinib inhibits cellular signaling via targeting multiple receptor tyrosine kinases (RTKs). These consists all receptors for platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs), that play a significant role in tumor angiogenesis and tumor cell proliferation. Alternatively, inhibition of targets reduces tumor vascularization as well as accelerates cancer cell apoptosis. Hence, leads to tumor shrinkage. This also prevents CD117 (c-KIT), the receptor tyrosine kinase which drives the majority of gastrointestinal stromal cell tumors. It is used as a second-line therapy for patients who have tumors develop mutations in c-KIT kinase which make them resisted to imatinib and to whom who are not able to tolerate the drug.

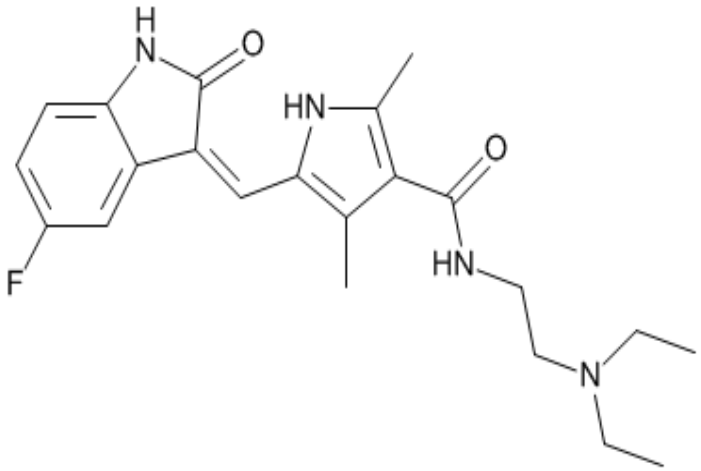
Side effects

Fatigue, nausea, diarrhea, hypertension, anorexia, skin discoloration, foot-hand skin reaction as well as stomates.

placebo included: anorexia, diarrhea, skin discoloration, stomatitis/mucositis, taste alteration, constipation, asthenia.

Hypothyroidism

Lymphocytes, Neutrophils, erythema



CHAPTER 10. SORAFENIB

mechanism of action:

sorafenib, protein kinase inhibitor having activity against protein kinases, constists of VEGFR, PDGFR and RAF kinases. Sorafenib treatment persuades autophagy, that might suppress tumor growth.

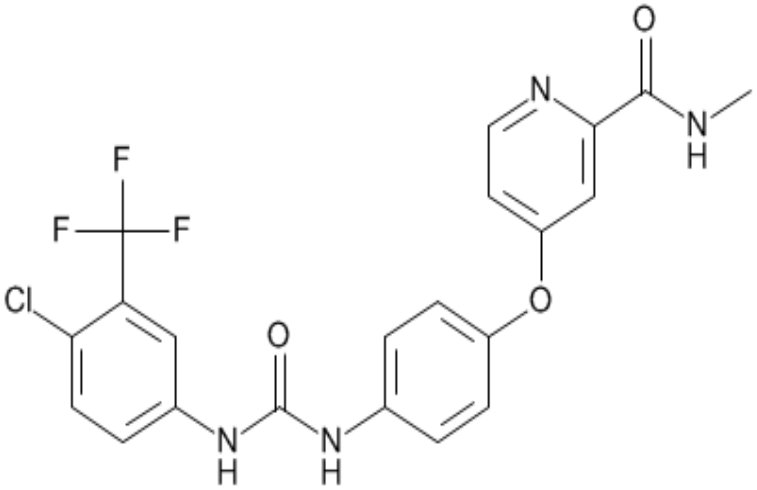
Side effects:

Rash, Hand - foot syndrome, diarrhea, Fatigue, High blood pressure(particularly in first 6 weeks of treatment), Hair loss[thinning or patchy hair loss], Nausea, Itching, Low white blood cell count. This could put you at increased risk for infection, Poor appetite, Vomiting, Bleeding, Increased amylase/lipase blood counts, Low phosphorus level, Constipation, Shortness of breath, Cough, Numbness, tingling or pain in hands and feet, Low platelet count.

risk for bleeding, Dry skin, Abdominal pain

Bone, muscle, joint pain,

Headache, Weight loss



CHAPTER 11. ERLOTINIB

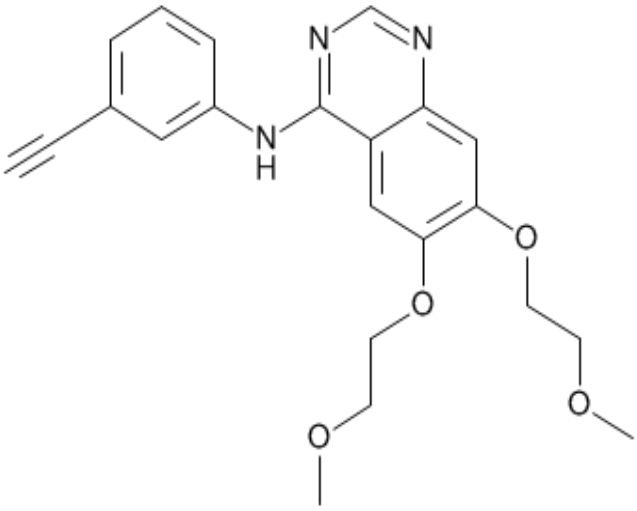
Mechanism of action:

Erlotinib stands an epidermal growth factor receptor inhibitor (EGFR inhibitor). The drug which was the first drug of this type. Erlotinib precisely goals the epidermal growth factor receptor (EGFR) tyrosine kinase, that is extremely expressed and infrequently mutated in various forms of cancer. It fixes in a reversible fashion with the adenosine triphosphate (ATP) binding site of the receptor. For signaling and transmission, 2 EGFR molecules need to composed to form a homodimer. Followed by, using the molecule of ATP to trans-phosphorylate each other on tyrosine residues, that generates phosphotyrosine residues, conscripting the phosphotyrosine-binding proteins to EGFR to gather protein complexes which transduce signal cascades to the nucleus and activate additional cellular biochemical processes. After erlotinib fixes to EGFR, development of phosphotyrosine residues in EGFR may not be possible and the signal cascades are not introduced.

Side effects:

- Rash, acne face and neck, Loss of appetite, Fatigue, Diarrhea, Interstitial pneumonitis, Partial hair loss (by strands, not typically in clumps)

- Ingrown hairs like eyelashes, fatal gastrointestinal tract perforations, skin toxicity: Stevens–Johnson syndrome, toxic epidermal necrolysis, exfoliative skin conditions, blistering, Disorders ocular: lesions corneal, Pulmonary toxicity: pulmonary fibrosis, bronchiolitis obliterans with organizing pneumonia (BOOP)



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