ISSN 2348-313X (Print)
International Journal of Life Sciences Research ISSN 2348-3148 (online)
Vol. 3, Issue 1, pp: (60-66), Month: January - March 2015, Available at: www.researchpublish.com

Histamine Receptors as Drug Targets in Current and Future Therapeutics

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***Abstract*: Histamine and histamine receptors are and will always be fruitful concern for the upcoming pharmacologists. Histamine is the most important mediator of mast cells in immunonureal signal transduction. They have a promising future in helping to form the main link in identification of new avenues in drug targeting to treat many disorders in mankind. Due to fascinating properties of histamine such as role in modulation of proliferation with in various malignant and normal cells in the body and its receptor's role in biological actions its value is enhanced. Considerably important discoveries done by scientists over several years has made its contribution to our basic knowledge of role of histamine and its receptors in paracrine and autocrine proliferation and its key value in pathological, physiological circumstances exposing novel functionality for paving the way for better perspectives and scopes in pharmacological drug research.**

***Keywords:* Histamine receptors, inflammation, drug therapeutics, histaminergic, drug targeting, antagonists, cell signalling.**

I. INTRODUCTION

Dale and Laidlaw in 1910 were the first two observe the biological effect of histamine. In the early 1930's, Bovet and Staub first discovered antihistamine. Histamine receptors have been enormously valuable as a tool in drug targeting since many years for the regulation and treatment of diseases and served human race. Histamine action is mediated by 4 G – protein coupled receptors [18].They influence the ion channel's opening and change the amount of intracellular messenger (Ca^{2+} ions and cyclic AMP).Role of histamine receptors in cytokines and in immunology still need more information. The scope and research are advancing in this field continuously. The newly discover H3 and H4 receptors have importance in cancers and other cognitive disorders and can be handy tool for targeting to achieve immensely high drug candidate. It serves as classic tool for elucidation of basic pharmacologic principles for drug receptor targeting and interaction [6].

New knowledge gained through present research has given its potential regarding therapeutic roles. Several pathways are influenced by histamine receptors which occur in various neurological disorders. Now a day's drug discovery and development is taking benefits of histamine receptors increasingly to broaden their horizon for search of new therapeutic compounds. Pharmacological drug development has been run by key availability of main component that is specific receptors and site for binding and has scope for therapeutic analysis if the action is enhanced or inhibited but now the focus is drifting towards search about appropriate agonists and antagonists [11].

II. H1 RECEPTORS

A. Mechanism of action:

H1 receptor antagonists have the main task of down regulation of H1 receptors activity. Histamines binds to receptor that activate G protein which further activates phospholipase C (PLC) and the signal transduction mechanism occurs as shown in fig 1.H1 receptors helps in activation of phosphatidylinositol which thereby leads to increase amount of inositol tris phosphate (IP3) and diacylglycerol (DAG); that further leads to triggering of Ca^{2+} release and activation pathway occur as depicted in figure 1.

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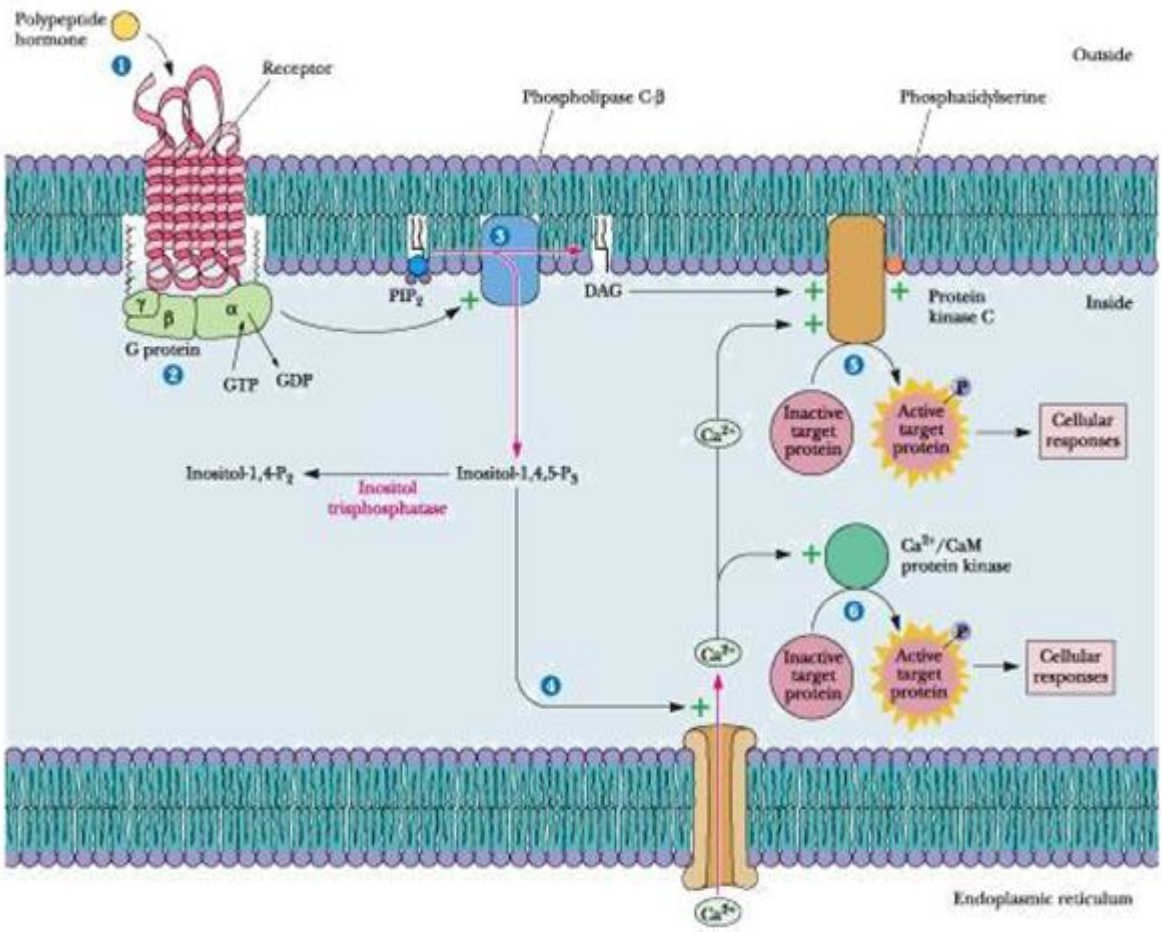

Figure 1- Ca^{2+} release and activation pathway

B. Function and location of H1 receptors:

H1 receptors occur usually on vascular endothelial cells and smooth muscle cells. They stimulate tissue- specific responses like bronchoconstriction, oedema, sensitising primary afferent nerves, inhibition of further release of histamine by acting as auto receptors in hypothalamus.

C. Future therapeutic of H1 receptors:

It is very evident that H1 receptor signalling is quite important in allergic reactions. As these reactions are multifactorial, developmental of new therapeutic targeting disease- sensitive gene is very much expected by the help of using novel therapy approach, done by different drug having various gene expression. We can use the fact that H1 receptor when up-regulated increases the signalling pathways [9]

III. H2 RECEPTORS

A. Mechanism of action:

Competitive inhibition of histamine at H2 receptor of parietal cells, thereby do inhibition of gastric acid with an advantage of reduction of gastric volume and concentration of hydrogen ions. Cimetidine is the most widely used H2 receptor antagonists. Its mechanism of action is for minimizing hepatic metabolism of drugs that are in the end biologically converted by cytochrome P 450 mixed oxidase system by either delaying the removal of these pharmacological agents or enhancing serum levels of these agents.H2 receptors help in stimulation of adenylyl cyclase also stimulates intracellular reactions through formation of second messenger cyclic AMP [15]

B. Pharmacological effects and location of H2 receptors:

H2 receptor antagonists like famotidine, ranitidine are generally used in the treatment of gastric, duodenal ulcers,

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oesophageal reflux. Their metabolism is done by liver.H2 receptors have their presence in enterochromaffin cells of gastric mucosa. They help in reduction of pepsin secretion.

Selective agonists include apromidine, impromidine. Due to activation of H2 receptors there is gastric secretion, high ratio of contraction of atria in heart and all these effects can be blocked by H2 receptor antagonists which are now being used for treating peptic ulcers [17].

C. Current therapeutics:

H2 receptors antagonists were first synthesized in 1970, and made their entry in scientific era. The fact that imidazole ring was important in H2 antagonism, this retrieval ranitidine came into picture. At the moment four H2 receptor antagonists are there in the market [12]

D. Future therapeutics:

Reversible competitive inhibition for histamine binding to H2 receptor is exhibited by H2 receptor antagonists. Approximately 90% inhibition of gastrin-induced acid secretion take place, thereby representing the usefulness in gastrin stimulated secretions. Due to the fact, that achievement of complete basal acid secretion can be realised and world-widely used in clinical drug therapeutics for diseases related to acid, where an agent is required to decrease the acidic secretion. Drugs acting on H2 receptors are in developing process for treating epilepsy, obesity and sleep disturbances [7]

IV. H3 RECEPTORS

A. Mechanism of signalling pathways of H3 receptors:

Due to activation of H3 receptor-mediated Gi/o proteins, different signalling pathways are activated and inhibited. When Gi/o proteins are activated; leads to reduction of cAMP levels and gene transcription[12] these activation also leads to the activation of several others second messengers pathways [10] which includes PI3K pathway, inhibition of Na+/H+ exchanger, reduction of intracellular Ca^{2+} levels by modulation of voltage gated ion channels, MAPK pathways as shown in fig 2.

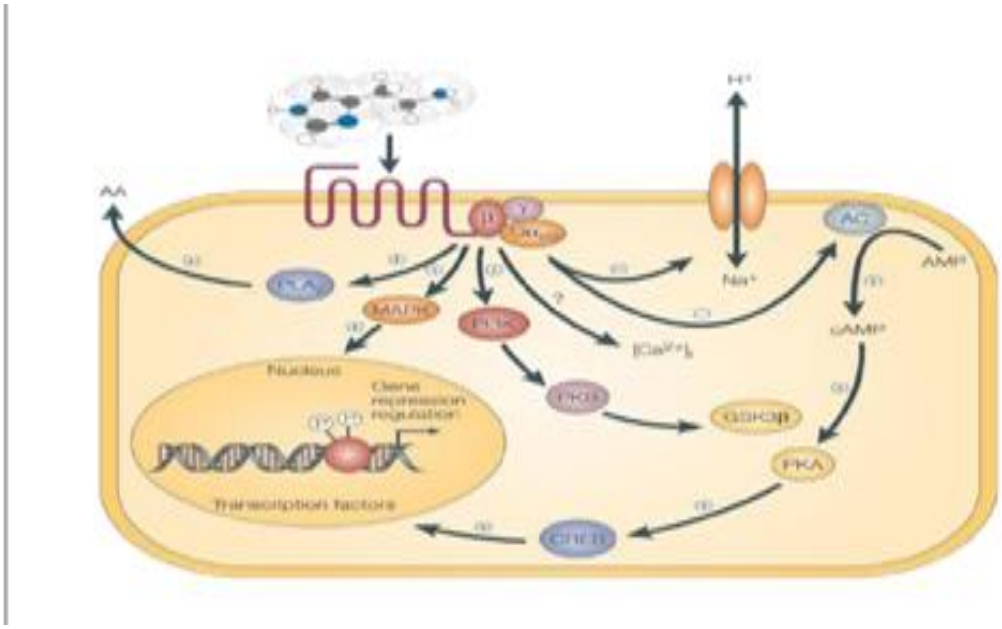

Figure 2- MAPK pathways

B. Location of H3 receptor and therapeutic role of histaminergic drugs in potential drug targeting:

H3 receptors are presynaptic, there location is on histaminergic neurons and they give negative feedback for controlling histamine synthesis and release [1]. Research on H3 receptors has made its evidence as auto receptors. Its cloning is still under observation. Its initial detection was auto receptors controlling the synthesis of histamine and its release in brain. So it seems that it does inhibition of presynaptic ally release of other monoamines in brain and peripheral tissues.

Till date, attempts for the isolation H3 receptor gene have been unsuccessful. So the molecular structure of H3 receptors has not yet been established. Various studies point to the fact of involvement of Gi/Go proteins in the coupling of H3 receptors. Like in the case of Pertussis toxin; abolishment of H3 receptor does mediation of stimulation of GTP-γS binding. In vascular smooth muscle, H3 receptor increases Ca^{2+} currents which are voltage-mediated through pertussis-insensitive G-protein [16].

The auto inhibitory effect of histamine shows high pharmacological specificity.

C. Anti-obesity effects of H3 receptor antagonists:

There is a central role of H3 receptors and their importance on neurotransmission in the region of brain; so this makes these receptors, a promising drug target for agents of anti-obesity. Several preclinical investigation show that blocking of H3 auto receptor aggravates release of CNS histamine from histaminergic neurons causing alteration in body weight [6]

D. Imidazole-based H3 receptor antagonists:

Thioperamide is a prototype of imidazole- based H3 receptor antagonists. It was used for the effective study of role of H3 receptor in regulation of appetite and feeding. When research was done, thioperamide revealed that H3 receptor has involvement in regulation of consumption of food in rats by neuropeptides. Ciproxifan, is also a well-known H3 antagonist for whom there are evidences of property of anti-obesity when it is given orally in peripheral cells; this drug elevates levels of histamine in hypothalamus [2]

E. Non imidazole-based H3 receptor antagonists:

Recent publications suggest that H3 antagonists having no imidazole moiety are effective in reducing weight in various animal models of obesity. Several non-imidazole-based H3 receptor antagonists have been researched and characterisation has been done by many scholars and research teams. These compounds have high potent drug to drug interaction and selective potential for H3 receptor with low pharmacological dissimilarities within species have very good CNS penetration.

F. Future therapeutics:

H3 receptor is different from other subtypes in location, function as it is prejunctionally located and exerts inhibitory effect on humoral and neural mediators.

Over many years; biochemical aspects and functional characterization of H3 receptors is the topic for huge investigation [5].

The major advancements in H3 receptor field occurred with high selective and discovery of enormously potent antagonists and agonists was done [10] which unfolded functionality of this receptor in various tissues.

G. H3 receptor as a new drug target in Alzheimer disease and other age-related disorders of memory:

It is a neurodegenerative brain disorder that leads to memory loss, dementia and then patients reveal that there is decrease in levels of histamine which leads to changes in central histaminergic system. This can be taken ad one of factors which leads to cognitive impairments. Agents like H3 receptor antagonists give extra benefit in restoration of cognitive ability in AD patients by modulatory effect. These agents can increase release of neurons and allow cognitive processing. Disruptions in sleep/wake cycles can also occur. This shows the normal loss of neuron related with ageing and similarly can be utilized with usage of H3 antagonists [13].

H3 receptor antagonists can give us a novel approach for AD's treatment. These receptors are hugely distributed in brain of mammals, specifically in cognition and arousal areas like cerebral cortex, hypothalamus, hippocampus and basal ganglia. Blocking H3 receptors through antagonists can inhibit the release of various neurotransmitters like histamine, dopamine, Ach and adrenaline.H3 antagonists recently are under clinical trials and till date no efficacy of data has been revealed but they pose greatly for symptomatic approach for treatment of AD [14].

V. H4 RECEPTORS

H4 receptor contains 390 amino acids and is the most recently found histamine receptor. A intron-containing gene encodes it on chromosome 18. It can do inhibition of adenylyl cyclase activity. H4 receptor is present in various

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inflammatory cells which includes eosinophils, mast cells, T-lymphocytes, dendritic cells, monocytes [19]. So it serves as an important drug target in allergy and auto-immunity.

A. Molecular mechanism and intracellular Signalling of H4 receptor

H4 receptor gene is structurally similar to H3 receptor gene, as it has 3 exons and 2 introns.H4 receptor has main coupling to Gi/o proteins, when stimulated results in lowering production of cyclic AMP and totally inhibits events like cyclic AMP responsive element-binding protein-dependent gene (CREB) transcription.it has been investigated and proved that mediation od mast cell chemotaxis by H4 receptors is done by this mechanisms of Gi coupled reduction in CAMP shown below in fig 3 [3].

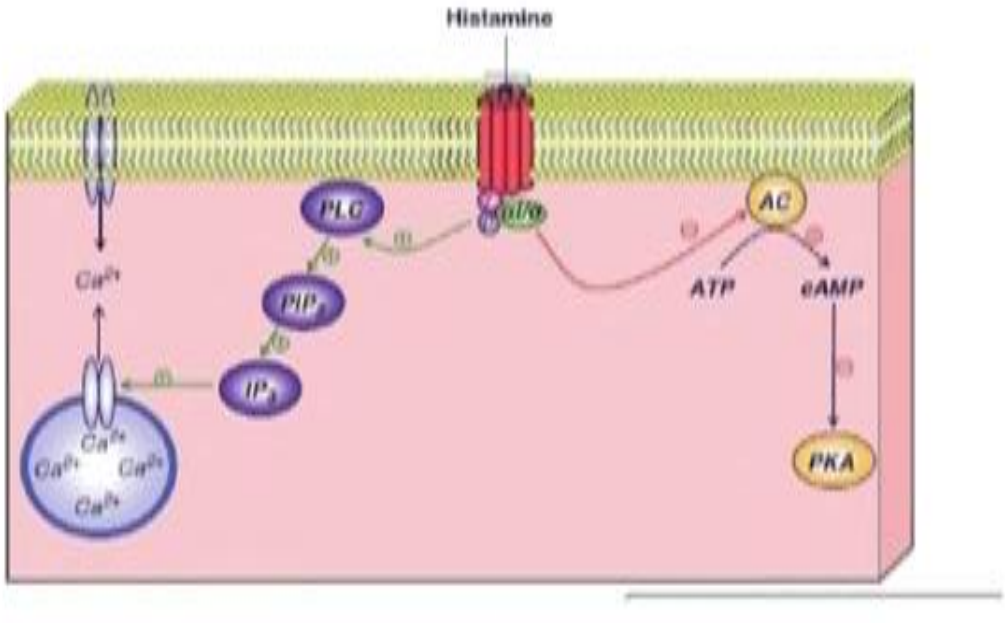

Figure 3- N- mechanisms of Gi coupled reduction in Camp [3]

B. Current therapeutics:

H4 agonists-a number of ligands can act as agonist of H4 receptors. These comprises of immepip, prioxyxan, N-methylhistamin, imetit [11]

C. H4 antagonist:

They include promethazine, cinnarzine, doxepin, thiopremide, clobenpropit which have high binding affinity with H4 receptors [8]

D. Future therapeutics:

H4 receptor discovery is an indication of new avenues of pharmacology and genetics. Cloning of H4 receptor to identify various kinds of selective ligands for treating inflammatory and allergic diseases can be done. Research shows that if H4 receptors are stimulated, they result in mediation of cell signalling and chemo taxis of mast cell [4]. Here, specific H4 antagonist can be tool of important in the treatment of allergic in the future. Another views shows that there are more chances for H4 antagonist to have therapeutics uses as neither H1 nor H2 antagonist can do inhibition of histamine induce congestion[7]

VI. CONCLUSION

H1 and H2 subtypes are very well investigated but H3 and H4 are still the topic of upcoming research. H1 receptor helps in mediation of allergic reactions and inflammation whereas H2 receptor is primarily responsible to mediate gastric secretion in human body. The newly found H3 and H4 receptors are still in the process of exploration for using them as drug targets in drug therapeutics [7]

REFERENCES

[1] Arrang, Bahn S. and Hemby E. S. (2006) Functional Genomics &Proteomics in Clinical Neuroscience 2nd edition Elsevier P O Box 256 Amsterdam, Netherland Available at library of University of Bedfordshire, Luton campus (Accessed : 18 November, 2011)

[2] Divya Vohra (2008) The Third Histamine Receptor: Selective Ligands as Potential Therapeutics in CNS Disorders Taylors &Francis Group CRC Press ltd. Boca Raton 12789 Available at Luton Library Centre (Accessed : 17 November, 2011)

[3] Falus Andras (2006) Immuno genomics and Human diseases Semmelweis University,

[4] Budapest, Hungary john Wiley & son's ltd. West Sussex England Available at lrweb.beds.ac.uk/ (Accessed: 17 November, 2011)

[5] Gugleitta Antony and Gaginella S. Timothy (2000) Drug Development: Molecular Target for GI Diseases Humana Press ltd. England 23786 -89-48 available at digital library of University of Bedfordshire, Luton campus (Accessed: 18 November, 2011)

[6] Hancock A. Arthur and Brune Gerard (2005) Cognitive enhancing effects of drugs that target histamine receptors Neuroscience Research, Abbott Lab, 100 Abbott road, USA [online] available at web.ebscohost.com.brum.beds.ac.uk/ (Accessed: 15 November, 2011)

[7] Howarth, Jim Skewer, Golan E. David (2000) Principles of Pharmacology: the Pathophysiology basis of drug therapy Lippincott Williams and Wilkins ltd .530 walnut streets Philadelphia USA [Online] Available at lrweb.beds.ac.uk/ (accessed: 16 November, 2011)

[8] Iversen L. Leslie, Iversen Susan, Bloom E. Floyd, Roth H. Robert (2009) Introduction to Neuropsychopharmacology Oxford University Press ltd. Oxford [online]Available at pubmed.beds.ac.uk/ (Accessed : 18 November, 2011)

[9] Khardori Nancy (2010) Biomedical Aspects of Histamine: Current Perspectives Springer Dordrecht Heidelberg New York Springer: Science Media [online] available at web.ebscohost.com.brum.beds.ac.uk/ (Accessed: 15 November, 2011)

[10] Leurs, Hofferman Stefan, Walter (1995) Molecular Pharmacology volume 1 Springer-Verlag Heidelberg New York: Springer Science Media [online] Available at advances in science and biology (Accessed: 16 November, 2011)

[11] Lim, Zuearth, Hollinger A. Manfred (2005) Introduction to Pharmacology 2nd edition CRC Press USA available at www.lrweb.beds.ac.uk/ (Accessed: 15, November, 2011)

[12] Lovenberg, Keri Gyorgy and Toth Istvan (1999) Molecular pathomechanisms and new trends in drug research Smith, Klein and French press (SK&F) available at library University of Bedfordshire, Luton campus (Accessed :16 November, 2011)

[13] Okamoto, T.; Iwata, S.; Ohnuma, K.; Dang, N. H.; Morimoto, C. (2009) Histamine H1- receptor antagonists with immunomodulating activities: potential use for modulating T helper type 1 (Th1/Th2) cytokine imbalance and inflammatory responses in allergic diseases. Clinical & Experimental Immunology, Vol. 157 Issue 1, p27-34, 8p, 1 Diagram, 2 Charts, 2 Graphs; DOI: 10.1111/j.1365-2249.2009.03958.x

[14] Pawankar Ruby, Holgate T. Stephen and Rosenwasser J. Lammy (2009) Allergy Frontiers: Classification & Path mechanisms Volume 1 [online] Available at lrweb.beds.ac.uk/ (Accessed: 18 November, 2011)

[15] Rose S. (2004) gastrointestinal and hepatobillary path physiology Hayes and Barton Press Raleigh North Carolina USA ISBN- 597777-178-89 available at the library of University of Bedfordshire, Luton campus (Accessed: 17 November, 2011)

[16] Roumestan, C.; Henriquet, C.; Gougat, C.; Michel, A.; Bichon, F.; Portet, K.; Jaffuel, D.; Mathieu, M.. (2008) Histamine H1-receptor antagonists inhibit nuclear factor-kappa and activator protein-1 activities via H1-receptor-

dependent and -independent mechanisms. Clinical & Experimental Allergy, Vol. 38 Issue 6, p947-956, 10p, 1 Diagram, 4 Graphs; DOI: 10.1111/j.1365-2222.2008.02990.x

[17] Shimizu, T.; Nishihira, J.; Watanabe, H.; Abe, R.; Ishibashi, T.; Shimizu, H. (2004) Cetirizine, an H1-receptor antagonist, suppresses the expression of macrophage migration action. Clinical & Experimental Allergy, Vol. 34 Issue 1, p103-109, 7p; DOI: 10.1111/j.1365-2222.2004.01836.x

[18] Thurmond Le Roy Robin (2008) Histamine in inflammation Austin, Tex.: Landes Bioscience; New York: Springer Science Business Media [online] available at www.advances in experimental medicine and biology// v. 709 (Accessed: 15 November, 2011).

[19] Zhang, Nijkamp P. F., Pranham J. Michael (2007) Principles of Immuno pharmacology Scottish press ,Ireland Available at Luton library centre, Luton (Accessed : 16 November, 2011).