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REVIEW

New perspectives on exploitation of incretin peptides for the treatment of diabetes and related disorders

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Abstract

The applicability of stable gut hormones for the treatment of obesity-related diabetes is now undisputable. This is based predominantly on prominent and sustained glucose-lowering actions, plus evidence that these peptides can augment insulin secretion and pancreatic islet function over time. This review highlights the therapeutic potential of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), oxyntomodulin (OXM) and cholecystokinin (CCK) for obesity-related diabetes. Stable GLP-1 mimetics have already been successfully adopted into the diabetic clinic, whereas GIP, CCK and OXM molecules offer promise as potential new classes of antidiabetic drugs. Moreover, recent studies have shown improved therapeutic effects following simultaneous modulation of multiple receptor signalling pathways by combination therapy or use of dual/triple agonist peptides. However, timing and composition of injections may be important to permit interludes of beta-cell rest. The review also addresses the possible perils of incretin based drugs for treatment of prediabetes. Finally, the unanticipated utility of stable gut peptides as effective treatments for complications of diabetes, bone disorders, cognitive impairment and cardiovascular dysfunction is considered.

Key words: Diabetes; Obesity; Incretin; Prediabetes; Gut hormones

Core tip: Stable gut hormones have well defined therapeutic actions for type 2 diabetes mellitus. In addition, simultaneous modulation of gut hormone receptors could increase therapeutic efficacy, but timing and receptor activation profile may be important. Finally, gut-derived peptides could possess benefits for bone disorders, cognitive impairment and cardiovascular dysfunction.

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INTRODUCTION

The human gastrointestinal tract (GIT) comprises the stomach, as well as the small (duodenum, jejunum

and ileum) and large (caecum, colon and rectum) intestines. Aside from nutrient digestion, absorption and assimilation, the GIT also has significant endocrine functions[1]. To date, the most important endocrine function of the gut relates to evidence that intestinal derived peptides are fundamentally involved in postprandial insulin release[2]. This action is termed the "incretin effect", and relates to the direct beta-cell insulin secretory effect of two hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) that are secreted from L- and K-cells, respectively (Figure 1)[3]. A number of other enteric peptide hormones released in response to feeding also have a role in energy regulation and possibly insulin secretion, including cholecystokinin (CCK) and oxyntomodulin (OXM) (Figure 1)[4,5]. However, only GLP-1 and GIP fulfil the criteria of a true incretin hormone that stimulates glucose-induced insulin secretion at physiological circulating concentrations[3]. Despite the obvious potential of incretin and incretin-like peptides for the treatment of conditions such as diabetes and obesity, the extremely short biological half-life of these peptides, due to efficient enzymatic degradation and subsequent renal filtration, severely limits therapeutic applicability[4,5]. However, interest in gut peptides has increased in recent years with knowledge that modified versions of these compounds, with vastly improved pharmacokinetic properties, have sustained beneficial physiological effects[6].

GLP-1

The biological actions of GLP-1 are largely preserved in type 2 diabetes and pharmacological doses of the peptide evoke robust insulin-releasing and antihyperglycaemic effects[7]. GLP-1 exerts its beta-cell effects through interaction with specific surface receptors that activate signal transduction pathways including the stimulation of intracellular cAMP mediated events[8]. GLP-1 also promotes beta-cell proliferation and islet cell neogenesis as well as inhibiting beta-cell apoptosis and alpha-cell glucagon secretion[8]. Notably, both GLP-1 and GIP expression and secretion has been described in islet alpha cells[9,10]. Indeed, it is feasible that intra-islet, rather than gut derived, GLP-1 and GIP make a significant contribution to these direct beneficial islet effects[11-13]. However, it should be noted that positive direct islets effects are still noted in rodents following prolonged exogenous delivery of stable GLP-1 mimetics[8].

GLP-1 not only targets pancreatic islet cells, but imparts positive actions in terms of inhibition of gastric emptying, suppression of appetite and weight loss[8]. Given this advantageous biological action profile, there are now several GLP-1 related enzyme-resistant, long-acting analogues available for clinical use in diabetes (Table 1), ranging from regimens that require twice daily injection to those that necessitate only once weekly administration[14]. Development of new GLP-1 mimetics, such as those conjugated to an antithrombin Ⅲ-binding pentasaccharide, are also in the pipeline[15]. Interestingly, a recent commentary highlights that differences in the structure and pharmacokinetics of currently available GLP-1 mimetics could significantly alter immunogenicity, CNS signalling and overall therapeutic effect[16]. Thus, physicians may need to re-evaluate the most appropriate GLP-1 treatment strategy for each patient. Encouragingly however, GLP-1-R agonists demonstrate an efficacy approaching that of insulin treatment, but unlike insulin have the added benefits of promoting weight loss with minimal risk of hypoglycaemia[17].

Despite the widespread use of GLP-1 mimetics (Table 1), there have been recent safety concerns regarding the ability of sustained GLP-1-R activation to cause pancreatitis, pancreatic and thyroid cancer, as well as glucagon-producing neuroendocrine tumours in man[18,19]. As such, it is well recognised that pancreatitis is a risk factor for pancreatic cancer[20]. However, a recent meta-analysis did not support increased risk of pancreatitis or cancer associated with GLP-1 therapy[21]. Indeed, issues with poorly matched patient groups treated with incretin-based *vs* non-incretin-based medications and problems with specifically identifying glucagon-producing cells also calls into question the validity of these safety concerns[22]. Thyroid cancer fears appear to stem largely from rodent studies[23], and reduced expression of the GLP-1 receptors in human, as opposed to rodent, thyroid cells is the likely explanation for this[24]. The most frequently reported side effect of GLP-1 therapy is dose-dependent and transient mild to moderate nausea, vomiting and diarrhoea[16]. Thus, taken together the safety profile of GLP-1 based therapeutics is largely reassuring. However, pharmacovigilance with GLP-1 drugs is still required, especially in relation to patients with a history, or increased risk, of pancreatitis or thyroid cancer.

GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE

Although initially thought to play a role in impeding histamine induced gastric acid secretion[25], the primary physiological role of GIP is now considered to be stimulation of postprandial insulin secretion[13], The insulinotropic action of GIP, mediated by specific receptors on the surface of pancreatic beta-cells, is initiated largely by intracellular cAMP generation (Figure 1) and subsequent Ca^{2+} ion influx leading to insulin granule exocytosis[13]. An additional beneficial action of GIP involves enhanced survival of beta-cells, which is also mediated through cAMP dependent cell signaling pathways[26,27]. GIP also acts as beta-cell growth factor by stimulating mitogen-activated protein kinase pathways[28] and modulating K_{ATP} channel expression[29]. Given this impressive bioactive profile at the level of the beta-cell, there has been significant interest in the potential for GIP-based pharmaceuticals as antidiabetic

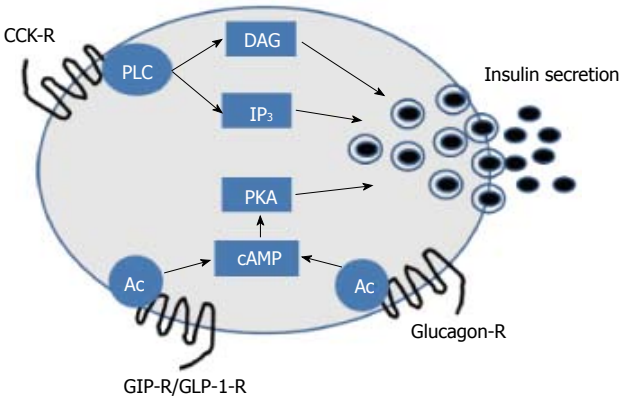

Figure 1 Schematic depicting the major signalling pathways involved in glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, glucagon and cholecystokinin induced insulin secretion from pancreatic beta-cells. AC: Adenylyl cyclase; cAMP: Adenosine 3'-5'-cyclic monophosphate; DAG: Diacyl-glycerol; IP_3: Inositol 1,4,5-trisphosphate; PKA: Protein kinase A; PLC: Phospholipase C; CCK: Cholecystokinin.

drugs. However, like GLP-1 the pharmacokinetic profile GIP is severely hindered due to rapid plasma degradation by the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-4), and clearance cleared from the body by efficient renal filtration[30]. In addition to this, the biological effects of GIP appear to be markedly reduced in patients with type 2 diabetes when compared to normal individuals[7].

The first of these barriers has been conquered, as with GLP-1 mimetics, through generation of N-terminally modified enzyme-resistant, long-acting GIP molecules, and these molecules has been reviewed extensively elsewhere[31,32]. However, the issue of reduced GIP responsiveness in type 2 diabetes still remains, and is thought to be linked to GIP receptor (GIP-R) down-regulation or desensitisation[7]. However, it is highly likely that that GIP desensitisation is a pathophysiological consequence as opposed to an aetiological factor of type 2 diabetes. In keeping with this, studies correcting hyperglycaemia using insulin or sulphonylureas indicate that GIP sensitivity can be restored[33,34]. It has also been demonstrated that a K-cell derived peptide co-secreted from the intestine with GIP, xenin-25, can potentiate the insulinotropic action of GIP[35,36]. As such, a novel long-acting palmitate-derivatised analogue of xenin-25 was shown to significantly augment GIP action *in vitro* and *in vivo*[37]. Moreover, sustained administration of this acylated xenin peptide exerted a spectrum of beneficial metabolic effects in high-fat-fed mice[38]. This presumably relates to restoration of GIP action in these diabetic mice[38]. In harmony with this, a recent study indicates that the impaired insulinotropic response to GIP under diabetic milieu involves mechanisms beyond simple expression of the GIP-R[39], further highlighting a potential role for xenin. Therefore, there still appears to be significant, as yet untapped, therapeutic potential for GIP-based compounds, especially in combination with molecules that can enhance GIP sensitivity directly or counter hyperglycaemia through other actions.

Table 1 Incretin-based drugs currently approved by the European Medicines Agency

Drug name	Primary mechanism of action	EMA approval date
Exenatide	GLP-1 receptor agonist	Nov-06
Sitagliptin	DPP-4 inhibitor	Mar-07
Vildagliptin	DPP-4 inhibitor	Sep-07
Liraglutide	GLP-1 receptor agonist	Jun-09
Saxagliptin	DPP-4 inhibitor	Oct-09
Exenatide-LAR	GLP-1 receptor agonist	Jun-11
Linagliptin	DPP-4 inhibitor	Aug-11
Lixisenatide	GLP-1 receptor agonist	Feb-13
Alogliptin	DPP-4 inhibitor	Sep-13
Dulaglutide	GLP-1 receptor agonist	Jan-15

DPP-4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide-1; LAR: Long-acting release; EMA: European medicines agency.

OXYNTOMODULIN

Similar to GLP-1, OXM is an L-cell derived proglucagon gene product secreted in response to feeding[40]. To date a specific OXM receptor has not been described, and the biological actions of OXM are attributed to binding and activation of GLP-1 and glucagon receptors (Figure 1), albeit with reduced potency compared to the native ligands[41]. *In vitro* and *in vivo* rodent studies suggest that through glucagon receptor agonism, OXM induces catabolic effects that favour weight loss and subsequent improved metabolic control, while glucose homeostasis and insulin resistance are improved through activation of GLP-1 receptors[5]. Promisingly, data from small clinical studies implies that beneficial effects on energy intake and weight loss also occur in humans[42,43]. However, as is this case for the incretin hormones, the therapeutic potential of OXM-based molecules is hindered by rapid cleavage of the first two N-terminal amino acids of OXM by DPP-4 in plasma, rendering the peptide inactive[44]. Nonetheless, structure-function studies show that N-terminal modification can protect against DPP-4 degradation without disproportionately affecting bioactivity of the molecule[44,45]. Indeed, a recent study of six novel OXM analogues has revealed that Oxm-based peptides with specific N-terminal position 2 modifications are stable and show particular promise for the treatment of diabetes[46]. These data suggest that further exploration of dual agonism of the GLP-1 and glucagon receptor is required for human diabetes. It is notable that co-administration of GLP-1 and glucagon in humans can replicate the beneficial actions of OXM[47], although this approach may be more cumbersome in clinical practice.

CHOLECYSTOKININ

CCK is an intestinal I-cell derived gut hormone secreted in response to meal ingestion[48]. CCK binds to specific CCK_1 receptors present on gastric mucosa and vagal afferent neurons which collectively leads to gallbladder secretions, release of pancreatic digestive juices, satiety and slowing

of gut motility[1]. CCK_2 receptors are mainly confined to the gastrointestinal tract and brain and may have a role in regulating anxiety and locomotion[49]. Importantly, CCK has also been shown to stimulate insulin secretion in rodents and man (Figure 1)[50,51], and act as a growth and anti-apoptotic factor for pancreatic beta-cells[52]. Thus, CCK agonists could have noteworthy potential for diabetes therapy, since their biological action profile is similar to the incretin hormones. However, native CCK is rapidly degraded by serum aminopeptidases upon secretion into the bloodstream[53], which hinders therapeutic potential. However, early studies have clearly shown that both N-terminal modification through glycation, or PEGylation, can prevent enzymatic degradation of CCK and extend biological action and therapeutic potential[53,54]. Following on from this, a more recently developed enzymatically stable, N-terminally modified, CCK analogue, namely (pGlu-Gln)-CCK-8, has been shown to have an improved pharmacodynamic profile, and to both alleviate and protect against obesity-related diabetes in animal models[51,55], with an encouraging safety profile[56]. The mechanism of action of (pGlu-Gln)-CCK-8 likely revolves around prominent and sustained reductions of energy intake, possibly related to modulation of central neuropeptide Y and melanocortin related pathways, and enhanced insulin release[57]. Encouragingly, a PEGylated version of (pGlu-Gln)-CCK-8 has now been fully characterised, that would be resistant to kidney filtration, and suitable for possible once daily dosing in man[58]. Further investigations relating to translation of beneficial effects to human type 2 diabetes together with safety evaluation are still required, but initial observations with specific and stable CCK_1 receptor agonists are encouraging.

MULTI-TARGET HYBRID PEPTIDE THERAPIES FOR DIABETES

Given the beneficial effects of OXM-based peptides, it follows that design of hybrid peptides capable of modulating more than one receptor pathway could have distinct therapeutic benefits for the treatment of obesity-related diabetes. By utilising the correct ratio of receptor pathway interactions, efficacy should be enhanced with the potential for administration of lower doses, thereby reducing, or removing, adverse side effects. The most logical starting point for design of a synthetic dual acting hybrid peptide would inevitably involve a modified incretin hormones capable of activating both GIP and GLP-1 receptors. As such, GIP/GLP-1 chimeric peptides were characterised almost 20 years ago, and the structural requirements for specific ligand-receptor interactions well defined[59]. Combined administration of individual long-acting GIP and GLP-1 mimetics has been considered in preclinical studies, with some success[60]. However, issues of separate drug formulation and dosing still remain, although these may not be insurmountable as indicated by recent introduction of IDegLira for combined insulin and GLP-1 therapy in type 1 diabetes[61]. In terms of a single hybrid peptide that can directly activate both GIP and GLP-1 receptors, only MAR701, Marcadia Biotech (now Roche) has progressed to the evaluation of beneficial effects in man. However, since the clinical benefits of DPP-4 inhibitors clearly involves increased circulating levels of both incretin peptides[62], concomitant activation of GIP and GLP-1 receptors does appear to have promise for the treatment of type 2 diabetes (Table 1).

Further studies have investigated the effects of GLP-1 receptor agonism combined with either glucagon receptor agonism or antagonism[63,64]. Although somewhat contradictory in nature, these contrasting regimens both utilise the beneficial glucose-lowering effects of GLP-1, combined with either inhibition of glucagon-mediated gluconeogenesis and glycogenolysis[65], or activation of glucagon pathways involved in energy turnover and weight loss[64], as is this case for OXM. Other modified hybrid peptides for dual activation of regulatory peptide receptors include, ZP3022, a combined GLP-1-gastrin agonist[66]. Through activation of GLP-1 and CCK_2 receptors, this peptide improved glycaemic control in *db/db* mice *via* enhancement of beta-cell mass[66]. However, perhaps more appealing is the potential for combined and sustained activation of GLP-1 and CCK_1 receptors. As such, two independent studies have clearly shown pronounced synergistic metabolic benefits with combined administration of long-acting GLP-1 and CCK_1 receptor agonists in rodent models of type 2 diabetes[67,68]. These extremely positive effects are believed to occur through activation of complementary pathways that lead to significant weight loss and dramatically improved metabolic control[67,68]. Furthermore, a novel CCK/GLP-1 hybrid peptide, based on the chemical structures of (pGlu-Gln)-CCK-8 and exenatide, has recently been described and shown to have significant therapeutic potential in high-fat fed mice[69]. This molecule clearly warrants further study as a potential new treatment option for type 2 diabetes.

Considering the evident therapeutic efficacy offered by dual peptide receptor interactions, single compounds with the ability to concurrently activate three or more regulatory peptide receptors could deliver even greater beneficial effects. Moreover, the celebrated success of bariatric surgery for restoring metabolic control in type 2 diabetic patients, independent of weight loss[70], results from a culmination of reduced energy intake and modulation of the secretion and biological action of numerous gut-derived peptides[71]. Thus, there is now significant enthusiasm arising from designer modified peptides with the ability to concurrently modulate GIP, GLP-1 and glucagon receptor signalling[72,73]. These triple-acting peptides have resulted in dramatic improvements in glucose homeostasis and overall metabolic control in high fat fed mice[72,73]. Despite their obvious potential, issues regarding the ratio of GIP, GLP-1 and glucagon receptor activation still need to be addressed, As such,

a subsequent study has reported the distinct beneficial effects of a balanced glucagon, GLP-1 and GIP receptor tri-agonist to correct obesity and diabetes in high fat fed mice[74]. Taken together, there is a clear and attractive rationale for further testing of combinatorial hormone therapies for the treatment of obesity and diabetes in humans.

Although the future trend for peptide-based anti-diabetic drugs seems to be development dual or triple agonists, treatment modalities that incorporate periods of beta-cell rest could be important for glycaemic control[75]. Thus, antidiabetic drugs that induce direct beta-cell stimulatory effects can erode beta-cell mass over time[76]. As such, intermittent periods of beta-cell rest may be useful to preserve long-term beta-cell function and lasting glycaemic control[75]. In contrast to sulphonylureas and meglitinides, incretin based drugs stimulate insulin secretion in a glucose-dependent fashion that should help preserve beta-cell mass and function[8]. Nonetheless, adequate periods of rest might still allow chronically stimulated pancreatic beta-cells to replenish both cell surface receptors and the immediately secretable insulin granule pool[77]. Such effects, together with the positive actions of incretins on beta-cell stimulus-secretion coupling, survival and growth, could be highly beneficial. Accordingly, the timing of injections of dual or triple acting therapies, as well as the profile of receptor pathways activated, could be of valuable clinical relevance. In relation to this, inhibition of GIP-R signalling has been shown to improve metabolic control and glycaemic status in animal models of obesity-related diabetes by enhancing insulin action and diminishing insulin secretion[78,79]. Thus a key aspect underlying the beneficial effects could be related to the induction of pancreatic beta-cell rest. Consistent with this, combination of morning injection of liraglutide, with stable GIP antagonist peptide in the evening, greatly improved glycaemic control in *db/db* mice compared with reciprocal administration or twice daily injection of liraglutide[80]. Further investigation of this potentially important treatment paradigm, in combination with other agents that stimulate and/or relieve beta cell insulin release, is required to fully explore therapeutic relevance and applicability.

INCRETIN THERAPIES AND PREDIABETES

Prediabetes describes to a situation where blood sugar is high, but not elevated sufficiently to classify as overt type 2 diabetes. However, the condition represents a high risk state for future development of diabetes, most likely linked to progressive beta-cell decline[81]. Thus, it follows that the positive effects of incretin mimetics on beta-cell function, including possible benefits for beta-cell proliferation and survival, plus additional weight-lowering and extrapancreatic actions[8], could hold significant promise for prediabetic patients. Moreover, patients with prediabetes have been shown to have an impaired incretin effect in response to oral nutrient delivery[82].

To date, there have been several tentative clinical studies conducted on the potential beneficial effects of incretin-based drugs for prediabetes. Studies with DPP-4 inhibitors (Table 1), which prevent incretin peptide degradation and increase active circulating levels of GIP and GLP-1, reported modest positive effects[83-85]. However, treatment with the stable incretin mimetics, exenatide or liraglutide, generated more positive outcomes[86,87]. This included significant reductions in the prevalence of prediabetes with reversion to normal glucose tolerance[86,87]. The inconsistency between DPP-4 inhibitors and GLP-1 mimetics most likely relates to differences in the circulating levels of active hormones achieved. However, issues of oral *vs* injectable delivery of DPP-4 inhibitors and GLP-1 mimetics, respectively, could significantly affect compliance in this patient subgroup. In addition, the potential adverse side-effect profile of incretin based therapies, as discussed above, would also have to be fully considered. Finally, the cost of therapy with DPP-4 inhibitors and particularly GLP-1 mimetics is greater when compared to other glucose-lowering agents[88]. Thus, given the limited experience to date regarding the effect of incretin therapies in prediabetes, future clinical trials would be recommended. In terms of GIP, CCK and OXM therapies, clinical effectiveness in type 2 diabetes would need to be fully established before beneficial actions in prediabetic patients could be considered.

UNEXPECTED THERAPEUTIC POTENTIAL OF INCRETIN BASED DRUGS

Bone

Although incretin hormones have been studied extensively for therapeutic effectiveness in diabetes, research has uncovered unexpected benefits in various other tissues. For instance, a role for gastrointestinal derived hormones in bone remodeling is suspected since serum levels of bone biomarkers rapidly alter after a meal[89]. Indeed, functional GIP receptors have been evidenced on the surface of bone cells[90]. Notably, GIP has been shown to inhibit bone resorption in humans under both euglycaemic and hyperglycaemic states[91]. Thus, the beneficial effects of GIP on bone could be independent of feeding state. Indeed, exogenous prolonged administration of an N-terminally modified stable GIP receptor agonist imparted various beneficial effects on tissue-level bone material properties of rats[92]. In terms of GLP-1 effects on bone, the picture is less clear. This mostly relates to data from animal models being clouded by the fact that GLP-1 receptors are highly expressed on rodent thyroid cells, resulting alterations of circulating calcitonin levels[93]. Nonetheless, GLP-1 receptors have been found on the surface of human osteoblast-like cells[94]. Moreover, very recent data suggest that liraglutide has anabolic effects on bone

in diabetic rats[95]. In keeping with this, a study in double incretin receptor knockout mice[89], reported a combination of detrimental bone abnormalities that mimicked observations from both GIP[96,97] and GLP-1[98] receptor knockout mice. Despite these observations in rodents, a preliminary meta-analysis suggests that GLP-1 mimetics do not modify the increased bone fracture risk in humans with type 2 diabetes[99], or could even potentially increase fracture risk in this population[100]. In keeping with this, a retrospective population based cohort study has suggested that DPP-4 inhibition is not associated with reduced fracture risk in humans[101], whereas bone loss and strength where significantly improved by sitaglitpin therapy in diabetic rats[102]. Care is required therefore when extrapolating data on the effects of incretin-like drugs on bone from rodents to man, particularly in the case of GLP-1. However, actions of GIP are particularly promising and further research is required to determine if incretin hormones can be useful to treat abnormalities of bone encountered in diabetes and osteoporosis.

Brain

In terms of the central nervous system, expression of functional GIP and GLP-1 receptors has been demonstrated in several brain regions[103]. Much of the therapeutic interest for incretin-like molecules in the CNS revolves around neuroprotective effects for the treatment of Alzheimer's and Parkinson's diseases, as well as cognitive impairments in diabetes[3,104]. Accordingly, GIP receptor knockout mice exhibit impaired memory learning, synaptic plasticity, and neurogenesis[105]. In agreement, transgenic mice that over-express GIP exhibit enhanced sensorimotor coordination and memory recognition[106]. Earlier studies have already shown that stable forms of GIP can beneficially modulate synaptic transmission and enhance the induction of long-term potentiation, an important physiological cellular means of monitoring learning processes[107]. In addition, prolonged GIP receptor activation improved cognitive function, hippocampal synaptic plasticity and glucose homeostasis in obese-diabetic high-fat fed mice[108]. In agreement with this, GLP-1 receptor knockout mice display an impairment of synaptic plasticity and memory formation[109]. Furthermore, sustained treatment with long-acting GLP-1 agonists improves memory and learning in various rodent models of neurodegeneration and diabetes[108,110,111]. Moreover, liraglutide treatment has recently been shown to restore cerebral and systemic microvascular architecture in a rodent model of genetically-induced cognitive dysfunction[112]. Based on the positive neuroprotective effects of incretin compounds, there are several ongoing clinical trials with these drugs that should reveal encouraging effects for the potential treatment of Alzheimer's and Parkinson's diseases[104]. Finally, in harmony with the positive effects of incretin molecules on brain function, sitaglitpin treatment was recently shown to improve recognition memory, oxidative stress and hippocampal neurogenesis in diabetic mice[113]. Collectively, these observations strengthen the possibility that incretin peptides play a direct role in modulating aspects of brain function and could possess key clinical pharmacological benefits for patients with diabetes and neurodegenerative disorders.

Heart and vasculature

The GLP-1 receptor has been demonstrated in the heart[114]. Although some controversy still exists as to the exact location of the receptor within the heart, various studies confirm the presence of GLP-1 receptor mRNA transcripts in rodent and human cardiac tissue[115]. In cardiomyocytes GLP-1 receptor signalling induced elevations in cAMP levels, but surprisingly this was not coupled to an increase in intracellular Ca^{2+} concentrations and cardiomyocyte contractility[116]. Indeed, there could be a paradoxical reduction in cardiomyocyte contractility despite elevated cAMP levels[116]. Moreover, GLP-1 receptor knockout mice present with decreased ventricular contractile function[117]. As such, the exact mechanism of action and physiological relevance of GLP-1 receptor signalling in the heart requires further detailed investigation. Despite this, and similar to the situation in pancreatic beta-cells, GLP-1 appears to have anti-apoptotic effects in cardiomyocytes and improves overall outcomes in mice after myocardial infarction[118]. Further to this, GLP-1 receptor protein has also been detected in human coronary artery endothelial cells and encouragingly, activation is believed to improve endothelial cell function in diabetic patients[119]. Thus, prospective clinical trials are ongoing to assess the cardiovascular safety profile of GLP-1 based peptides, and initial observations in humans with diabetes are positive[120]. Whilst the GIP receptor is believed to be present in the heart and on vasculature[103], there is a paucity of knowledge in relation to GIP effects on these tissues. Stimulation of GIP receptors may induce conflicting effects in different vascular beds[121], and this could explain for its unaccounted physiological effects in these tissues. In keeping with this, the overall effect of DPP-4 inhibition on cardiovascular function is still not clear[122].

FUTURE DIRECTIONS

Stable gut hormones have considerable potential for the treatment of obesity-related diabetes, and possibly other related pathologies. Whilst disorders of bone, cognitive function and the cardiovascular system can be considered as complications of diabetes, they are also standalone distinct illnesses in their own right. Thus, the therapeutic outlook of incretin mimetics may stretch well beyond diabetes. However, to date only GLP-1 based drugs are clinically available, exclusively for the treatment of type 2 diabetes and associated obesity. Concerns regarding the safety of GLP-1 analogues in man appear to have been allayed, but pharmacovigilance is still required. The potential promise of incretin based drugs

such as GLP-1 mimetics for the treatment of prediabetes still requires detailed investigation. Stable forms of GIP, OXM and CCK also appear to offer distinct therapeutic possibilities for the treatment of type 2 diabetes based on data from animal models and preliminary human studies. Given this, and the multifactorial pathological nature of diabetes, it is not unexpected that concurrent activation of more than one regulatory peptide receptor signalling pathway appears to have promise for the future treatment of diabetes. This may be achieved through the development of double or triple acting agonists or use of a cocktail of existing peptidergic drugs. However, note should be taken of emerging evidence suggesting the utility of sequential peptide exposures to facilitate essential periods of beta-cell rest. Taken together, future advances in our understanding of gut peptide biology, coupled with therapeutic application, should lead to an expansion of clinically available gut peptide-based drugs with far-reaching benefits to the patient.

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REVIEW

Role of adiponectin and some other factors linking type 2 diabetes mellitus and obesity

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Abstract

Because of the intimate association of obesity with type 2 diabetes mellitus (T2DM), during the last two decades, extensive research work is being conducted to find out whether the coexistence of the two is a simple association or there is a positive correlating link between the two. In this article, an attempt has been made to collect and analyse the recent developments in this field and to arrive at a conclusion on the subject. The possible role of several important factors (obtained from adipocytes/not of adipocyte origin) in linking the two has been discussed in detail. Some of the agents, specifically adiponectin, are beneficial (*i.e.*, reduce the incidence of both), while others are harmful (*i.e.*, increase their incidence). From the analysis, it appears that obesity and T2DM are intimately linked.

Key words: Obesity; Insulin; Insulin resistance; Type 2 diabetes mellitus; Adipocyte

Core tip: The objective of this article is to establish the connection of obesity with that of insulin resistance (IR) and type 2 diabetes mellitus (T2DM) by analyzing the recent developments in this field. The factors linking the three have been found to be some adipocytokines as well as certain other factors not of adipocyte origin. Of these, adiponectin appears to play the most beneficial role (so also leptin, peroxisome proliferator-activated receptors, apelin, *etc.*), while others (tumour necrosis factor-alpha, interleukin-6, resistin, retinol binding protein-4, dipeptidyl peptidase-4, plasminogen activator inhibitor-1, visfatin, free fatty acid, angiotensin Ⅱ and toll-like receptors) are harmful. Agonists and antagonists of these factors may be designed to fight against obesity, thereby achieving protection for IR and T2DM.

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INTRODUCTION

It is practically established that type 1 diabetes

mellitus is an autoimmune disorder where the tissue-specific antibodies target and cause complete or near complete destruction of islet-β-cells, leading to absolute insulin deficiency. In contrast, type 2 diabetes mellitus (T2DM) is usually a hereditary disorder, commonly (80%) associated with obesity, where deficient insulin action may be due to a real deficiency of insulin or a relative one associated with normal or even elevated plasma concentrations of insulin, *i.e.*, insulin resistance (IR). Such simultaneous occurrence of the two (T2DM and obesity) suggests the possibility of a strong link between them, and during the past two decades several positive correlations between them have been established by many workers[1-4]. Besides obesity which is directly linked to T2DM *via* adipocytokines, some nonadipocytokines have been found to be related with T2DM indirectly by interfering with the growth, development and functions of adipocytes (mentioned later). In this article, an attempt has been made to collect and analyse some such authentic work-results together that will help the reader to comprehend and assess the developments in this field.

The intimate association of T2DM and obesity is a world-wide phenomenon. Though much knowledge about the pathophysiology, course and consequences of T2DM has been gathered, it is not so with obesity, which was almost practically considered as a cosmetic problem. But recently, because of its frequent association with T2DM as well as with hypertension, extensive work is being continued on the adipocyte anatomy, distribution pattern, physiological function, pathological role and its possible link with T2DM and hypertension.

PHYSIOLOGICAL ROLE OF ADIPOCYTES AND ADIPOSE TISSUE

Primary physiological role of adipose tissue is to insulate and cushion the body, to store fat when it is in excess and to supply it when needed[5]. The exogenous and endogenous pathways of lipid metabolism, during which free fatty acids (FFAs) are released from the lipoprotein (chylomicron, very low density lipoprotein, *etc.*) - triglyceride (TG) content upon hydrolysis by the enzyme lipoprotein lipase (LPL), their (FFAs) subsequent storage in fat depots as TG again, and their remobilisation into the periphery by hydrolysis of these stored TGs by the hormone sensitive lipase (HSL), is well established[5,6]. Insulin plays a major role for maintenance of adipocyte-fat content as it is a potent activator and inhibitor of LPL and HSL, respectively[5].

SECRETIONS OF ADIPOCYTES (ADIPOCYTOKINES)

Recently, adipocytes are considered as endocrine structures because of their wide variety of chemical secretions (adipocytokines), which affect many diverse physiological functions and related pathological processes of the body, like metabolism of carbohydrates and lipids, coagulation of blood, maintenance of blood pressure, feeding behaviour and inflammation, affecting almost all the organs of the body. Increased adipocyte number and adipose-tissue mass have been found to result in increased plasma adipocytokine level except adiponectin, whose plasma concentration is actually low in obesity[5]. Diseases like obesity, T2DM and metabolic syndrome are associated with altered plasma adipokine levels.

A brief discussion of the adipocytokines known till-date along with their possible roles in genesis or amelioration of IR and T2DM is made below. Besides the adipokines, possible involvement of certain other factors (not of adipocyte origin) has also been taken into account (Figure 1).

Leptin

Several physiological functions of leptin along with its source and metabolism have been extensively discussed. This adipokine, which is a product of "*ob*" gene but mediates its function through the receptor coded by "*db*" gene, is involved in energy homeostasis of the body by interfering with the food-behaviour of the animal centrally (hypothalamus) *via* several hormones[7].

Many studies on mice and human beings have shown a beneficial and balancing complementary relationship between leptin and insulin where leptin has been found to reduce appetite, obesity and IR along with improvement of metabolic disturbances associated with T2DM. Moreover, mice with *db*/*db* gene (deficient leptin action) have been found to be obese and diabetic[7].

Though the receptors for insulin and leptin are different, both of them mediate their action through some common second messengers. Therefore, it is possible that leptin may trigger some of the same downstream events triggered by insulin. Increase in tissue sensitivity of insulin by leptin may be due to later's action on oxidation of FFAs which is increased in skeletal muscles leading to its (FFAs) decreased blood concentrations[7].

Because of such functional cooperation, it may be assumed that obesity due to inadequate leptin action may predispose or get associated with IR and T2DM.

Tumour necrosis factor-α

The role of tumour necrosis factor-α (TNF-α) as a pro-inflammatory cytokine is well established[8]. It is produced by macrophages (mainly) as well as by some other cell types including visceral adipocytes[8-10]. Recently, it has been shown that besides its pro-inflammatory property, increased TNF-α inhibits insulin transduction mechanism, resulting in inadequate glucose metabolism, IR and obesity. Because visceral fat is a source of TNF-α, increase in such fat (obesity) leads to increased production of this cytokine, which aggravates obesity and a vicious cycle is established leading to predisposition, onset and progression of T2DM along with IR. Hence, reduction of obesity, which in

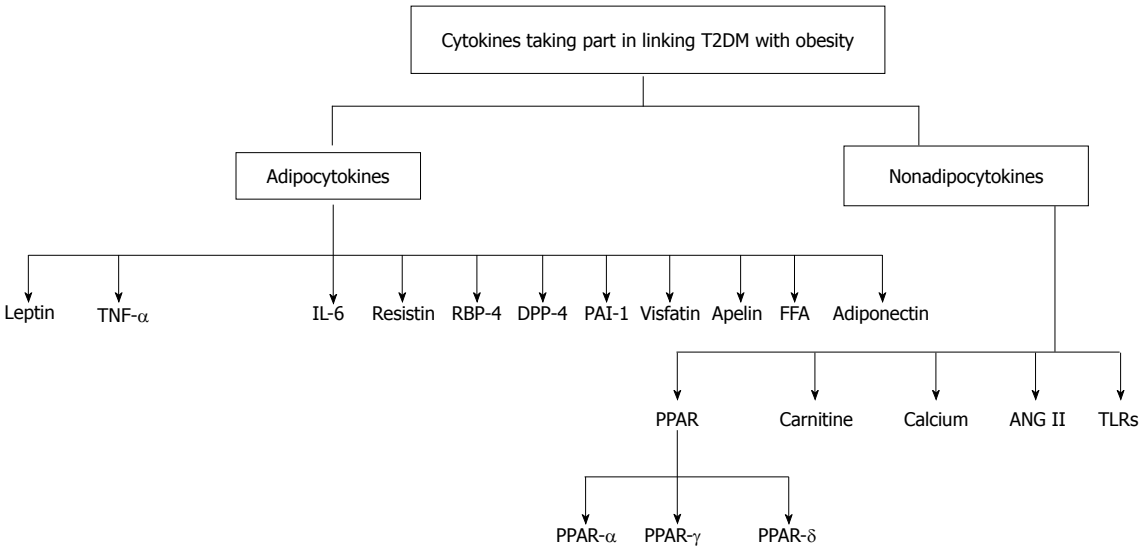

Figure 1 Cytokines linking type 2 diabetes mellitus with obesity. TNF-α: Tumour necrosis factor-alpha; IL-6: Interleukin-6; RBP-4: Retinol binding protein-4; DPP-4: Dipeptidyl peptidase-4; FFA: Free fatty acid; PPAR: Peroxisome proliferator-activated receptor; Ang Ⅱ: Angiotensin Ⅱ; TLRs: Toll-like receptors; T2DM: Type 2 diabetes mellitus; PAI-1: Plasminogen activator inhibitor-1.

turn may lead to decreased formation of TNF-α, may help to prevent genesis, progression and complications of T2DM[8]. Besides inhibiting insulin signalling mechanism, TNF-α also has been found to inhibit glucose-induced insulin secretion from β-cells, cause damage to insulin strand and enhance β-cell apoptosis. However, such functions of TNF-α have been demonstrated *in vitro* with concentrations of the cytokine, which was much higher than *in vivo* plasma concentrations[5]. Moreover, besides visceral adipocytes, macrophages and other cells also produce TNF-α, which may contribute towards the elevated level of this cytokine in obesity[10]. Therefore, obesity and increased TNF-α levels cannot be directly and definitely implicated with T2DM, although they seem to have a role which needs further investigations[5,8,9].

Interleukin-6

It is another pro-inflammatory cytokine produced by many cell types (fibroblast, endothelial cells, monocytes) in the body including adipocytes, the production (by adipocytes) being increased in obesity. *In vitro* studies as well as investigations on mice have shown interleukin (IL)-6 to upregulate the production of vascular endothelial growth factor, which is thought to support angiogenesis during adipose tissue growth, leading to increase in the production of IL-6 further (similar to TNF-α)[5,10].

IL-6 action is mediated through a cytokine class one receptor subtype involving Janus kinase/signal transducers and activators of transcription (JAK/STAT) signal transduction pathway, whereas insulin action is mediated through a receptor family having intrinsic tyrosine kinase activity, signal transduction being carried out through insulin receptor substrate (IRS) proteins. It has been clearly demonstrated that inspite of entirely different receptor involvement, a strong interaction occurs between the receptor signalling pathway of IL-6 and insulin, leading to impaired biological effect of the later. Though not fully clear, the interaction may involve activation of tyrosine phosphatase, leading to dephosphorylation and inactivation of tyrosine kinase activity or an interaction between suppressor of cytokine signalling proteins and insulin receptors, resulting in deficient insulin action[10]. Therefore, it appears that elevated plasma levels of IL-6 due to any cause (not necessarily of body fat) may get associated with IR and hence, increased risk of diabetes[5].

Resistin

This pro-inflammatory cytokine, besides monocytes and macrophages, is also produced by adipocytes. It is so named, because of its capacity to resist insulin action[1,10,11]. It has a molecular weight of 12.5 kDa and possesses 108 amino acid residues in humans. Unlike adiponectin, this polypeptide has a low circulatory level, which is increased in subjects with IR, T2DM and metabolic syndrome[3].

Several workers have demonstrated a definite role of resistin in linking obesity to T2DM, during which the cytokine has been found to modulate the insulin signalling pathway, leading to development of IR[2]. Increased production of resistin has been found to be a result of adipocyte differentiation as well as increase in their number. Locally (from adipocytes) released resistin may play a paracrine role, resulting in inhibition of insulin-induced glucose uptake by adipocytes, which prevents their (adipocytes) further differentiation, thereby reducing its own synthesis and release. This observation may suggest a reciprocal relationship between the two hormones which may further be supported by the fact that rosiglitazone (an oral antidiabetic drug) decreases the circulating concentration of resistin, whereas diet-

induced and genetic forms of obesity increases it[11]. Moreover, neutralization of resistin has been found to increase the insulin-induced uptake of glucose by adipocytes, whereas resistin itself decreased it.

Recently, it has been observed that resistin-knockout mice show lower fasting blood sugar with increased glucose tolerance and insulin sensitivity associated with reduced hepatic output of glucose. The possible mechanism of this observation may be an overactivity of AMP-activated protein kinase (AMPK) resulting from lack of resistin, leading to reduced expression of genes responsible for hepatic neoglucogenesis. This possible mechanism suggests an opposite role of resistin to that of adiponectin. Again, it was observed that when these resistin-knockout mice were fed with high fat diet, they became obese and IR like their wild counterparts[10]. All these observations suggest a potential positive link between obesity and T2DM[1].

Retinol-binding protein-4

This adipocytokine, which is primarily a vitamin A -transport protein, has been recently shown to be linked with IR. Down-regulation of adipocyte GLUT-4 (glucose transporter) has been found to increase the secretion of retinol-binding protein-4 (RBP-4) from adipocytes. In mice, increased serum levels of RBP-4 has been found to be associated with decreased uptake of glucose by skeletal muscles and increased hepatic neoglucogenesis. On the other hand, insulin sensitivity was found to be increased when serum RBP-4 levels were low[12]. Similar positive correlations between raised plasma RBP-4 level and IR, plasma glucose, BMI and homeostatic model assessment-IR have also been shown in nondiabetics with a high genetic predisposition for T2DM. Interestingly, in this experiment, it was observed that serum RBP-4 levels were raised before significant appearance of diabetic markers[13]. Such an observation indicates the "elevated plasma RBP-4 level" to be a signal for development of insulin resistance and subsequent T2DM in future[12,13]. In another experiment, it has been shown that excess of RBP-4 relative to retinol (RBP to retinol ratio) is more accurate in predicting the development of T2DM than raised RBP-4 levels alone[14].

Dipeptidyl peptidase-4

The incretins (glucagon-like peptide-1 and glucose-dependent insulinotropic hormone) are known to possess favourable effect on carbohydrate and lipid metabolism as they increase postprandial insulin release along with a decrease in release of glucagon. The two incretins, like several other glycoprotein and peptide substrates, are metabolically degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), which reduces their favourable metabolic effects in relation to diabetes and therefore may be considered as diabetogenic. Hence, DPP-4 inhibitors (sitagliptin, vildagliptin, *etc*.) are now used extensively for management of T2DM along with other antidiabetic agents[15].

Recently, it has been shown that like other cells, adipocytes also express DPP-4 and substantial over-expression is found in visceral fat of obese persons. Experiments have demonstrated that DPP-4 expression and circulating DPP-4 concentration are well-correlated with adipocyte size and adipose tissue inflammation. This may suggest a stimulatory role of pro-inflammatory adipokines on expression of DPP-4 from adipocytes and other tissues. Thus, increased release of DPP-4 from visceral adipocytes of obese persons may enhance the metabolic degradation of incretins in an autocrine or paracrine manner, thereby reducing their favourable effect on carbohydrate and lipid metabolism which in turn may predispose the concerned obese person for developmen of T2DM and metabolic syndrome. In another study, it has been shown that explants from subjects release more DPP-4 and the release is reduced after weight reduction[15]. Moreover, in insulin- sensitive obese patients, plasma concentration of DPP-4 has been found to be lower than those of insulin-resistant obese diabetics[16]. All these physiological and experimental observations suggest a strong link between T2DM and obesity, where the linking factor appears to be DPP-4.

Plasminogen activator inhibitor-1

This prothrombotic cytokine, besides being produced by vascular endothelial cells, is also produced by adipocytes, production being more from omental adipose tissue than that of subcutaneous adipocytes[17]. Some recent studies have found a direct contribution of this cytokine towards the complications of obesity like T2DM and coronary thrombosis, as well as increased accumulation of visceral fat[18]. Nowadays, plasminogen activator inhibitor-1 (PAI-1) is being considered as a strong predictor of T2DM, and has been found to stimulate adipocyte differentiation, which may be mediated through reducing *peroxisome proliferator-activated receptor* (PPAR)-γ activity, resulting in more production of resistin. It has been demonstrated that adipocyte-PAI-1 increases the production of TNF-α (an autocrine action) in adipocytes that reduces insulin action and predisposes to T2DM. Moreover, PPAR-γ receptor has been found to be downregulated both by PAI-1 and TNF-α. Hence, inhibition of PAI-1 action on adipocytes may prevent obesity and IR, and retard adipocyte differentiation and fat accumulation by removing not only its (of PAI-1) own antiinsulin action but also that of resistin and TNF-α[7,17].

Visfatin

This adipocytokine, a pro-inflammatory marker of adipose tissue, is mainly produced by visceral adipocytes of humans and mice, whose plasma concentration increases along with the progression of obesity[19-21]. Its production is upregulated by hypoxia, inflammation and hyperglycemia, and downregulated by insulin, somatostatin and cholesterol reducing statins. Besides visceral fat, intracellular presence of visfatin has also

been demonstrated in many other tissues and organs, the location being both cytoplasmic and nuclear[21].

Functions of visfatin are difficult to explain as they appear to be contradictory. The cytokine has been found to possess insulinomimetic effect in cultured cells[19,20] and lowers plasma glucose concentration in mice[19]. It has also been shown to cause hypoglycaemia by reducing hepatic output of glucose and increasing utilisation of glucose in adipocytes and monocytes[21]. Inspite of such favourable insulinomimetic action[19,20], this cytokine has been found to be associated with IR and possesses a direct relationship between its plasma concentration and T2DM[21,22]. This anomaly may be explained by the fact that it also produces hyperlipidemia, which may be responsible for IR and hence T2DM (As T2DM may either be due to deficiency of insulin or IR)[22]. The resultant effect seems to be favouring the development of T2DM, which in turn suggests the pernicious role of visceral adipose tissue (VAT) in human obesity-related T2DM and accompanying metabolic disorders[20].

Besides these T2DM-related pathological functions, visfatin, by its endocrine, autocrine as well as paracrine function, has been found to cause increase in cell proliferation and biosynthesis of nicotinamide mono- and dinucleotides[16], significance of which is yet to be ascertained.

Apelin

Apelin, a small peptide adipokine, has also been found to be present in a number of tissues. It is the ligand of the G-protein-coupled receptor (GPCR) APJ, and has several active forms, which include apelin 13, apelin 17 and apelin 36. It is considered as a beneficial adipokine as it has been found to possess antiobesity and anti-diabetic properties, because of its potent positive role[23,24] in energy metabolism and insulin sensitivity improvement[24]. Such actions appear to be due to promotion of complete lipid combustion[23] in muscle of IR mice through mitochondrial biogenesis and tighter matching between fatty acid oxidation and TCA cycle. Such apelin- stimulated improvement of FA oxidation led to decreased levels of acyl-carnitines and enhanced insulin-stimulated glucose uptake in soleus muscle[25]. For such beneficial actions, apelin may be considered as a promising useful therapeutic agent for T2DM and other metabolic disorders[23].

FFA

FFAs, which are produced during the metabolism of exogenous and endogenous lipids, play an important role in the development of IR and hence, genesis of T2DM, when their plasma concentration is abnormally raised[26].

Mechanisms of FFA-induced IR include inhibition of insulin-induced release of NO from endothelial cells, resulting in decreased blood flow, inhibition of insulin-stimulated glucose transport across the cell membrane and/or inhibition of intracellular phosphorylation of glucose by interfering with insulin signal transduction pathway. Acute elevation of FFA in plasma has been found to be associated with IR, which may account for 50% of IR in obese individuals with T2DM[27].

Intracellular mechanism of FFA-induced IR has been demonstrated both *in vivo* and *in vitro*, where there was an activation of pro-inflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. It has been shown *in vivo* that acute increase in FFA level resulted in activation of NF-κB pathway in human skeletal muscle and rat liver, leading to increased production of pro-inflammatory cytokines, *i.e.*, TNF-α, IL-1β and IL-6, in both the test organs along with an increase in the concentration of macrophage chemoattractant protein-1 (MCP-1) in circulation. In health as well as in T2DM, insulin tends to reduce FFA-induced-IR by lowering the plasma concentration of FFAs through its lipogenic as well as antilipolytic action along with increased intracellular oxidation of FFA. However, in obesity, which is considered as an inflammatory state, there is not only an increase in FFA, but also an increase in the plasma concentration of pro-inflammatory cytokines, which together are liable to cause IR and T2DM[27].

Thus, obesity alone or along with increased FFA, can create and maintain a low grade inflammatory state by production of pro-inflammatory cytokines (TNF-α, IL-6, *etc.*), which may induce IR and T2DM. The condition may be further aggravated by antiinsulin action of FFA on glucose metabolism[27].

Adiponectin

This adipocytokine is being extensively studied world-wide since the past decade because of its remarkable insulin sensitizing property (IR is the major problem in T2DM) as well as antiatherogenic action (dyslipidemia, commonly associated with T2DM, is responsible for atherosclerotic complications of T2DM), thereby playing an important role in delaying and suppressing the metabolic derangements, which result in IR, T2DM, metabolic syndrome and complications of diabetes including vascular and cardiac. These two important functions of adiponectin involves myriads of interrelated molecular mechanisms, which interconnect it with other diabetogenic/antidiabetic adipokines as well as with many physiological and biochemical processes associated with maintenance of energy balance from metabolism of carbohydrates and lipids[3]. Because of such widespread metabolic involvement, an attempt has been made to discuss the pathophysiological role of this key adipocytokine in detail, which in concert with its siblings appears to play an important role in linking T2DM with obesity.

Source and location: Adiponectin, secreted by both white and brown adipose tissue, has several other names like gelatin binding protein-28, AdipoQ, Adipocyte complement-related protein-30 and OP-MI.

Adiponectin mRNA presence is lower in VAT than that of subcutaneous adipose tissue[4,10]. Normal plasma concentration of this cytokine varies from 5-30 μg/mL and is inversely proportional to abdominal obesity, IR and T2DM. In some animal models, a decrease in plasma adiponectin concentration was found to precede the onset of T2DM and was parallel with decreased insulin sensitivity. The cytokine circulates in blood in multimeric forms, like trimeric, hexameric and high molecular mass species, each of which plays a specific role in maintenance of energy homeostasis[4,7].

Control of secretion: Control of adiponectin secretion is effected by: (1) some hormones; (2) many adipokines; (3) certain receptor families including its own; (4) endoplasmic reticulum (ER) and oxidative stresses; and (5) several other factors.

Hormonal control: Sex hormone: Adiponectin plasma concentration has been found to be higher in women than men, which may be due to the difference in concentration of oestrogen and androgen, suggesting a presumably stimulating role of oestrogen on synthesis and secretion of this adipokine[5,7]; Insulin: The relationship between plasma insulin concentration and adiponectin secretion appears to be peculiar, confusing and contradictory, as the experimental observations do not correlate as expected.

Though insulin favours adiponectin biosynthesis through PPAR-γ *via* inhibition of Fox01 (an inhibitor of PPAR-γ), type I diabetic patients who practically have no circulating insulin, contrary to the expectations, show elevated levels of plasma adiponectin. Moreover, patients, with defective insulin receptors due to abnormal genes coding for them, also show raised circulating adiponectin levels. Furthermore, adiponectin concentration, unlike other insulin-resistance-inducing adipokines, has been found to be decreased in obesity and insulin-resistant models. From such observations it seems that IR decreases plasma adiponectin concentration. This may be explained by taking into account the role of oxidative stress which is known to increase IR and to decrease adiponectin production. In obesity, adipocytes may develop oxidative stress, leading to decreased expression of adiponectin by them. That IR decreases adiponectin expression may further be supported by the observation that hyperinsulinemia associated with euglycemia (an IR state) significantly decreases the plasma adiponectin concentration and selectively downregulates its high molecular weight (HMW) form. The disparity between the above mentioned experimental observations in relation to role of insulin on adiponectin formation is not known and appears to be complicated[4].

Control by adipokines: TNF-α and IL-6 are considered to be established inhibitors of adiponectin synthesis[28]. As their synthesis and secretion increase in obesity, adiponectin plasma concentration decreases accordingly[4,29].

Control by certain receptors: PPAR-γ: This PPAR subfamily transcription factor, which is mainly found in adipocytes, has been shown to possess a positive regulatory role on adiponectin gene expression leading to increased production of proteins like Erol-La and DsbA-L, which take part in synthesis and secretion of adiponectin[4]; Own receptors: Circulating adiponectin concentration has been found to be inversely related to muscle $AdipoR_{1/2}$ (receptor subtypes), but directly related to subcutaneous $AdipoR_2$[4,30].

ER and oxidative stresses: ER is known to be an intracellular fine network of microtubules. It is continuous with the nuclear membrane, and is called sarcoplasmic reticulum in muscles. It controls intracellular calcium ion uptake and release besides its other functions, thereby effecting muscular contraction and relaxation. ER stress, which is produced in obesity, has been shown to be negatively related to adiponectin production by adipocytes. The molecular mechanism involved has been studied in 3T3LI-cells, where oxidative stress in ER lead to increased production of H_2O_2, which, *via* protein kinase B (Akt) and JAK/STAT pathway, appreciably suppressed the expression of adiponectin mRNA and consequent reduction in synthesis of proteins required for adiponectin formation. Moreover, in this model H_2O_2 has been found to increase the production of PAI-1 and IL-6, which are known to inhibit adiponectin synthesis[31].

Other factors: Obesity: Unlike other adipokines, adiponectin secretion has been found to be decreased in obesity. Though the exact cause of such reduction is not known, the suggested causes include increased production of TNF-α and IL-6[28], generation of a hypoxicmicroenvironment in the adipocyes of increased fat mass, and obesity-induced increased production of insulin like growth factor binding protein-3, which inhibits adiponectin transcription *via* hypoxia inducible factor-1α dependent pathway[4,32]; Drugs: PPAR-γ agonists (thiazolidinediones-TZDs), which increase insulin sensitivity, have been found to increase the plasma concentration of adiponectin, whereas anti-HIV drugs like protease inhibitors decrease it[29].

Physiological functions of adiponectin: Adiponectin, along with other adipokines, interferes in several metabolic functions, like lipid synthesis and storage, neoglucogenesis and peripheral utilisation of glucose, which have been demonstrated in skeletal and cardiac muscles, adipocytes and hepatocytes[31]. But, it differs from other adipokines in several aspects. Unlike others, its circulating concentration has been found to be decreased in obesity (particularly abdominal obesity) and T2DM, and instead of increasing insulin resistance, it decreases it in addition to possessing antiatherosclerotic effect. In animal models and in

patients with obesity and T2DM, the cytokine has been shown to stimulate fatty acid (FA) oxidation, reduce lipid accumulation in muscles, decrease plasma FA concentration and increase insulin sensitivity. Because of such beneficial involvement in metabolic functions (lipids and carbohydrates), IR and atherosclerosis, this adipokine is expected to impart protection against coronary heart diseases, steatohepatitis, non-alcoholic fatty liver diseases and a wide variety of cancers[33].

Cellular basis of mechanism of action: Functions of adiponectin have been found to be mediated by three receptor subtypes namely, AdipoR1, AdipoR2 and T-cadherin. AdipoR1 and AdipoR2 are 7 transmembrane proteins but dissimilar to GPCRs. Its receptor distribution pattern varies from cell type to cell type - AdipoR1 being found abundantly in muscles, while AdipoR2 is mainly expressed in hepatocytes. Both the receptors are present in almost every tissue, but in a particular tissue, usually one type predominates. Moreover, degree of affinity of these receptors for different forms of adiponectin also varies[4,7]. AdipoR1 has high affinity for globular adiponectin (a cleaved part of full-length adiponectin) but low affinity for full-length adiponectin, whereas AdipoR2 has intermediate affinity for both forms. Hypoadiponectinemia, associated with IR, upregulates both the receptor types. Such upregulation also occurs in physical activity, suggesting an association between adiponectin hormone system and exercise-induced improvement in IR[7]. Adiponectin, binding to its cell surface receptors, activates several intracellular signalling molecules like p38MAPK, PPAR, the RAS-associated protein Rab5, PI3K, Akt and AMP-activated protein kinase (AMPK), of which AMPK system and PPARs play an important and dominant role leading to modification of lipid and carbohydrate metabolism[4,7,29].

As has already been mentioned, in this article emphasis would be given on two important protective physiological functions of adiponectin, *i.e.*, protection against IR and artherosclerosis. Obesity, T2DM, dyslipidemia and IR are intimately related, where one leads to the other and once developed, aggravate each other thereby establishing a vicious cycle, leading to development of practically all the dangerous complications of T2DM[34]. Increased fatmass, as found in obesity, not only increases the production of bad adipokines who enhance this cycle further but also decreases the production of the good one-adiponectin, deficiency of which contributes significantly towards the development, continuation and aggravation of this cycle. Adiponectin has been shown to prevent the development as well as to break this dangerous cycle, thereby posing itself as a potential therapeutic agent in such condition.

Mechanisms of antiatherosclerotic and IR preventing actions of adiponectin: As these two actions are interrelated, it is convenient to discuss them together. It has already been mentioned that adiponectin increases FA oxidation in mitochondria that leads to a decrease in plasma concentration of FA. Reduced level of FA in circulation prevents the development and progression of atherosclerosis and IR. Multiple biochemical actions at cellular level are modified for this action of adiponectin that needs an extensive discussion and correlation between them to arrive at a conclusion.

Adiponectin-induced FA oxidation is primarily mediated by phosphorylation (activation) of AMPK - a multi-subunit protein kinase, which appears to be a sensor of intracellular energy status through activation of PPAR-α receptor. It has been demonstrated that when muscles were treated with adiponectin or when its receptors were expressed ectopically, there occurred an increase in AMPK phosphorylation and FA oxidation in the muscles that was abolished by dominant-negative AMPK use. Stressful conditions, like heat shock, hypoxia, starvation and exercise, *etc*., which need expenditure of more energy (denoted by high AMP - to - ATP ratio) have been found to cause AMPK activation. This important signalling molecule (AMPK) is also directly activated by other upstream kinases, where they cause phosphorylation of its threonine residue in the kinase domain. In skeletal muscle, activated AMPK increases FA oxidation by stimulating the phosphorylation (leading to inactivation) of the key enzyme acetyl-CoA carboxylase (ACC). Reduced ACC activity, in turn, decreases intracellular malonyl-CoA concentration along with stimulation of carnitine palmitoyl transferase 1 (CPT1) activity, leading to increased entry of long-chain FAs into mitochondria and hence, more of their peripheral oxidation. The fact, that adiponectin increases insulin sensitivity by decreasing plasma FA concentration, has been demonstrated in obese and T2DM patients, where serum adiponectin concentration is low. In such patients, administration of adiponectin has been found to increase insulin sensitivity by decreasing their plasma FA and TG[33].

Metabolic stressful conditions like muscle contraction, hypoxia, ischemia and hyperosmolality, *etc*., not only increase AMPK activation (as mentioned before), but also stimulate the activity of p38MAPK (a signalling molecule activated by inflammatory cytokines). This indicates an association between the two signalling molecules during signal transduction, though the agonists (adiponectin, inflammatory cytokines) inducing the signals are different. In fact, adiponectin has been found to stimulate the activity of not only AMPK but also that of p38MAPK and PPAR-α in target tissue though the subsequent signal transduction pathway following these three activations is not fully known. Other evidences in muscles suggest a sequential activity of these three, leading to increased FA oxidation and increased glucose uptake by muscles. But it has been shown that when primary hepatocytes are treated with adiponectin, their FA oxidation is not increased, which suggests a differential effect of the cytokine on FA oxidation of muscles and liver[33].

ER stress decreases adiponectin secretion: Several workers have shown that ER stress in adipocytes decreases adiponectin secretion. It has been demonstrated that properly integrated mitochondrial function in adipocytes is necessary for adequate secretion of adiponectin. Like other cells, growth and development of adipocytes occur through differentiation and hypertrophy, which need increased mitochondrial function, because of greater energy requirement. Newly differentiated adipocytes are small in size, because of less accumulated TG due to increased FA oxidation in them, as the mitochondrial content and activity are more[29].

It has been shown that these small adipocytes synthesise and secrete more adiponectin because of their high mitochondrial functional level, whereas large hypertrophied fat cells, as found in obesity, produced the cytokine to lesser extent because of impaired mitochondrial function. Though till now, adiponectin synthesis has not been properly correlated with increased mitochondrial function, it may be due to much greater consumption of energy for the synthesis of this cytokine protein in comparison with other proteins. Therefore, it appears that synthesis of adiponectin in adipocytes needs high consumption of energy, which is produced by elevated (adequate) mitochondrial function. In support of this, it has been shown that rosiglitazone and others agents like Ad-NFR-1, which increase mitochondrial biogenesis, also cause an increase in adiponectin synthesis. This observation points the finger towards mitochondrial dysfunction as the cause of low adiponectin level in obesity[29].

Moreover, several evidences have been put forward where obesity-induced mitochondrial dysfunction has resulted in ER stress, which decreases adiponectin secretion and development of IR. Both ER stress and mitochondrial dysfunction have been demonstrated to activate a series of reactions involving sequential activation of JNK and activating transcription factor 3 (ATF3), which in turn decrease the transcription of adiponectin. When JNK and ATF3 are inhibited, adiponectin transcription is restored. It has also been suggested that ER stress and impaired mitochondrial function are separately responsible for genesis of IR in various tissues of obese persons[29].

Adiponectin-induced increase in FA oxidation *via* activation of AMPK and phosphorylation of ACC is of short duration, as ACC phosphorylation is short-lived. Hence, this pathway cannot be considered to be fully responsible for the long term effect of adiponectin in causing weight loss and FA oxidation, for which action through PPAR-α is thought to be involved, because PPAR-α action has been found to persist even after initial signalling is over. This is so, because adiponectin has been found to increase transcriptional activity of PPAR-α and subsequent expression of its target genes *via* activation of AMPK. Involvement of AMPK is supported by the fact that when PPAR-α agonists were administered to obese animals, there occurred an equivalent and sufficient lowering of lipids, as was found with adiponectin. This fact was further supported by *in vivo* administration of 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) to lean and obese Zucker rats where the compound was found to decrease plasma FA and TG levels significantly, because AICAR is known to increase the transcriptional activity of PPAR-α *via* activation of AMPK[33].

Anti-inflammatory action of adiponectin: Mention has been made about the decreased secretion of inflammatory cytokine TNF-α by adiponectin from macrophages that contribute towards its antiatherogenic effect. This anti-inflammatory property is also likely to be involved in its IR reducing action, because TNF-α and IL-6 are known to decrease adiponectin formation and to induce IR[10,28].

Recently, it has been shown that NF-κB activation in endothelial and monocytic cells, which is involved in causation of inflammation and metabolic alteration in obesity, is suppressed in these cells by adiponectin. Moreover, both forms of adiponectin-globular as well as full-length, have been found to decrease the production of pro-inflammatory cytokines IL-6 and MCP1 from inflammed adipocytes that may be due to inhibition of NF-κB activity as well as PPAR-α expression[35].

Insulin sensitizing actions of adiponectin: Adiponectin aids to insulin sensitivity by several novel mechanisms, which include - increased FA oxidation, decreased ER stress, improvement in insulin signalling pathway, increased (improved) mitochondrial number and function, increased insulin secretion, decreased hepatic output of glucose, increased uptake of glucose by liver and muscle, and increased glucose metabolism.

Adiponectin-induced increase in FA oxidation has been demonstrated by several workers[5,10,33,36]. This action of adiponectin contributes significantly towards its insulin sensitizing action and prevention of development of IR, as increased plasma FA concentration is the most important cause of IR. In some animal models, adiponectin has been shown to decrease FFA concentration in plasma by increasing its uptake and oxidation in skeletal muscles. On the other hand, acute reduction of plasma FFA has been found to be associated with low adiponectin concentration, though the exact role of FFA in such action is not known[36]. It is well documented that the key enzyme responsible for FA oxidation is AMPK, which is activated by adiponectin[4,10,31,33]. It has already been mentioned that once activated, AMPK inhibits the activity of ACC, which not only leads to reduced contents of intracellular malonyl-COA but also increases activity of CPTI. Such an action increases the entry of long-chain FAs into mitochondria and hence, an increase in their oxidation. Works on FA oxidation in skeletal muscles have shown a sequential activation of AMPK, p38MAPK and PPAR-α to be responsible for increased FA oxidation. But the signalling pathways and components involved in such sequential activation is

not known. PPAR-α, a ligand-activated nuclear receptor, plays an important role in FA oxidation. This receptor is abundantly expressed in tissues like liver, heart, kidney and skeletal muscles, who meet their metabolic energy consumption from oxidation of FAs. It has been shown that HMW adiponectin fraction increases the PPAR-α target gene expression. Moreover, in IR rodent models, PPAR-α ligands have been found to reduce lipid levels and to improve insulin sensitivity. Several studies on humans and rodents have shown that both forms of adiponectin, HMW as well as low molecular weight (LMW), not only increase target gene expression of PPAR-α but also increase the phosphorylation of AMPK and p38MAPK. But such activity is more pronounced and better correlated with HMW fraction than that of LMW, suggesting a differential efficacy between the two fractions or involvement of multiple pathways in increasing FA oxidation in muscles[33].

It has already been mentioned that mitochondrial dysfunction in adipocytes induces ER stress, which in turn reduces adiponectin transcription, leading to decreased production of this adipokine along with development of IR[29,31]. Moreover, as discussed earlier, adiponectin, *via* activated AMPK, also improves mitochondrial number and function in skeletal muscles[29]. From these two observations it may be inferred that adiponectin, by counteracting mitochondrial dysfunction (through improvement of mitochondrial function), decreases ER stress and improves its own secretion, which in turn may contribute towards reduction of IR. Mention has already been made about the IR-inducing and diabetogenic adipocytokine resistin[1,10,11], whose plasma concentration is high in IR, T2DM, metabolic syndrome and cardiovascular diseases[3]. In contrast, its sibiling adiponectin plasma concentration is low in such conditions[4], and it has favourable effects on them. Such contrasting effects of the two adipokines may be due to their comparable domain architecture, assembled in a multimeric form, which suggests a common regulatory mechanism (opposite to each other) on insulin-signalling pathway, as well as on mechanisms involved in glucose and lipid homeostasis. In IR and T2DM, hypoadiponectinemia along with hyperrestinemia have been found to antagonise insulin signalling by causing dephosphorylation and deactivation of the key enzyme AMPK in skeletal muscles and liver along with increased expression of genes coding for the synthesis of neoglucogenic enzymes as well as reduced expression of IRS-2 and glucose transporter, GLUT-2. The resultant effects of such action were decreased FFA oxidation in muscles, decreased hepatic uptake of glucose, increased neoglucogenesis and glycogenolysis leading to hyperglycemia and increased plasma FFA. Impaired FFA oxidation may be further aggravated by downregulated PPAR-α action[3].

It is well established that insulin resistance is very often associated with inadequate functioning of post receptor signalling molecules including IRS. It has been demonstrated that adiponectin upregulates IRS-2 by activation of STAT-3 in liver. Such activation was also associated with increased production of IL-6 from macrophages - an adiponectin action mediated through activation of NF-κB, which does not require activation of classical AdipoR$_1$ and AdipoR$_2$ receptors. Upregulation of IRS-2 definitely improves insulin sensitivity, but exact mechanisms of such upregulation are not known. Probably, it is effected by an IL-6 dependent pathway, which is initiated by adiponectin, through its combination with yet another unidentified adiponectin receptor. Moreover, though adiponectin activates AMPK and PPAR-α through activation of its classical AdipoR$_1$ and AdipoR$_2$ receptors leading to increased FA oxidation and insulin sensitisation, it has not been possible to link AMPK and PPAR-α activation with the proper functioning of post-receptor insulin signalling molecules[37]. Experiments on skeletal muscles have demonstrated that AMPK activation by adiponectin occurs by two pathways, out of which one is a major one while the other plays a minor role. In the major pathway (the APPL1/LKB1-dependent pathway), AMPK activation needs the binding of adapter protein APPL1, which promotes the translocation of APPL1-dependent LKB1 into the cytosol where it is anchored. The same pathway has been found to be followed by the insulin sensitising drug metformin. Through the minor pathway (the phospholipase C/Ca^{2+}/Ca^{2+}/calmodulin-dependent protein kinase kinase-dependent pathway), *via* activation of phospholipase C, Ca^{2+} is released from the intracellular calcium ion stores that plays a minor role in activation of AMPK[38].

Works on skeletal muscles have shown that adiponectin, through AMPK activation, not only increases mitochondrial function, but also increases their number. As activated AMPK in skeletal muscles has been found to stimulate mitochondrial biogenesis under conditions of chronic energy deprivation or endurance training, it appears that adiponectin-induced-increase in mitochondrial number is due to stimulation of mitochondrial biogenesis. This action of the adipokine points towards its insulin sensitising action, because mitochondrial function in skeletal muscles is taken as an indicator of whole-body insulin sensitivity. Thus, it may be presumed that adipocyte-mitochondrial action, which regulates adiponectin synthesis in adipocytes (already discussed), also regulates skeletal muscle-mitochondrial (or metabolic) activity and insulin action in skeletal muscles through adiponectin[29].

Though adiponectin does not have any effect on normal insulin secretion, the adipokine has been found to increase it in insulin resistant mice fed with high fat diet. But in such mice, augmentation of secretion occurs only in response to high plasma glucose, but actually inhibited when plasma glucose was low. Adiponectin appears to possess a protective effect on islet-β-cells, as it has been found to reduce the pro-apoptotic effect of FFAs and other cytokines on β-cells[5].

Several workers have demonstrated the capacity of adiponectin to decrease hepatic output of glucose,

thereby contributing towards reduction of plasma glucose concentration and hence, increased insulin sensitivity[5,10]. One of the important causes of increased hepatic output of glucose in diabetes mellitus is increased neoglucogenesis due to inadequate insulin action. As mentioned earlier, adiponectin inhibits hepatic neoglucogenesis by decreasing the formation of two important enzymes concerned, through interference with the mRNA expression that is necessary for the synthesis of these enzymes[10]. Moreover, adiponectin, by increasing the oxidation of FAs, decreases their availability for utilization in the process of neoglucogenesis.

Adiponectin has been found to increase the uptake of glucose by liver and muscles which appears to result from improvement in insulin signalling pathway, leading to better insulin action and hence, decreased blood sugar and increased insulin sensitivity[5].

It has been observed that in obese individuals with IR and in patients having metabolic syndrome (who are IR), adiponectin receptors are downregulated, which suggests inadequate adiponectin action as the cause of IR. *In vitro* and *in vivo* experiments on skeletal muscles have shown adiponectin to increase glucose metabolism and insulin sensitivity *via* activation of AMPK[31].

AR (adiponectin: Resistin) and IR$_{AR}$ indices: Upregulated resistin, which is followed by PPAR-α downregulation, has been found to impair adipocyte differentiation, leading to dramatic decrease in adiponectin formation. Because of such inverse relationship with respect to both secretion and function, it seems to be more predictive to use their ratio (AR index-adiponectin: Resistin) in linking obesity with T2DM than using either of them alone[3].

Besides AR index another novel IR$_{AR}$ index has been coined that seems to be a strong indicator of degree of IR in T2DM. The index appears to relate IR with AR. As expected, AR index value gets smaller and smaller according to the degree of obesity (which determines the magnitude of hypoadiponectinemia with hyperresistinemia), resulting in a parallel rise of IR. Hence, greater the IR$_{AR}$ index value, more is the degree of IR in T2DM.

As IR in T2DM is the major determinant of progression into metabolic syndrome, which in turn, laids the foundation for other complications of diabetes, this index may also be used to predict the arrival of T2DM complications[3].

FACTORS NOT OF ADIPOCYTE ORIGIN

In addition to these adipokines, there are some other factors (not of adipocyte origin), whose role in linking obesity with T2DM cannot be ignored. These factors include PPARs, carnitine, calcium, angiotensin Ⅱ and toll-like receptors (TLRs).

PPARs

This nuclear receptor family, consisting of PPAR-α, PPAR-γ and PPAR-δ, are primarily related with lipid metabolism having fatty acids and their derivatives as their endogenous ligands.

PPAR-α: Besides interference with several steps of lipid metabolism, the main results of this receptor activation is increased oxidation of FA that leads to decreased plasma level of TG by decreasing its synthesis and storage in adipocytes. Moreover, PPAR-α activation, along with activation of PPAR-γ, has been found not only to increase the formation and secretion of adiponectin but also to upregulate AdipoR$_1$/AdipoR$_2$[7].

PPAR-γ: These receptors, mainly expressed in liver and adipose tissue, on stimulation, cause gene expression necessary for differentiation of fibroblasts into adipocytes, and for lipid synthesis and storage in adipocytes. Because of their lipogenicity, they seem to decrease insulin sensitivity rather than increase it. But, their exogenous agonists-TZDs, have been found to decrease IR and increase insulin sensitivity. Such paradoxical actions of TZDs, have been shown to be due to reduced lipotoxicity in liver and skeletal muscles because of lipid storage in adipocytes, and increase in number of small adipocytes, which are not only more sensitive to insulin action, but also secrete large quantity of adiponectin (insulin-sensitising), while decreasing the release of resistin and TNF-α (both are IR-inducing)[7].

PPAR-δ: Main result of this receptor activation is increased FA oxidation, which contributes towards decreasing IR and increasing insulin sensitivity[7].

It may be noted that the results of activation of these three receptors, particularly activation of those of PPAR-α and PPAR-γ, are beneficial in IR and insulin sensitivity through their interference with adipocyte number (increased number of small adipocytes) and function (increased production of adiponectin and decreased production of resistin and TNF-α), FA oxidation (which decreases TG formation in adipocytes resulting in decreased obesity) and upregulation of AdipoR$_1$ and AdipoR$_2$ (decreased IR and increased insulin sensitivity). As all these functions finally lead to reduced obesity, this receptor family can be considered to play a role in linking obesity and T2DM.

Carnitine

This vitamin and amino acid, which is derived from yeast, milk, liver and muscles (in large quantities), increases FFA oxidation through carnitine shuttle reactions. In this reaction, carnitine has been found not only to favour entry of long-chain FFAs across the mitochondrial membrane, but also facilitate the transport of fatty acyl-CoA into mitochondrial matrix for β-oxidation. Therefore, carnitine deficiency, which is commonly found in several IR cases, leads to increased concentration of plasma FFA and hence, their increased conversion into TG in adipocytes, resulting in obesity and further aggravation of IR. Moreover, relative carnitine deficiency may occur in prolonged metabolic stress, which may add to mito-

chondrial dysfunction, leading to reduced glucose tolerance. These two factors may contribute towards obesity-associated IR in T2DM. Therefore, like PPAR-receptor family action, carnitine function in the body may contribute towards linking obesity with diabetes as its deficiency is reflected upon genes of obesity and IR[7].

Calcium

Role of calcium in vario us cellular secretory processes[39], including secretion of insulin from islet β-cells, is well established. Improper regulation of intracellular calcium has been found to affect insulin secretion and its tissue sensitivity adversely[40]. High calcium intake alone or with vitamin D has been shown to reduce not only body weight and fat mass, but also to decrease weight gain and adipocyte fat accumulation. The mechanisms suggested for such beneficial actions include adipocyte apoptosis and reduced adipogenesis along with deranged lipid metabolism[40,41]. Moreover, epidemiological studies have shown that low calcium intake and poor vitamin D status are associated with increased risk of obesity[36]. From such observations, it may be inferred that obesity, thus developed, may lead to increased production of IR-inducing and diabetogenic adipokines, thereby linking it (obesity) with IR and T2DM.

Angiotensin II

Renin-angiotensin-aldosterone system, whose primary function is to maintain water and electrolyte balance of the body and to regulate blood pressure, is known to mediate its function by formation of angiotensin Ⅱ (Ang Ⅱ). Ang Ⅱ formation occurs through several steps where renin of renal origin converts angiotensinogen of hepatic origin to Ang Ⅰ, which is then converted to Ang Ⅱ by the enzyme angiotensin-converting enzyme (ACE) of endothelial cell origin[42]. But recently, a local RAAS has been demonstrated in several tissues of the body including adipose tissue, which is involved in several functions of the adipocytes including adipose tissue growth and cell differentiation. It has been shown that when AT_2 receptors (one of the subtypes of angiotensin receptor) are deleted from adipocytes, the cell size is reduced, and there is protection from diet-induced obesity and IR[43]. Such observations suggest an additional beneficial role of ACE inhibitors and AT_2 receptor blockers, when used as antihypertensives in patients having hypertension with obesity and T2DM[44]. Moreover, like low Ca^{2+} and poor vitamin D status, locally generated Ang Ⅱ, *via* its action on adipocytes, may link obesity with T2DM.

TLRs

TLRs are transmembrane glycoprotein receptors whose known function is antigen recognition[6,45]. Recently, substantial evidences have been put forward which suggest their pathological role in genesis of obesity. In this respect, both TLR-2 and TLR-4 have been found to be overexpressed on adipocytes in obese persons having T2DM. Such overexpressed TLR receptors along with similarly overexpressed adipokines in adipose tissue of obese individuals may play an important role in obesity-associated meta inflammation resulting in IR and T2DM. It has been demonstrated that inhibition of TLR-2 in skeletal muscles and white adipose tissue of mice fed with high fat diet, improves insulin sensitivity and signalling[43].

Moreover, overexpression of TLRs on adipocytes may also suggest an important role of adipose tissue in the regulation of inflammation and innate immunity in human beings by modulating TLR/NF-κB regulatory pathway. Such observations suggest a modulatory role of TLRs in the interaction between the pathways of inflammation and metabolism[43]. The above- discussed roles of TLRs in genesis of obesity, reduction of insulin signalling and sensitivity, and modulation of the interacting pathways of inflammation and metabolism appear to support the correlation between obesity and T2DM.

CONCLUSION

From the discussions made so far, it may be observed that results obtained from extensive research work on the factors supposed to link obesity with T2DM, very clearly show an intimate relationship between the two, for which both adipocytokines as well as some factors not derived from adipocytes have been implicated. Of them, few (Adiponectin, Leptin, PPAR, Carnitine, Apelin and Calcium) are beneficial, while others (TNF-α, IL-6, Resistin, RBP-4, DPP-4, PAI-1, Visfatin, FFA, Ang Ⅱ and TLR) are harmful, but all of them play a definite role in linking obesity with T2DM (mentioned earlier). Among these, adiponectin has been found to play a crucial and seemingly complicated but definite role. Such studies may be extended to all concerned factors giving emphasis on mitochondrial and ER stresses. Finally, using these agents, drugs may be designed which will be helpful to prevent the development of obesity, thereby producing a beneficial response in prevention, progression and treatment of T2DM.

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