Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans

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Am J Physiol Endocrinol Metab 287: E199–E206, 2004; 10.1152/ajpendo.00545.2003.—The available evidence suggests that about two-thirds of the insulin response to an oral glucose load is due to the potentiating effect of gut-derived incretin hormones. The strongest candidates for the incretin effect are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). In patients with type 2 diabetes, however, the incretin effect is lost or greatly impaired. It is hypothesized that this loss explains an important part of the impaired insulin secretion in patients. Further analysis of the incretin effects in patients has revealed that the secretion of GIP is near normal, whereas the secretion of GLP-1 is decreased. On the other hand, the insulintropic effect of GLP-1 is preserved, whereas the effect of GIP is greatly reduced, mainly because of a complete loss of the normal GIP-induced potentiation of second-phase insulin secretion. These two features, therefore, explain the incretin defect of type 2 diabetes. Strong support for the hypothesis that the defect plays an important role in the insulin deficiency of patients is provided by the finding that administration of excess GLP-1 to patients may completely restore the glucose-induced insulin secretion as well as the β-cells’ sensitivity to glucose. Because of this, analogs of GLP-1 or GLP-1 receptor activations are currently being developed for diabetes treatment, so far with very promising results.

THE INCRETIN EFFECT

INCRETIN HORMONES ARE PEPTIDE HORMONES secreted from the gut that can explain the incretin effect: the augmentation of insulin secretion observed after oral glucose intake compared with that observed after an intravenous infusion of glucose resulting in identical elevations of plasma glucose. In normal subjects the augmentation is three- to fourfold (61). Similar increases are noted for arterial C-peptide concentrations, ruling out that differences in hepatic insulin uptake are responsible for the differences. It has been inferred that the intravenous load of glucose required to reproduce the glycemic response to oral glucose by intravenous infusion is much less (about one-third) and that the amount of insulin secreted per unit of glucose administered is about the same. According to this view, the incretin effect therefore merely represents a misinterpretation of data. This, however, raises the question of how the pancreas learns to adjust its insulin secretion to the incoming glucose when the immediate signal, the arterial plasma glucose concentration, is the same. The answer could be neural reflexes, such as the cephalic-phase stimulation of insulin secretion generated by sensory signals, as well as impulses transmitted to the brain via glucose-sensitive neurons in the upper intestinal mucosa (62). Although there is little doubt that such impulses may play a role in the integrated responses of the healthy organism to glucose, they are not indispensable components of the incretin effect. This is evident from studies of subjects with transplanted and therefore completely denervated pancreases, where the magnitude of the incretin effect was the same as in control subjects (the control group consisted of patients with a kidney transplant, because the pancreatic transplant patients all had a simultaneous kidney transplantation as well as the same anti-immune therapy) (58). Rather, the effect is due to the release, from the gut, of hormones capable of potentiating glucose-induced insulin secretion (48). The incretin hormones are thought to constitute an important part of the enteroinsular axis, by which is meant the combined input to the endocrine pancreas of substrates, nerve impulses, and hormones generated by ingestion of mixed meals (7, 76). Clearly, in this complex situation, it is much more difficult to identify the relative contribution of the incretin hormones to the total insulin response. An analysis of the consequences of ablation of the incretin effect for insulin secretion, and hence for glucose tolerance, will of course require a detailed knowledge.
of the contribution of each of the individual factors involved but would, as a first approximation, be expected to result in a reduction of insulin secretion to levels approaching those resulting from intravenous glucose administration in the case of the oral glucose tolerance test. There exists, however, a clinical correlate of great interest in this respect, namely patients with type 2 diabetes mellitus. When investigated using isoglycemic oral and intravenous glucose challenges, such patients have almost no, or a greatly reduced, incretin effect (56). This raises the important question of the extent to which the defective incretin function is responsible for the impaired insulin secretion in this disease. It is the hypothesis of these authors that the impaired incretin effect in type 2 diabetes contributes importantly to the inadequate insulin secretion. This contention is further supported by the recent demonstration that administration of (excess) incretin hormone to diabetic patients may completely normalize their β-cell responsiveness to glucose as well as partly restore the missing first-phase insulin secretion and completely normalize second-phase secretion in response to a glucose clamp (80). It is therefore important to understand the biology of the incretin hormones under normal as well as pathological conditions.

INCRETIN HORMONE CANDIDATES

Glucose-dependent insulinotropic polypeptide. A large number of peptides produced in the gastrointestinal tract, in particular those belonging to the glucagon-secretin superfamily of peptides, can be demonstrated to enhance glucose-induced insulin secretion. Secretin itself is a good example. Secretin powerfully stimulates insulin secretion in healthy subjects as well as in patients with type 2 diabetes (8, 20). The plasma concentrations of secretin required to influence insulin secretion are in the upper range of those normally observed but comparable to those elicited by intraduodenal acidification. Secretin is not released by intraduodenal or oral glucose and therefore does not qualify as an incretin in the strict sense (20) but may contribute in the more complex setting of mixed-meal ingestion. Among the peptides that actually are released in response to oral glucose, two additional members of the same peptide family, namely glucose-dependent insulinotropic polypeptide (GIP, formerly known as gastric inhibitory polypeptide) and glucagon-like peptide 1 (GLP-1) have attracted the most attention.

GIP was discovered in 1973 on the basis of its ability to inhibit acid secretion in denervated gastric pouches, but its insulinotropic properties were discovered soon after (11). GIP is a peptide of 42 amino acids processed from a precursor of 153 amino acids (71). The GIP receptor is a type II G protein-coupled receptor belonging to a superfamily of receptors the ligands of which (with a few exceptions) are constituted by the members of the secretin-glucagon family of peptides (47). It is expressed in the pancreatic islets and also in the gut, adipose tissue, heart, pituitary, adrenal cortex, and several regions of the brain. Its functions in many of those locations are generally unknown. GIP is secreted from specific endocrine cells, the so-called K cells, which exhibit the highest density in the duodenum, but GIP-producing cells may be found in the entire small intestinal mucosa (54). Secretion is stimulated by absorbable carbohydrates and by lipids. GIP secretion is therefore greatly increased in response to meal ingestion, resulting in 10- to 20-fold elevations of the plasma concentration.

Interaction of GIP with its receptor on the pancreatic β-cells causes an elevation of cAMP levels, which, in turn, increases the intracellular calcium concentration and enhances the exocytosis of insulin-containing granules (9, 83) (Fig. 1). A number of other signaling pathways may also be activated (presumably secondarily to the rise in cAMP), including the
MAP kinase as well as the phosphatidylinositol 3-kinase/protein kinase B pathways (17, 18, 47, 73).

The incretin function of GIP has been probed in immunoneutralization studies (12, 41) and, more recently, in studies employing a fragment, GIP-(7–30) amide, which turns out to be a GIP receptor antagonist (74), or antibodies to the GIP receptor (43). All treatments reduced insulin responses to oral glucose and impaired glucose tolerance. Mice with a targeted deletion of the GIP receptor gene become glucose intolerant (52). Using the Pro3 GIP antagonist in ob/ob mice, Gault et al. (26) found that GIP might be responsible for as much as 80% of the incretin effect in these animals. Using the mimicry approach, wherein endogenous concentrations are mimicked by intravenous infusion (in this case infusions of both GIP and glucose), Nauck et al. (55) demonstrated that the elevated GIP concentrations elicited by oral glucose can completely account for the accompanying augmented insulin release. Nevertheless, from other experiments it is evident that GIP is not the only incretin hormone. Immunoneutralization experiments clearly showed that intestinal extracts contain potent insulinotropic agents in addition to GIP (13). Furthermore, investigations by Lauritsen et al. (42) in patients with resections of different parts of the small intestine, as well as in patients with celiac disease, showed that their incretin effect (as studied using isoglycemic intravenous and oral glucose challenges as described above) did not correlate to the secretion of GIP. The distal small intestine, therefore, had to release an additional incretin hormone (42).

Glucagon-like peptide 1. The other incretin hormone released from the distal small intestine in these experiments (but not necessarily from the distal small intestine in healthy subjects, in whom the upper small intestine may participate) is probably glucagon-like peptide 1 (GLP-1).

GLP-1 is a product of the glucagon gene. This gene is expressed not only in the pancreatic α-cells but also in the L cells of the intestinal mucosa, perhaps the most abundant endocrine cells of the gut (53). Here, the primary translation product proglucagon is cleaved, not to produce glucagon, as in the islets, but to release from its COOH-terminal part the two glucagon-like peptides GLP-1 and GLP-2 (64), both showing ~50% sequence homology with glucagon. The NH2-terminal part of the precursor, which includes the glucagon sequence, is secreted as a single, rather large peptide designated glicentin (formerly called gut glucagon or GLI), which most likely is biologically inactive. Some of the glicentin moieties are cleaved further to release the peptide oxyntomodulin, which corresponds to the glucagon sequence plus the additional COOH-terminal octapeptide of glicentin. This peptide is insulinotropic (2) and probably explains the insulinotropic activity of some preparations of “gut glucagon,” described in earlier publications. However, as a circulating hormone in humans, its concentration is probably too low to significantly influence insulin secretion under physiological circumstances (31). However, it has recently attracted considerable interest because of its appetite-inhibiting properties (6). GLP-1 secretion is stimulated by the presence of nutrients in the lumen of the gut (but additional neural or endocrine mechanisms may also operate), and the secretion of GLP-1 throughout the day is highly correlated to the release of insulin.

GLP-1 is one of the most potent insulin-releasing substances known, with half-maximal effective concentrations for its effects on the β-cells ~10 pmol/l (22). It is strongly insulinotropic in mimicry experiments (39), and animal experiments involving an antagonist of the GLP-1 receptor have indicated that GLP-1 is responsible for a substantial part of the insulin response to oral glucose (37, 82). Furthermore, experiments with the same antagonist in humans have suggested that GLP-1 may be essential for normal glucose tolerance (14). In agreement with these observations, mice with a targeted deletion of the GLP-1 receptor become glucose intolerant and may develop fasting hyperglycemia (69).

GLP-1’s insulinotropic activity, which is strictly glucose dependent, is exerted via interaction with a specific receptor located on the cell membrane of the β-cells. The GLP-1 receptor belongs to the same family as the GIP receptor (47). Binding of GLP-1 to the receptor causes activation, via a stimulatory G protein, of adenylate cyclase, resulting in the formation of cAMP. Figure 1 shows that subsequent activation of protein kinase A and the cAMP-regulated guanine nucleotide exchange factor II (cAMP-GEFII, also known as Epac2) leads to a plethora of events, including altered ion channel activity, intracellular calcium handling, and enhanced exocytosis of insulin-containing granules (34). As mentioned, a certain level of glucose must be present for GLP-1 to have any effect on insulin secretion. In addition, GLP-1 strongly potentiates the insulinotropic actions of glucose itself. Conversely, it seems that GLP-1 (or perhaps any hormone that causes sufficient cAMP accumulation in the β-cells?) is required for glucose to exert its activity. Thus experiments revealed that, in a subpopulation of single β-cells, neither glucose nor GLP-1 alone affected intracellular calcium levels or membrane potential, whereas together they brought about a strong activation (28, 35). In other words, GLP-1 conveys “glucose competence” to β-cells. The effects of glucose and GLP-1 may converge at the level of the ATP-sensitive K+ (KATP) channels of the β-cells. These channels are sensitive to the intracellular ATP levels and, thereby, to glucose metabolism of the β-cells, but may also be affected (closed, resulting in subsequent depolarization of the plasma membrane and opening of voltage-sensitive calcium channels) by protein kinase A activated by GLP-1 (27, 35). However, there is also evidence that GLP-1 acts as a glucose sensitizer. Thus GLP-1 may facilitate glucose-dependent mitochondrial ATP production (75) (Fig. 1). At any rate, it is of potential clinical importance that sulfonylurea drugs, which bind to and close the KATP channels and thereby cause membrane depolarization and calcium influx, may uncouple the glucose dependence of GLP-1. Thus GLP-1 administration to isolated perfused rat pancreases at low perfusate glucose concentrations, which normally does not affect insulin secretion, resulted in dramatic stimulation of insulin secretion after pretreatment with sulfonylurea drugs (30). It is has been shown that cAMP generated by activation of the GLP-1 receptor may also influence the exocytotic process directly, and this process has been estimated to account for up to 70% of the entire secretory response. ATP may directly influence the exocytotic process, which may therefore represent another site of convergence for the glucose- and GLP-1-mediated signals (29). The clinical implication of the dependence on blood glucose concentrations at or above normal fasting glucose levels is, of course, that GLP-1 is incapable of causing profound hypoglycemia (except perhaps in the presence of sulfonylurea drugs). It should be noted, however, that
GLP-1 receptor signaling is not indispensable for glucose responsiveness, as GLP-1 receptor knockout mice exhibit normal insulin responses to glucose in vitro (25).

Second, GLP-1 stimulates all steps of insulin biosynthesis as well as insulin gene transcription (23), thereby providing continued and augmented supplies of insulin for secretion. Activation of pancreatic duodenal homeobox-1, a key regulator of islet growth and insulin gene transcription, may be involved (4). In addition, GLP-1 upregulates the genes for the cellular machinery involved in insulin secretion, such as the glucokinase and GLUT2 genes (4).

Finally and most importantly, GLP-1 has been shown to have trophic effects on β-cells (15). Not only does it stimulate β-cell proliferation (70, 84), it also enhances the differentiation of new β-cells from progenitor cells in the pancreatic duct epithelium (86). A proliferation was also induced in aging glucose-intolerant rats, with a resulting improvement of glucose tolerance (66). Most recently, GLP-1 has been shown to be capable of inhibiting apoptosis of β-cells (21, 44). Because the normal number of β-cells is maintained in a balance between apoptosis and proliferation (3), this observation is of considerable interest and also raises the possibility that GLP-1 could be useful in conditions with increased β-cell apoptosis. All of this suggests that GLP-1 may be capable of providing new β-cells in individuals such as patients with type 2 diabetes mellitus with an insufficient number of functioning cells (5) (although it is not yet established to what extent this process occurs in humans).

**GIP, GLP-1, or both?** For reasons that will be evident below, the number of published studies regarding the effects of GLP-1 on the β-cells greatly exceeds the number of studies describing the effects of GIP. But in essence, important differences between the actions of the two peptides on β-cells have not been discovered so far (Fig. 1). All of the effects discussed above for GLP-1 would therefore be expected to be shared by GIP. However, when it comes to effects on the non-β-islet cells, a dramatic difference emerges. GLP-1 strongly inhibits glucagon secretion (39, 65), whereas GIP is a weak stimulant of glucagon secretion (49). This differential effect cannot be explained on the basis of our current knowledge of the effects of the two peptides on the islets. Both peptides stimulate the secretion of insulin and somatostatin, both of which might inhibit glucagon secretion in a local manner. These effects, therefore, cannot explain the difference. So far, reported direct effects of both peptides on α-cells have included only stimulatory effects (10).

Are the two hormones equally important physiologically? GIP circulates in up to 10-fold higher concentrations than GLP-1 after a meal. On the other hand, most investigators have found that GLP-1 is more potent than GIP (59). In many reports, GIP was found incapable of stimulating insulin secretion at fasting glucose levels and was even reported to have little effect at glucose concentrations <8 mmol/l. Vilsboll et al. (81), therefore, recently reinvestigated the insulinotropic effects of the two hormones infused at rates that would result in physiological elevations of their concentrations. The infusions were carried out while glucose concentrations were clamped at fasting or slightly elevated levels to mimic as accurately as possible the prandial situation (81). At their physiological postprandial concentrations, the two hormones had similar and highly significant insulinotropic effects at fasting glucose levels as well as at 6 mmol/l, whereas at 7 mmol/l GLP-1 was somewhat more effective. It was concluded that both hormones normally contribute to the incretin effect in humans and do so nearly from the beginning of the meal (because increases in their concentrations are seen already after 5–10 min). Together, the two hormones appear to act in an additive manner. Thus, when GIP and GLP-1 infusions, which separately provided about the same insulin response, were combined, the resulting response amounted to approximately the sum of the two individual responses (57). Recently, mice with a double knockout of the GIP and GLP-1 receptors have been generated. Preliminary results obtained in these animals are consistent with an additive effect of the two hormones, with additive effects on glucose tolerance of the double knockout compared with each of the single receptor knockouts (67). These double knockouts should also allow the investigation of whether an incretin effect remains after deletion of the two most prominent candidates so far.

**INCRETIN EFFECT IN TYPE 2 DIABETES MELLITUS**

Assuming that GIP and GLP-1 are the most important incretin hormones, it is possible to analyze the nature of the incretin defect in patients with type 2 diabetes. Theoretically, the defect could be due to impaired secretion or accelerated metabolism of the incretin hormones; alternatively, the effect of the hormones could be compromised.

There are many publications on the secretion of GIP in type 2 diabetes, and increased, normal, and decreased secretion has been reported (38). Generally, GIP secretion has been reported to be normal or slightly impaired. In a recent study in patients with type 2 diabetes, covering a very wide clinical spectrum of the disease, Toft-Nielsen et al. (72) found near-normal fasting levels and meal responses, with no correlations between metabolic parameters and GIP responses. In the same study, a very significant impairment of the secretion of GLP-1 was observed. By multiple regression analysis, the impairment was found to be related to impaired β-cell function. Individuals with impaired glucose had an intermediary GLP-1 response. In a previous study in a small group of identical twins discordant for type 2 diabetes, the GLP-1 response was lower in the diabetic twin (77). Furthermore, in first-degree relatives of diabetic patients, 24-h GLP-1 profiles were normal (63). These observations probably indicate that the impaired secretion is a consequence rather than a cause of diabetes. Theoretically, the lower GLP-1 concentrations could be caused by an increased elimination of GLP-1 in diabetic subjects compared with healthy subjects, but in a recent study (78), elimination rates were nearly identical in the two groups, indicating that differences in elimination cannot explain the lower concentrations in type 2 diabetic patients.

An impaired secretion of GLP-1, therefore, is likely to contribute to the impaired incretin effect in type 2 diabetes. Regarding the effect of the hormones, another important difference emerges. Nauck et al. (59) studied the effects of intravenous infusions of GIP and GLP-1 in moderately type 2 diabetic patients and matched controls and found that the insulinotropic effect of GIP was almost lost in the patients, whereas the insulin response to GLP-1 was similar to that observed in the controls. Similar results were obtained by Elahi et al. (19). This raises the question of the function of GIP
receptors in these patients. Loss-of-function mutations or impaired expression of GIP receptors could explain the impaired effect (33). Several groups have reported polymorphisms in the coding region of the GIP receptor gene, but these were associated neither with diabetes (40) nor with defective signaling of the receptor (1). On the other hand, a defective expression of the GIP receptor has been observed in animals with experimental diabetes (45). Studies in glucose-tolerant first-degree relatives of diabetic patients showed a reduced insulinotropic effectiveness of GIP in 50% of the subjects compared with controls without a family history of diabetes, indicating that the GIP defect could be a genetically determined and possibly primary defect (50). In a recent study, Vilsboll et al. (80) studied the differential effects of high doses of GIP and GLP-1 in type 2 diabetic patients during the conditions of a 15 mmol/l hyperglycemic clamp. In those studies, the GLP-1 infusion was capable of restoring the late-phase (30–120 min) insulin response to glucose (which was nearly absent in those patients) to values indistinguishable from those observed in the healthy controls. In other words, with GLP-1, the subjects showed a completely normal insulin response to glucose. A similar observation (that GLP-1 can restore β-cell responsiveness to glucose in patients with type 2 diabetes) was made by Kjems et al. (36) by use of an entirely different approach. Moreover, the normal glucose-induced inhibition of glucagon secretion, which is lost in the patients, was completely restored. GIP, however, regardless of dose, had no effect either on second-phase insulin secretion or on glucose turnover but induced a first-phase response that was reduced to the same extent as the first-phase response to GLP-1. It was concluded that the GIP defect in type 2 diabetes is very severe indeed but restricted to late-phase insulin secretion, which may be particularly relevant for postprandial insulin secretion. The preserved first-phase response was taken to indicate that absence of GIP receptor function could not explain the lost effect on second-phase secretion. In further studies using the same technique, Vilsboll et al. (79) investigated groups of diabetic patients known or suspected to have diabetic etiologies different from those of the classical obese elderly type 2 patients. The groups included patients with type 1 diabetes, diabetes secondary to pancreatitis, monogenic diabetes [maturity onset of diabetes in the young (MODY 3)], lean type 2 diabetic patients and patients with latent autoimmune diabetes in adults (LADA). It was the underlying hypothesis that these patients would not exhibit a comparable GIP defect, on the basis of the assumption that the GIP defect was a genetic defect contributing to the phenotype of the typical type 2 patient. Again, however, the results were unexpected. The different groups had clearly lower relative insulin responses to GIP compared with nondiabetic controls, and, for example, the patients with secondary diabetes had virtually absent late response to GIP and no effect on glucose turnover. It was concluded that the observed GIP defect in those patients was a consequence of the diabetic state, and although a genetic component may also be involved in type 2 diabetic patients, as demonstrated in the study of the first-degree relatives (50), the defect induced by diabetes itself is very severe. Because the intracellular machinery of the β-cell of the diabetic pancreas functions normally when tested with GLP-1, the mechanism of action of which is identical to that of GIP (Fig. 1), it is tempting to speculate that the lack of late-phase insulin secretion in the different groups of diabetic patients (79) might result from an enhanced desensitization and/or internalization of a normal or reduced number of GIP receptors (46). This observation raises the interesting question whether the GIP response will be at least partially restored in type 2 diabetic patients with completely normalized blood glucose levels. It may therefore be concluded that the incretin defect in type 2 diabetes has two causes, namely a decreased secretion of GLP-1 and a dramatically impaired insulinotropic effect of GIP. Detailed studies of the effects of GLP-1 in type 2 diabetic patients (36), involving analysis of prehepatic insulin secretion during stepwise increases in blood glucose in the absence or presence of varying doses of GLP-1, revealed that the massive enhancement of β-cell responsiveness to glucose (which was normalized in the presence of even the lowest dose of GLP-1, 0.5 pmol·kg⁻¹·min⁻¹) was, nevertheless, much weaker in the patients than in the matched controls. Therefore, a reduced β-cell sensitivity to GLP-1 is likely to also contribute to the impaired incretin effect. Under the assumption that the incretin defect is of pathogenetic importance for type 2 diabetes mellitus and that the main causes are impaired secretion of GLP-1 and loss of insulinotropic effects of GIP, it would seem logical to try to administer GLP-1 to ameliorate the deficiencies. As might have been expected, GLP-1 is uniquely effective in restoring glucose metabolism in these patients. Low doses of GLP-1 invariably normalize blood glucose levels in the fasting state regardless of severity of diabetes (60), and intravenous infusions of GLP-1 were reported to cause near normalization of plasma glucose levels also during meal intake (68). The main problem associated with the utilization of GLP-1 as a therapeutic agent is its instability in plasma [resulting in an apparent half-life of 1–2 min (78)], and several pharmaceutical companies are currently developing stable GLP-1 receptor agonists to circumvent this problem (32). Zander et al. (85) employed continuous subcutaneous infusion to investigate the potential of GLP-1 treatment in type 2 diabetes. Two groups of patients were washed out with respect to oral antidiabetic treatment and were given either saline or GLP-1 for 6 wk. The patients were evaluated before, after 1 wk, and after 6 wk of treatment. No changes were observed in the saline-treated group, whereas in the GLP-1 group fasting and average plasma glucose concentrations were lowered by ~5 mmol/l, hemoglobin A₁c decreased by 1.3%, free fatty acids were significantly lowered, and the patients had a significant weight loss of ~2 kg. In addition, insulin sensitivity, as determined by a hyperinsulinemic euglycemic clamp, almost doubled, insulin secretion capacity (measured using a 30 mmol/l glucose clamp + arginine) was greatly improved, and the lost first-phase insulin secretion was restored. There was no significant difference between results obtained after 1 and after 6 wk of treatment, but there was a tendency toward further improvement of plasma glucose as well as insulin secretion. There were very few side effects and no differences between saline- and GLP-1-treated patients in this respect. It should be noted that the dose selected was not necessarily maximal (and was not associated with side effects). Further studies using the same technique indicated that a higher infusion rate might be even more effective (16). Essentially similar results were found by Meneilly et al. (51). Very recent studies with a stable GLP-1 agonist, exendin-4, have given similarly encouraging results (24).
Currently, there are no indications as to whether or not a trophic effect of GLP-1, as observed in rodents, will also be demonstrable in humans. Given that the extent of adaptive changes in the β-cell mass in humans is much lower than that observed in, for example, mice (5), it seems likely that such changes will be much more difficult to demonstrate, or that relevant therapy might be maintained for a long time, before significant effects might be apparent.

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REFERENCES


