Nutrient secretagogues can increase the production of succinyl-CoA in rat pancreatic islets. When succinate esters are the secretagogue, succinyl-CoA can be generated via the succinate thiokinase reaction. Other secretagogues can increase production of succinyl-CoA secondary to increasing α-ketoglutarate production by glutamate dehydrogenase or mitochondrial aspartate aminotransferase followed by the α-ketoglutarate dehydrogenase reaction. Although secretagogues can increase the production of succinyl-CoA, they do not increase the level of this metabolite until after they decrease the level of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). This suggests that the generated succinyl-CoA initially reacts with acetoacetate to yield acetoacetyl-CoA plus succinate in the succinyl-CoA-acetoacetate transferase reaction. This would be followed by acetoacetyl-CoA reacting with acetyl-CoA to generate HMG-CoA in the HMG-CoA synthetase reaction. HMG-CoA will then be reduced by NADPH to mevalonate in the HMG-CoA reductase reaction and/or cleaved to acetoacetate plus acetyl-CoA by HMG cleavage enzyme. Succinate derived from either exogenous succinate esters or generated by succinyl-CoA-acetoacetate transferase is metabolized to malate followed by the malic enzyme reaction. Increased production of NADPH by the latter reaction then increases reduction of HMG-CoA and accounts for the decrease in the level of HMG-CoA produced by secretagogues. Pyruvate carboxylation catalyzed by pyruvate carboxylase will supply oxaloacetate to mitochondrial aspartate aminotransferase. This would enable this aminotransferase to supply oxaloacetate to mitochondrial aspartate aminotransferase. This would enable this aminotransferase to supply α-ketoglutarate to the α-ketoglutarate dehydrogenase complex and would, in part, account for secretagogues increasing the islet level of succinyl-CoA after they decrease the level of HMG-CoA. Mevalonate could be a trigger of insulin release as a result of its ability to alter membrane proteins and/or cytosolic Ca++. This is consistent with the fact that insulin secretagogues decrease the level of the mevalonate precursor HMG-CoA. In addition, inhibitors of HMG-CoA reductase interfere with insulin release and this inhibition can be reversed by mevalonate. Diabetes 51:2669–2676, 2002
FIG. 1. Scheme 1: Interaction between succinate and HMG-CoA metabolism. This scheme shows how a high mitochondrial level of succinate (as would be present when succinate esters are added) could increase the level of succinyl-CoA (S-CoA) by reversing the succinate thiokinase reaction (reaction 1). Succinyl-CoA could then divert acetocetate (AcAc) from the 3-hydroxybutyrate dehydrogenase (reaction 14) and to the succinyl-CoA-acetoacetate transferase reaction (reaction 2) so that succinate would be regenerated and acetocetyl-CoA (AcAc-CoA) would be produced, AcAc-CoA would then react with acetyl-CoA (Ac-CoA) in the HMG-CoA synthetase reaction (reaction 3) to produce HMG-CoA. The latter would then be reduced to mevalonate by HMG-CoA reductase (reaction 4) and/or cleaved to Ac-CoA plus AcAc by HMG-CoA cleavage enzyme (reaction 5). Scheme 1 also shows how nutrient secretagogues, which increase production of \( \alpha \)-ketoglutarate (aKG) by mitochondrial aspartate aminotransferase (reaction 16), glutamate dehydrogenase (reaction 17), or NAD-isocitrate dehydrogenase (reaction 15), can enhance production of succinyl-CoA by the \( \alpha \)-ketoglutarate dehydrogenase complex (reaction 13). This scheme shows that succinate would then be utilized to produce mevalonate and succinate as described above for the case when succinate is the secretagogue. The generated succinate, as exogenous succinate, would be converted into malate (Mal) by the combined succinate dehydrogenase-fumarase reactions (reactions 6 and 7, respectively). Malate would then leave the mitochondria and enter the cytosol where it would be converted into pyruvate (Py) by malic enzyme (reaction 8). The generated pyruvate then enters the mitochondria where it is converted into acetyl-CoA (Ac-CoA) by the pyruvate dehydrogenase complex (reaction 10). Ac-CoA is utilized to produce AcAc-CoA in the ketothiolase reaction (reaction 11), and Ac-CoA plus AcAc-CoA then provide HMG-CoA synthetase with its substrates. Pyruvate is also converted into oxaloacetate by pyruvate carboxylase (reaction 9), which supplies citrate synthase (reaction 12) and mitochondrial aspartate aminotransferase with substrate. Also shown is the production of HMG-CoA by the metabolism of leucine (Leu). The basic reactions for the synthesis of mevalonate, the proposed signal of insulin release, are enclosed by the dashed lines. Additional abbreviations are glutamate (Glut), fumarate (Fum), 3-hydroxybutyrate (3-hydroxybut), and malonyl-CoA (Mal-CoA).

entering the mitochondria, where it is converted into Ac-CoA and oxaloacetate by pyruvate dehydrogenase (reaction 10 of Scheme 1) and pyruvate carboxylase (reaction 9 of Scheme 1), respectively. The generated Ac-CoA plus AcAc-CoA produced from Ac-CoA by ketothiolase (reaction 11 of Scheme 1) would then be utilized as substrates by HMG-CoA synthetase.

Succinate metabolism would also enhance insulin release as a result of increased NADPH production by malic enzyme. This, in turn, would increase the production of mevalonate by HMG-CoA reductase. The importance of malic enzyme is indicated by the fact that succinate is not a secretagogue in mouse islets that, unlike rat islets, do not possess malic enzyme activity (M.J.M., unpublished observations).

According to our proposed mechanism, which we refer to as the succinate mechanism, a basic requirement for insulin release would be the generation of mevalonate. Thus, the insulinotropic action of succinate and other nutrient secretagogues could be mediated by an increase in flux through the reactions enclosed in Scheme 1. These reactions are SAT, HMG-CoA synthetase, HMG-CoA reductase, and HMG-CoA cleavage enzyme (reactions 2–5 of Scheme 1). The net of these four reactions (starting with the SAT reaction with succinyl-CoA) is succinyl-CoA + HMG-CoA + two NADPH + two H\(^+\) \(\rightarrow\) succinate + two CoA + mevalonate + two NADP. When succinate esters are the secretagogues, the succinyl-CoA that reacts with SAT would be produced by succinate thiokinase. The \( \alpha \)-ketoglutarate dehydrogenase complex (reaction 13 of Scheme 1) would generate succinyl-CoA in the case of many other nutrient secretagogues. In this sequence of reactions, HMG-CoA is consumed, while mevalonate is generated. This is consistent with the fact that an early event after administration of insulin secretagogues is a marked decrease in the level of HMG-CoA (10,11). In addition to mevalonate, succinate is another net product of this sequence of reactions. Therefore, when succinate esters are the secretagogue or when other secretagogues generate succinate via this reaction sequence, succinate metabolism could lead to a buildup of oxaloacetate by pyruvate carboxylase, as previously described. This could enhance the activity of citrate synthase (reaction 12 of Scheme 1) and mitochondrial aspartate aminotransferase (reaction 16 of Scheme 1). Consequently, \( \alpha \)-ketoglutarate production by this aminotransferase and isocitrate dehydrogenase (reaction 15 of scheme 1) could be increased, which would increase succinyl-CoA production by the \( \alpha \)-ketoglutarate dehydrogenase complex (reaction 13 of Scheme 1). This could, in part, explain why nutrient secretagogues, after decreasing the level of HMG-CoA, increase the level of succinyl-CoA (10,11). In addition, increased citrate production could result in increased utilization of citrate for the production of malonyl-CoA (Scheme 1). This could account for the fact that after decreasing the level of HMG-CoA, nutrient secretagogues also increase the level of malonyl-CoA (10,11).

The succinate mechanism is also consistent with the fact that we (L.A.F. and M.J.M., unpublished observations) found that the specific activity of SAT, with AcAc as a substrate, was quite high in rat islet mitochondrial fractions, and others (12–17) have found that islets have the capacity to oxidize ketone bodies. This indicates that in islet mitochondria, the level of SAT is sufficiently high for it to play the role that we propose.

According to the succinate mechanism, flux through aminotransferases would not be essential for insulin release promoted by succinate esters, but flux through succinate dehydrogenase would be essential for the insulinotropic action of essentially all secretagogues. Consequently, we found that in rat islets, the insulinotropic actions of both glucose and methylsuccinate was completely blocked by the potent succinate dehydrogenase inhibitor 3-nitropropionate (1 mmol/l). However, even 10 mmol/l levels of the aminotransferase inhibitor aminooxy-
ROLE OF MEVALONATE
According to the succinate mechanism, production of mevalonate by the reactions enclosed in Scheme 1 results in insulin release. This concept is supported by the fact that before insulin secretagogues promote insulin release, they decrease the islet level of the mevalonate precursor HMG-CoA (10,11). Furthermore, it is known that intact pancreatic islets synthesize and metabolize mevalonate (18,19). In addition, lipid-soluble HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, inhibit glucose-promoted insulin release from rat islets, and this can be prevented by mevalonate (18–20).

Triggering of insulin release by mevalonate could be related to the known ability of mevalonate to alter membrane proteins and/or the cytosolic level of Ca^{2+}. For example, G-proteins require isoprenylation for their association with membranes, and many GTP-binding proteins are modified by mevalonate-dependent isoprenylation (18,19). In islets, lovastatin decreases protein isoprenylation and produces accumulations in the cytosol of low-molecular weight GTP-binding proteins. However, adding mevalonate totally prevented these effects (18).

In addition, simvastatin inhibits the first phase increase in oscillations of cytoplasmic Ca^{2+} induced by glucose in β-cells, reversibly inhibits β-cell L-type Ca^{2+} channels, and inhibits the increase in cytosolic Ca^{2+} produced by L-arginine and KCl (20).

ROLE OF GLUTAMATE DEHYDROGENASE AND MITOCHONDRIAL ASPARTATE AMINOTRANSFERASE
According to the above discussion, succinate and other nutrient secretagogues enhance mevalonate production and insulin release by increasing flux through the reactions enclosed in Scheme 1. As shown in the following section, in the case of many nutrient secretagogues, the succinyl-CoA required to increase flux through this pathway is generated as a result of the secretagogue associating with and thereby enhancing α-ketoglutarate production by either glutamate dehydrogenase or mitochondrial aspartate aminotransferase (reactions 16 and 17 of Scheme 1) (21–24). This would be followed by increased production of succinyl-CoA by the α-ketoglutarate dehydrogenase complex.

Glutamate dehydrogenase and mitochondrial aspartate aminotransferase could be more efficient in supplying the α-ketoglutarate dehydrogenase complex with α-ketoglutarate than other mitochondrial enzymes that generate α-ketoglutarate. This is because, according to our results obtained with a system of pure enzymes (25–28) as well as with intact mitochondria obtained by others (29), glutamate dehydrogenase and mitochondrial aspartate aminotransferase can form a complex with the α-ketoglutarate dehydrogenase complex. Consequently, via substrate channeling α-ketoglutarate bound to glutamate dehydrogenase or aspartate aminotransferase can be a better substrate than free α-ketoglutarate for the α-ketoglutarate dehydrogenase complex (25–29).

Glucose cannot directly enhance the activity of either glutamate dehydrogenase or mitochondrial aspartate aminotransferase. However, according to the succinate mechanism, glucose is an ideal secretagogue because it can be metabolized to pyruvate, which can be utilized to generate Ac-CoA via the pyruvate dehydrogenase reaction (reaction 10 of Scheme 1). Ac-CoA plus AcAc-CoA generated from Ac-CoA via ketothiolase (reaction 11 of Scheme 1) can then supply HMG-CoA synthetase with its substrates. Pyruvate can also be utilized in the pyruvate carboxylase reaction (reaction 9 of Scheme 1) to generate oxaloacetate. α-Ketoglutarate production by mitochondrial aspartate aminotransferase can then be enhanced as a result of this enzyme transaminating oxaloacetate with glutamate.

COMPATIBILITY OF SECRETAGOGUES WITH SUCCINATE MECHANISM
According to the above sections, nutrient secretagogues increase mevalonate production secondary to increasing succinyl-CoA production followed by the reactions enclosed in Scheme 1. In the following discussion, we will determine whether the succinate mechanism can explain how known and proposed secretagogues can promote insulin release.

Phenylpyruvate. Phenylpyruvate is insulinotropic (30, 31). According to the succinate mechanism, this could be because phenylpyruvate can enhance production of α-ketoglutarate by mitochondrial aspartate aminotransferase as a result of associating with this enzyme followed by transaminating with glutamate (21). Furthermore, although γ-aminobutyric acid (GABA) alone has no effect on insulin release, it enhances the insulinotropic effect of phenylpyruvate (30). This would be consistent with the succinate mechanism because, when phenylpyruvate plus glutamate are transaminated by mitochondrial aspartate aminotransferase, GABA could facilitate a bypass of the generated α-ketoglutarate away from the α-ketoglutarate dehydrogenase complex and toward GABA aminotransferase to yield succinate semialdehyde. The latter can then be directly converted to succinate by succinate semialdehyde dehydrogenase. Succinate thiokinase could then convert succinate into succinyl-CoA, which via the reactions enclosed in Scheme 1, could be utilized to generate mevalonate. This “bypass” mechanism would be enhanced by the high affinity GABA aminotransferase has for succinate semialdehyde dehydrogenase (32) and the considerably higher level of GABA aminotransferase and succinate semialdehyde dehydrogenase present in islet mitochondria than in the mitochondria of other peripheral organs (33). This system of reactions is also of interest because GABA is generated by glutamate decarboxylase, a known β-cell antigen in insulin-dependent diabetes (34).

Glutamate. It has been proposed that glutamate is the primary messenger of insulin release (35). However, this is not the case in rat islets, where we (36) found that although glucose (16.7 mmol/l), methylsuccinate (10 mmol/l), leucine (10 mmol/l), and α-ketoisocaproate (10 mmol/l) markedly enhanced insulin release, none of these secretagogues increased the intracellular level of glutamate over its basal level of 21–25 nmol/mg protein. We also found that glutamine (10 mmol/l) did not promote insulin release, even though it increased the intracellular level of glutamate to 10-fold over basal levels. Therefore, as pre-
vously shown (3,23,24), these results demonstrate that although glutamine provides ample glutamate to function as a putative signal and ample NH₄⁺ for the generation of glutamate by glutamate dehydrogenase, increasing the intracellular level of glutamate with glutamine alone does not promote insulin release. In addition, we (36) found that although the combination of leucine (10 mmol/l) plus glutamine (10 mmol/l) decreased the level of glutamate to 138 nmol/mg protein from its value of 256 nmol/mg protein with glutamine alone, it markedly increased insulin release over that produced by leucine alone. This is consistent with previous results (23,24) that demonstrated that the combination of leucine plus glutamine increases glutamate utilization by glutamate dehydrogenase more than that produced by either alone. This could be because leucine plus glutamate functions synergistically in increasing α-ketoglutarate production by glutamate dehydrogenase (37). According to the succinate mechanism, this increase in α-ketoglutarate, and ultimately succinyl-CoA and mevalonate, production would be responsible for the observation that the combination of leucine plus glutamine increases insulin release more than that produced by leucine alone (23,24).

**Leucine.** Leucine and its nonmetabolized analog 2 amino (2.2.1) heptane carboxylic acid (BCH) are the only amino acids that by themselves can promote insulin release, and they are also the only ones that can allosterically activate glutamate deamination by glutamate dehydrogenase (3,22–24). Furthermore, metabolites that can increase glutamate deamination by glutamate dehydrogenase can also enhance leucine-induced insulin release, and leucine-induced insulin release can be decreased by metabolites that lead to the inhibition of glutamate deamination (3).

According to the succinate mechanism, leucine would enhance insulin release because, as mentioned above, increased generation of α-ketoglutarate by glutamate dehydrogenase would lead to enhanced production of mevalonate and succinate via the reactions enclosed in Scheme 1. However, as also shown in Scheme 1, the metabolism of leucine to HMG-CoA and ultimately mevalonate might also contribute to the insulinotropic action of leucine. Consequently, leucine is not a secretagogue in glucose-treated islets, which have a decreased level of branch chain ketoacid dehydrogenase, unless glutamine is also added (38,39). However, BCH alone that is not metabolized can promote insulin release. This could be because BCH, unlike leucine, can activate glutaminase (40). This indicates that if leucine metabolism is absent, as is the case with glucose-treated islets or when BCH is the secretagogue, then glutamate is also required for insulin release. Glutamate would be produced by glutaminase reacting with exogenous glutamine when leucine is the secretagogue. When BCH is the secretagogue, glutamate would be produced by glutaminase reacting with endogenous glutamate.

In the absence of leucine or BCH, glutamine neither promotes insulin release nor markedly increases glutamate dehydrogenase activity (23,24,36). This could be because glutamate is the most abundant amino acid in islets, where its level is at least 1–2.5 mmol/l (36,41). In the absence of BCH or leucine, the Kₘ of glutamate in the glutamate dehydrogenase reaction is 0.2–0.5 mmol/l. Thus, the addition of glutamine might fail to increase flux through glutamate dehydrogenase because this enzyme is already saturated with glutamate. However, the Kₘ of glutamate in the mitochondrial aspartate aminotransferase is high, ~18 mmol/l (25). Therefore, in islet mitochondria in the absence of leucine or BCH, glutamine by increasing glutamate levels markedly increases flux through this aminotransferase. This results in the production of a large amount of α-ketoglutarate (23,24). This is because in islet mitochondria the level of aspartate aminotransferase is quite high and considerably higher than that of glutamate dehydrogenase (L.A.F. and M.J.M., unpublished observations).

The high level of α-ketoglutarate does not cause insulin release, possibly because high levels of α-ketoglutarate inhibit glutaminase, glutamate dehydrogenase, and mitochondrial aspartate aminotransferase (29,37). Consequently, when the level of α-ketoglutarate is high, glutamine cannot produce additional flux through the α-ketoglutarate dehydrogenases complex and the enzymes represented in Scheme 1. In addition, α-ketoglutarate inhibits ketothiolase (42). This would decrease the ability of ketothiolase to produce AcAc-CoA for HMG-CoA synthetase, which in turn would decrease mevalonate production.

Leucine and BCH increase the Kₘ of glutamate, the Kₘ of α-ketoglutarate, and the Vₘax in the glutamate dehydrogenase reaction (37). The increase in the Vₘax and Kₘ of glutamate increases α-ketoglutarate production by glutamate dehydrogenase and as a result increases insulin release (23,24). The increase in the Kₘ of α-ketoglutarate would decrease inhibition of glutamate dehydrogenase by α-ketoglutarate. However, in islet mitochondria there is considerably less total glutamate dehydrogenase than aspartate aminotransferase activity, and leucine and BCH do not protect mitochondrial aspartate aminotransferase against inhibition by α-ketoglutarate (3,37). Therefore, the enhanced production of α-ketoglutarate by glutamate dehydrogenase, mediated by the combination of leucine plus glutamine, results in enhanced inhibition by α-ketoglutarate of the more abundant mitochondrial aspartate aminotransferase. This results in the level of α-ketoglutarate being lower in the presence of both leucine and glutamine than in the presence of glutamine alone (23,24). This favors insulin release by relieving ketothiolase of inhibition by α-ketoglutarate and thus permits ketothiolase to play its role in generating mevalonate, thereby promoting insulin release. The concept that these activators in the presence of glutamine enhance insulin release by favoring glutamate dehydrogenase over aspartate aminotransferase activity is consistent with our observation that leucine-glutamine–promoted insulin release is not inhibited but slightly enhanced by the aminotransferase inhibitor aminooxyacetate (4).

**α-Ketoisocaproate.** α-Ketoisocaproate can also promote insulin release (43). According to the succinate mechanism, its insulinotropic action could result from its catalysis to HMG-CoA plus its transamination to leucine, followed by leucine activating glutamate dehydrogenase (22–24).

**Glucose.** The metabolism of glucose to pyruvate, followed by the transport of pyruvate into mitochondria and the pyruvate dehydrogenase and pyruvate carboxylase reactions, is apparently essential in glucose-stimulated insulin release.
release. Consequently, we found that 1) the rates of the pyruvate carboxylase and pyruvate dehydrogenase reactions in islets are roughly equal and directly proportional to the level of extracellular glucose and thus insulin secretion (44), 2) treated islets that are deficient in both pyruvate carboxylase and pyruvate dehydrogenase activity do not release insulin when supplied with glucose (38), and 3) the level of pyruvate carboxylase activity in islets is high and approximately the same as in gluconeogenic organs, such as liver and kidney (45).

According to the succinate mechanism, the Ac-CoA generated by the pyruvate dehydrogenase complex and the oxaloacetate produced by pyruvate carboxylase would be important for mevalonate production and glucose-stimulated insulin release. This is because Ac-CoA produced by the former would be utilized by HMG-CoA synthetase, while the oxaloacetate generated by the latter would be utilized by the combined mitochondrial aspartate aminotransferase-α-ketoglutarate dehydrogenase reactions for the production of succinyl-CoA. Support for the concept that glucose increases mitochondrial aspartate aminotransferase activity and that this increase is essential for glucose-stimulated insulin release is derived from experiments that demonstrated that in rat islets, the increase in the level of α-ketoglutarate (46) and insulin release produced by glucose was almost completely inhibited by the aminotransferase inhibitor aminooxyacetate (4).

Cytosolic malate dehydrogenase (reaction 2 of Scheme 2) could also play an important role in insulin release by promoting glycolysis. This is because by reducing oxaloacetate with NADH, this enzyme would resupply NAD to glyceraldehyde-3-phosphate dehydrogenase and prevent potent product inhibition of this latter enzyme by NADH (57). In islets, cytosolic malate dehydrogenase could be the major enzyme that plays this role. This is because it is present in high levels (51) and because it removes hydrogen from the A side instead of the B side (Scheme 3, Fig. 3) of the pyridine ring of NAD (58). According to previous results (58), this can permit cytosolic malate dehydrogenase to associate with the complex between NADH and pyruvate via glycolysis enables pyruvate to be utilized for the production of mevalonate via the combined pyruvate carboxylase-mitochondrial aspartate aminotransferase-α-ketoglutarate dehydrogenase (reactions 9, 16, and 13 of Scheme 1) plus the reactions enclosed in Scheme 1.

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in islets, cytosolic glyceraldehyde-3-phosphate dehydrogenase can be more reactive with NADPH than with NADH, this enzyme could be a source of NADP for malic enzyme and cytosolic NADP-isocitrate dehydrogenase. The latter two are by far the most abundant NADP-linked dehydrogenases in rat islet cytosol, since very little glucose is metabolized via the hexose monophosphate pathway (44,45,63,64). Production of NADP would be important in the islet cytosol, because then citrate can be utilized in the combined aconitase-cytosolic NADP-isocitrate dehydrogenase-cytosolic aspartate aminotransferase reactions to generate the oxaloacetate, which is reduced by cytosolic malate dehydrogenase. In addition, malic enzyme could provide HMG-CoA reductase with NADPH and could also generate the pyruvate, which could be utilized for oxaloacetate, Ac-CoA, and ultimately mevalonate production (Scheme 1).

Mitochondrial glyceraldehyde-3-phosphate dehydrogenase. Islets from mutant mice that lack mitochondrial glyceraldehyde-3-phosphate dehydrogenase activity have normal glucose-stimulated insulin release (56,65). This is consistent with the succinate mechanism, which does not require an intact glyceraldehyde-3-phosphate shuttle for glucose-stimulated insulin release.

Some physiological aspects of succinate mechanism. An insulin deficiency can result in decreased entry of glucose into cells and therefore less utilization of glucose for the production of oxaloacetate. Because of the latter, less Ac-CoA is utilized by citrate synthase and more is utilized for the production of the ketone bodies AcAc and 3-hydroxybutyrate, as shown in Scheme 1. The major site of production of ketone bodies is the liver. From the liver, they are transported in the blood to peripheral tissues, where they can be a major source of metabolic fuel and can increase the level of Ac-CoA, glutamate, and Krebs cycle metabolites. These are the same effects that can be produced by insulin (62,66,67), which, in addition to increasing glucose transport, increases pyruvate dehydrogenase activity. Thus, ketosis, which is a physiological response to insulin deprivation during starvation, is equivalent in metabolic effects to the action of insulin. Ketone bodies can bypass the block in glucose transport caused by a lack of insulin by utilizing the monocarboxylate carrier. Ketone bodies also bypass the inhibition of pyruvate dehydrogenase induced by insulin deficiency by providing an alternative source of mitochondrial Ac-CoA (62,66,67).

According to the succinate mechanism, ketone bodies
are utilized in islets to generate mevalonate, a trigger of insulin release. However, to prevent ketone bodies from promoting insulin release during starvation, they are not insulinotropic (12–17) by themselves. They are only effective if there is a source of succinyl-CoA to enable AcAc-CoA and ultimately mevalonate to be produced. Succinyl-CoA is generated as part of the action of glucose and other insulin secretagogues.

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