Published in final edited form as:

J Drug Deliv Sci Technol. 2008 November ; 18(6): 387–391.

Pharmacokinetic Modeling of the Glucoregulatory System

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Abstract

A pharmacokinetic model is proposed to describe the glucoregulatory process. The model describes the dynamics of glucose, amino acids, and fatty acids, as well as both the hormonal actions and dynamics of insulin, glucagon, epinephrine, and glucagon-like peptide-one. The model was developed assuming that the dynamics of each species occurs in only one compartment. Several forms of the metabolic absorption and elimination rates, along with possibilities for increasing the complexity of each compartmental model are discussed. Once properly identified and validated, the novel model has the potential to be more descriptive than other models describing glucose dynamics in the body

Keywords

pharmacokinetics; model; glucose; insulin; dynamics

The development of novel medical therapeutic systems can be greatly improved using detailed models. By being able to perform an accurate simulation of the behavior of patients treated by the therapeutic methods, two important advantages are realized relative to development without simulation.

First, the use of simulation is a significantly cheaper alternative to testing in patients and animals, both in terms of dollars spent and time spent in gaining approval for such experiments, the development of experimental protocols, and experimental setup and performance. Second, a simulation can quickly reveal device design characteristics that will not be effective, preventing any catastrophic results from occurring, including the loss of lives. In addition to these two primary advantages, the ability of simulations to show the system response for a large number of design configurations and scenarios in a relatively short amount of time demonstrates that, at the very least, the use of simulations as a precursor to experiments is a highly effective way to improve the design process.

Among patient models, the pharmacokinetic model [1] simply describes the kinetics of absorption and elimination of a species for a certain number of theoretical compartments. Often a single compartment representing the circulation is chosen. Elimination and absorption kinetics are most often described by first order kinetics. When the model does not

match the data, the model structure is changed by either increasing the number of compartments used or by changing the mathematical description of the kinetic rates.

Physiologically-based models [2] require that most significant organ tissues are chosen as well-mixed compartments and the concentration of species is uniform within that compartment. Mass balances describing blood flow convection, mass transfer within each compartmental space, and the metabolic processes are written for each species at each compartment. The result is a large, multi-compartment model based on physiology.

Both the pharmacokinetic and the physiologically-based models have their advantages and disadvantages. The physiologically-based model has the potential to simulate and to be used in model-based control methods, as a result of its thorough description of each species in the body. However, because there are so many parameters to be identified with such a large model, the pharmacokinetic models have the advantage that, while perhaps not describing metabolism as accurately as the physiologically-based models, an estimate of the model parameters is easier to obtain, thus making them easier to use.

Previous modeling work has focused mostly on insulin and glucose modeling, while some models do exist that describe glucagon [2–4], and fatty acids [4,5]. The purpose of this contribution was to develop a model framework to describe all the biochemical species associated with glucose metabolism. A novel pharmacokinetic model was developed by first noting the relevant metabolic sources and sinks for each species. Next, the basic differential equations were developed for each species. Finally, each metabolic source and sink term were described as a general function of the biochemical species involved.

I. Pharmacokinetic Model Development

To develop pharmacokinetic models of each species, the significant metabolic processes associated with each species was investigated and summarized in a compartment diagram [2,6–8]. For each species, the dynamic change of species concentration within the constant volume compartment was assumed to be a function of both endogenous and exogenous inputs and uptake or elimination. To develop the pharmacokinetic framework, each species was initially assumed to be best described as existing in a single compartment. Each species was determined to be a function of its metabolic processes. Based on the physiology studies, the metabolic process equations were described as general functions of the species that are known to affect that particular metabolic process. A description of the various model variables and parameters, including units, is provided in Table 1.

Physiologically, glucose appears endogenously, through gluconeogenesis or glycogenolysis, or exogenously, either orally or via an injection. Glucose disappears by being taken into cells and either stored as glycogen, converted to fat, or used in the formation of ATP. The pharmacokinetic description of glucose dynamics is shown in Figure 1 and represented mathematically by Equations (1–4).

$$\frac{dS}{dt} = r_{S,end} + r_{S,ex} - r_{S,elim} \quad \text{Eq. 1}$$

$$r_{S,end} = f(t, S, I, G, E, F, A, K_{S,end}) \quad \text{Eq. 2}$$

$$r_{S,ex}=g(t, M_s) \quad \text{Eq. 3}$$

$$r_{S,elim}=h(t, S, I, E, K_{S,elim}) \quad \text{Eq. 4}$$

Endogenous glucose production and uptake were assumed to be functions of glucose, insulin, glucagon, and epinephrine, as well as amino acids, fatty acids, and glycogen. Insulin and glucose both act to decrease production, while glucagon and epinephrine act to increase production. Also included in this function were the glycogen levels, which allow for glycogenolysis, and the fatty acid and amino acid levels, which allow for gluconeogenesis. Therefore, these kinetic rates were assumed to be functions of the other species and metabolites, as well as any kinetic parameters associated with the process. Exogenous glucose was considered a function of the source, including the amount given and the particular absorption kinetics associated with the source.

Amino acids play many different roles in glucose metabolism. Many are important for gluconeogenesis. Some amino acids, especially, lysine and arginine, are able to cause an increase in insulin secretion. Others, including alanine, cause an increase in glucagon secretion. These effects show the importance in including amino acids in the overall glucose metabolism process. Like glucose, amino acids appear as a result of both endogenous production and from external sources of proteins. They are taken up into various cells to form proteins or are converted to glucose. Amino acid pharmacokinetics are shown in the PK diagram of Figure 2. The amino acid mass balances were described by Equations (5–8).

$$\frac{dA}{dt}=r_{A,endogenous}+r_{A,exogenous}-r_{A,uptake/elimination} \quad \text{Eq. 5}$$

$$r_{A,endogenous}=f(t, S, I, G, E, F, A, K_{A,End}) \quad \text{Eq. 6}$$

$$r_{A,exogenous}=g(t, M) \quad \text{Eq. 7}$$

$$r_{A,uptake/elimination}=h(t, A, I, K_{A,uptake/elim}) \quad \text{Eq. 8}$$

The amino acid model was made very similar to the glucose model. Endogenous production occurs by breaking down proteins. This occurs primarily for gluconeogenesis, making endogenous production a strong function of glucose, epinephrine, and glucagon levels. Insulin is also known to promote protein formation, meaning that increased insulin would be expected to decrease production. Finally, during starvation, once glucose and fatty acid levels are diminished, amino acids become the primary source of fuel, resulting in increased production. Amino acid uptake depends on the acid levels, and insulin has been shown to increase uptake promote protein formation. Finally, an exogenous source was described as a function of the method of administration, including absorption kinetics associated with the administration technique and the volume administered.

Like glucose and amino acids, fatty acids are produced endogenously and supplied exogenously, in the form of a meal. Fatty acids combine with amino acids to form glucose via gluconeogenesis. In addition, when glucose levels are low, fatty acids become the primary source of fuel for the body. The fatty acid PK diagram is given in Figure 3, and Equations (9–12) show the fatty acid PK model.

$$\frac{dF}{dt} = r_{F, \text{endogenous}} + r_{F, \text{exogenous}} - r_{F, \text{uptake/elimination}} \quad \text{Eq. 9}$$

$$r_{F, \text{endogenous}} = f(t, S, I, G, E, F, K_{F, \text{End}}) \quad \text{Eq. 10}$$

$$r_{F, \text{exogenous}} = g(t, M) \quad \text{Eq. 11}$$

$$r_{F, \text{uptake/elimination}} = h(t, S, I, E, F, K_{F, \text{uptake/elim}}) \quad \text{Eq. 12}$$

Fatty acid production was assumed to be a function of glucose, insulin, glucagon, and epinephrine. The existence of the glucose-fatty acid cycle results in a direct dependence on glucose. Low glucose levels result in low insulin and high glucagon levels. Glucagon is known to increase fatty acid production while also decreasing fatty acid conversion to lipids. Epinephrine is also known to result in increased fatty acid production. However, both glucagon and epinephrine are also responsible for increasing the rate of gluconeogenesis, which results in increased fatty acid elimination. Thus, both fatty acid production and elimination were modeled as functions of glucose and the regulatory and counter-regulatory hormones of glucose metabolism. Like glucose and amino acids, the exogenous source of fatty acids was assumed to depend on the source type and the amount of fatty acid delivered.

Insulin was assumed to appear either through endogenous production from the pancreas or from an external source. It was assumed to be degraded primarily at the binding sites and at the kidneys. Figure 4 shows the insulin PK diagram. Insulin pharmacokinetics were represented by Equations (13–16).

$$\frac{dI}{dt} = r_{I, \text{endogenous}} + r_{I, \text{exogenous}} - r_{\text{degradation/elimination}} \quad \text{Eq. 13}$$

$$r_{I, \text{endogenous}} = f_I(t, I, S, A, E, G1, K_{I, \text{endogenous}}) \quad \text{Eq. 14}$$

$$r_{I, \text{exogenous}} = g_I(t, M) \quad \text{Eq. 15}$$

$$r_{I, \text{degradation}} = h_I(t, I, K_{I, \text{degradation}}) \quad \text{Eq. 16}$$

Insulin secretion was considered to be a function of many variables besides simply glucose. It was considered to be a function of its own values. In addition, insulin production is increased by an increase in gastrointestinal hormones, including glucagon like peptide-1 (GLP-1), and amino acids are known to have a potentiating effect on insulin secretion [6]. Finally, epinephrine, when produced at levels to restore falling glucose levels, is able to inhibit insulin secretion [9]. An exogenous source was described as a function only of the amount given, and any absorption kinetics associated with the method of delivery. Uptake was assumed to occur only as a function of the insulin concentration and the kinetic rates.

Glucagon was assumed to appear only endogenously, although the idea of exogenous glucagon infusion is gaining acceptance [10]. Glucagon elimination was assumed to occur at the liver cell binding sites and the kidneys. Glucagon dynamics were described by Equations (17)–(19), and its pharmacokinetic diagram is shown in Figure 5.

$$\frac{dG}{dt} = r_{G, \text{endogenous}} - r_{G, \text{degradation/elimination}} \quad \text{Eq. 17}$$

$$r_{G, \text{endogenous}} = f_G(t, S, I, A, E, K_{G, \text{endogenous}}) \quad \text{Eq. 18}$$

$$r_{G, \text{degradation/elimination}} = g_G(t, G, K_{G, \text{degradation/elimination}}) \quad \text{Eq. 19}$$

Endogenous glucagon production was modeled as a function of glucose, insulin, amino acids, and epinephrine. As the counter-regulatory hormone, glucagon secretion is inhibited by high glucose levels. Because the glucagon-producing alpha cells are downstream of the insulin-producing beta cells, the presence of insulin is also able to inhibit glucagon secretion [9]. Amino acids are known to increase glucagon secretion, and exercise is also known to result in an increase in glucagon levels. Because most of the effects of exercise result from the increased epinephrine production, a functional relationship was assumed to exist between the two hormones. Glucagon elimination was assumed to occur as a function only of glucagon levels.

While epinephrine is present in the body at normal glucose levels, the effects of epinephrine on glucose regulation are not usually observed unless the person is exercising or if a person is experiencing hypoglycemia and his or her glucagon response is insufficient to return glucose levels to normal. The appearance of epinephrine in these circumstances was assumed to occur endogenously only, and disappearance was assumed to occur via degradation. The epinephrine model diagram is shown in Figure 6, and the model equations were represented by Equations (20)–(22).

$$\frac{dE}{dt} = r_{E, \text{endogenous}} - r_{E, \text{degradation/elimination}} \quad \text{Eq. 20}$$

$$r_{E, \text{endogenous}} = f_E(t, S, G, K_{E, \text{endogenous}}) \quad \text{Eq. 21}$$

$$r_{E,degradation/elimination} = g_E(t, E, K_{E,degradation/elimination}) \quad \text{Eq. 22}$$

Epinephrine secretion for the purpose of glucose regulation was modeled as a function of both glucose and glucagon levels. Like the other hormones previously mentioned, epinephrine elimination was assumed to be a function only of the epinephrine levels.

GLP-1 is secreted only in response to a meal, and as such it was assumed that its appearance only occurs endogenously. Its disappearance occurs through general degradation at the liver and kidneys. Figure 7 shows the hormone's pharmacokinetic diagram, and the PK model equations are given by (23)–(25).

$$\frac{dG1}{dt} = r_{G1,endogenous} - r_{G1,degradation/elimination} \quad \text{Eq. 23}$$

$$r_{G1,endogenous} = f_{G1}(t, S, K_{G1,endogenous}) \quad \text{Eq. 24}$$

$$r_{G1,degradation/elimination} = g_{G1}(t, G1, K_{G1,degradation/elimination}) \quad \text{Eq. 25}$$

As previously mentioned, the production of GLP-1 occurs as result of the digestion process. As a gastrointestinal hormone, GLP-1 would likely best be modeled as a function of the glucose levels in a compartment associated with a meal, such as Hovorka's meal description. Elimination was assumed to be a function only of GLP-1.

II. Discussion

As both Hovorka et al. [11] and Cobelli et al. [12] have shown, glucose is more accurately represented as having two compartments. Given the recent praise of the Hovorka model, Eq. (1) is likely best represented as two different equations, each representing a different compartment. Endogenous production and most cellular uptake would likely occur in a second compartment, and exogenous production, and transport to and from cells would be represented in the central compartment.

Given both circulation and intracellular amino acids, two compartments may be appropriate for amino acid kinetics. A recent paper by Roy and Parker [5] showed a developed fatty acid PK model that treated fatty acids as existing in a single compartment and included additional remote compartments to describe the effects of fatty acids on glucose metabolism. Given the uptake and production of fatty acids in certain cells in the body, it may be appropriate to represent fatty acids as existing in two circulating compartments in addition to any compartments describing action. However, as fatty acid binding does not affect glucose uptake, it may be inappropriate to use remote compartments in the model description.

Many authors [13,14] have demonstrated that insulin is best modeled using multiple compartments. While Hovorka's representation of a single insulin compartment being responsible for three different type of insulin action, which vary dynamically, the addition of its action on glucagon production and fatty acid and amino acid levels may result in the full scale model consisting of many insulin action compartments.

Glucagon was assumed to exist in only a single compartment. However, given that glucagon also binds to various cells, it may also be best represented as having a central compartment, and two different action compartments. One of these compartments could represent the activation of the glucose production, and the other could represent fatty acid production. Perhaps a third action compartment could represent the inhibition of fatty acid uptake in some cells.

It should be mentioned that the sympathetic hormones naturally exist as both epinephrine and norepinephrine. However, because most norepinephrine is converted to epinephrine, and because most of the effects mentioned are in response to the sympathetic nervous system responses to low glucose, the epinephrine/norepinephrine complex is simply being lumped together as a single hormone. Given that epinephrine increases glucose levels by either increasing production, decreasing uptake, and decreasing insulin secretion, a total of four compartments may be appropriate to represent all of the dynamics associated with epinephrine. Finally, an additional term, perhaps best represented in the kinetic rate parameter, would be the increased epinephrine secretion in response to exercise.

To be more accurate, GLP-1 is actually a part of many gastrointestinal hormones responsible for what is known as the incretin effect of increasing insulin secretion [15]. GLP-1 accounts for more than 70% of the total incretin effect, with the remaining effect caused by gastric inhibitory polypeptide (GIP) and a minimal effect from other hormones. For simplicity the two have been lumped together, as both are generated in response to a meal and both act to increase insulin production. As the hormone is known to increase insulin secretion, a two-compartment representation, in which one describes its circulation levels, and the other describes its activation with respect to insulin secretion potentiation, may be appropriate.

The metabolic source and sink terms were left in a general form. Without data, the exact form of the terms could not be determined. However, the representation of the metabolic processes of previous models provides a foundation of possible representations that is discussed here for use with data when it becomes available.

Perhaps the simplest representation of each source or sink is a simple rate law that is a particular order with respect to each species known to affect the process. Most commonly, kinetic rates are assumed to be first order with respect to each species involved. The general representation is shown by Equation (26).

$$r_i = k(t)G^a(t)I^b(t)S^c(t)F^d(t)A^e(t)E^f(t)G1^g(t) \quad \text{Eq. 26}$$

Other types of kinetic relationships, including Michaelis-Menten and additive relationships have also been used to describe the rate, and could be considered as possible descriptions. Others have made use of a nonlinear equation in which the basal rate is multiplied by dimensionless multiplicative terms described by each influencing species.

$$r_i = r_{i, \text{basal}} M_{i,S} M_{i,I} M_{i,G} M_{i,F} M_{i,A} M_{i,E} M_{i,G1} \quad \text{Eq. 27}$$

Where M_i is the multiplicative function in each variable for metabolic process i . Each M has associated parameters that must be estimated. It may also be necessary to describe the nonlinear functions as differential equations describing the binding of a hormone to a receptor, in which case the rate is a function of the receptor-bound species, which is a function of the circulation species concentrations.

In order to capture parameter variability, either among patients, or within a specific patient (from exercising, circadian rhythms, etc.), the parameters in each set, k_i , will likely be functions of time themselves.

Of notable exception to the above description are the descriptions for exogenous glucose and insulin inputs. The exogenous glucose input is in the form of a meal, and the term is used to describe glucose absorption from a meal. Similarly, the insulin infusion rate is adjusted by either the user in the case of an infusion pump, or by the release mechanism of the device. However, for both types, the parameters are still time varying to account for parameter variability.

The next step in the process would be to identify the model, based on simplifications, a literature search for parameter values, and finally, fitting model responses to data in order to estimate certain parameter values. The desired data would show recorded observations of the all metabolites and hormones as a function of time. If such data were available and parameters were estimated, the developed models would have the potential to be an improvement over existing models in their ability to describe the glucoregulatory process. This could lead to multivariable control algorithms, in which multiple metabolites are controlled by the precise infusion of multiple hormones.

It has been suggested that a large number of the model parameters may be constant within specific classes of patients. Such classes could be based on age, gender, ethnicity, and body weight. If parameter values were indeed constant within patient classes, the number of parameters to be estimated for an individual patient would be dramatically reduced. However, given the size of the models, with respect to equations and model parameters, and the lack of appropriate data, it was decided that model identification and validation was outside the scope of this work.

III. Conclusions

Two different systems of equations have been developed to describe glucose homeostasis. A pharmacokinetic model was provided, with recommendations on the number of compartments to develop based on the metabolic processes of each species. A detailed physiological model was developed to more fully describe the process at each tissue region. Finally, several possible equation forms were proposed as possible descriptions of the metabolism kinetics.

Acknowledgments

This work was supported in part by the National Institutes of Health (grant EB 00146 to NAP) and a National Science Foundation Fellowship to TGF.

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Figure 1.

Pharmacokinetic model diagram for glucose. The solid lines represent metabolic sources and sinks. The dashed lines represent actions by the species on the metabolic source or sink. For simplicity, each contribution toward a metabolic action is represented as first order kinetics in the contributing species.

Figure 2.

Pharmacokinetic model diagram for amino acids. The solid lines represent metabolic sources and sinks. The dashed lines represent actions by the species on the metabolic source or sink. For simplicity, each contribution toward a metabolic action is represented as first order kinetics in the contributing species.

Figure 3. Pharmacokinetic model diagram for fatty acids. The solid lines represent metabolic sources and sinks. The dashed lines represent actions by the species on the metabolic source or sink. For simplicity, each contribution toward a metabolic action is represented as first order kinetics in the contributing species.

Figure 4.

Pharmacokinetic model diagram for insulin. The solid lines represent metabolic sources and sinks. The dashed lines represent actions by the species on the metabolic source or sink. For simplicity, each contribution toward a metabolic action is represented as first order kinetics in the contributing species. Note that for a Type I diabetic patient, $r_{\text{I,endogenous}}$ is approximately zero, and thus all actions associated with endogenous release are eliminated.

Figure 5. Pharmacokinetic model diagram for glucagon. The solid lines represent metabolic sources and sinks. The dashed lines represent actions by the species on the metabolic source or sink. For simplicity, each contribution toward a metabolic action is represented as first order kinetics in the contributing species.

Figure 6. Pharmacokinetic model diagram for epinephrine. The solid lines represent metabolic sources and sinks. The dashed lines represent actions by the species on the metabolic source or sink. For simplicity, each contribution toward a metabolic action is represented as first order kinetics in the contributing species.

Figure 7. Pharmacokinetic model diagram for glucagon-like peptide-1. The solid lines represent metabolic sources and sinks. The dashed lines represent actions by the species on the metabolic source or sink. For simplicity, each contribution toward a metabolic action is represented as first order kinetics in the contributing species.

Table 1

Pharmacokinetic Model Variables and Parameters

Variable	Definition	Units
S	Plasma glucose concentration	mmol/L
A	Plasma amino acid concentration	mg/L
F	Plasma fatty acid concentration	nmol/L
I	Plasma insulin concentration	mU/L
G	Plasma glucagon concentration	ng/L
E	Plasma epinephrine concentration	nmol/L
GI	Plasma glucagon-like peptide-1 concentration	nmol/L
$r_{i,endogenous}$	Rate of endogenous production	species dependent
$r_{i,exogenous}$	Rate of exogenous input	species dependent
M_i	Quantity of exogenous input	species dependent
$K_{i,endogenous}$	Kinetic rate coefficients for endogenous input	species, coefficient dependent
$r_{i,uptake/elimination}$	Rate of species disappearance	species dependent
$K_{i,uptake/elimination}$	Kinetic rate coefficients for species disappearance	species, coefficient dependent