Mechanism-Based Pharmacokinetic-Pharmacodynamic Modeling: Biophase Distribution, Receptor Theory, and Dynamical Systems Analysis

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Key Words

target site distribution, operational model of agonism, transduction, pharmacodynamic interaction, functional adaptation, disease progression

Abstract

Mechanism-based PK-PD models differ from conventional PK-PD models in that they contain specific expressions to characterize, in a quantitative manner, processes on the causal path between drug administration and effect. This includes target site distribution, target binding and activation, pharmacodynamic interactions, transduction, and homeostatic feedback mechanisms. As the final step, the effects on disease processes and disease progression are considered. Particularly through the incorporation of concepts from receptor theory and dynamical systems analysis, important progress has been made in the field of mechanism-based PK-PD modeling. This has yielded models with much-improved properties for extrapolation and prediction. These models constitute a theoretical basis for rational drug discovery and development.

INTRODUCTION

PK-PD: pharmacokinetic-pharmacodynamic

The primary objective of pharmacokinetic-pharmacodynamic (PK-PD) modeling is prediction of the time course of the drug effect intensity in vivo in health and disease (1). PK-PD modeling has become a key success factor in drug discovery and development. PK-PD modeling is widely used as the theoretical basis for optimization of the dosing regimen and the delivery profile of new (and existing) drugs in Phase II clinical trials. Moreover, the use of PK-PD modeling for optimization of the design of Phase III clinical trials, using clinical trials simulation has become well established (1, 2). In recent years, PK-PD modeling has been increasingly applied in drug discovery and early drug development. Within this context, PK-PD modeling constitutes the theoretical basis for (*a*) the selection of drug candidates, (*b*) lead optimization, and (*c*) the optimization of early proof-of-concept clinical trials on the basis of information from preclinical studies.

The applications of PK-PD modeling described above rely on the prediction, in a strictly quantitative manner, of the PK-PD properties of novel drugs in man using prior information from in vitro bioassays, in vivo animal studies, or early clinical studies in man. Not surprisingly, PK-PD modeling has developed from an empirical and descriptive approach into a scientific discipline based on the (patho-) physiological mechanisms behind PK-PD relationships. It is now well accepted that mechanism-based PK-PD models have much improved properties for extrapolation and prediction.

A pertinent feature of mechanism-based PK-PD models is that they contain specific expressions to characterize processes on the causal path between drug administration and effect, thereby relying on relevant biomarker data (3). This includes (*a*) target site distribution, (*b*) target binding and activation, (*c*) pharmacodynamic interactions, (*d*) transduction, (*e*) homeostatic feedback mechanisms, and ultimately, (*f*) the effects of the drug on disease processes and disease progression.

A key element in mechanism-based PK-PD modeling is the explicit distinction between parameters to describe (*a*) drug-specific properties and (*b*) biological system-specific properties. Drug-specific parameters describe the interaction between the drug and the biological system in terms of target affinity and target activation, whereas system-specific parameters describe the functioning of the biological system. This concerns within-system pharmacodynamic interactions, time-dependent transduction mechanisms, and homeostatic feedback mechanisms. In this review, disease processes and disease progression are described in terms of biological system-specific parameters.

The explicit distinction between drug-specific parameters and biological system-specific parameters is crucial to the prediction of in vivo drug effects. It has been demonstrated that drug-specific properties (i.e., receptor affinity, intrinsic efficacy) can often be predicted on basis of in vitro bioassays (4, 5). Furthermore, the values of drug-specific parameters are identical between species and individuals. This implies that these parameters do not require scaling when they are applied in interspecies extrapolation. Moreover, there is, typically no intra- and interindividual variability in the values of these parameters (4, 5). In contrast, biological system-specific parameters

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can only be estimated by in vivo systems analysis. The values of biological system-specific parameters can vary between species, individuals, and conditions. This implies that interspecies scaling of biological system-specific parameters may be required (6). Finally, intra- and interindividual variation in biological system-specific parameters must be taken into account.

PB-PK: physiologically based pharmacokinetic

In this review, we present an overview of the basic principles and recent developments of mechanism-based PK-PD modeling. In particular, the utility of incorporating concepts from receptor theory and dynamical systems analysis is discussed.

MECHANISM-BASED PK-PD MODELING CONCEPTS

Target Site Distribution

Typically, PK-PD modeling utilizes the time course of the drug concentration in plasma as a measure of internal exposure. This is important because drug concentration versus time profiles can differ widely between drugs, and for the same drug, between species and individuals. Compartmental models are commonly used to describe the time course of the drug concentration in plasma. In a compartmental model, drug disposition is characterized as the transfer of drug between interconnected hypothetical compartments, which serves to mimic the drug absorption, distribution, and elimination processes. A limitation of this approach is that, although useful for descriptive purposes, it is not truly mechanistic. As a result, it is of limited value for extrapolation and prediction. This is particularly the case in relation to the interspecies extrapolation. Physiologically based (PB)-PK modeling has been proposed to improve interspecies extrapolation of the pharmacokinetics (7). However, discussion of the various PB-PK modeling concepts is beyond the scope of this review (7a, 7b, 7c).

An important factor in PK-PD modeling is that most drugs have their target site in an organ or a peripheral tissue, rather than in plasma. For those drugs, distribution to the site of action may represent a rate-limiting step in the onset to the biological effect. This is reflected in a delay of the pharmacological effect relative to the drug concentration in plasma, which is often referred to as hysteresis. Moreover, steady-state drug concentrations in plasma may not be representative for the concentrations at the site of action (i.e., the biophase).

The most common approach to model distribution delays in PK-PD relationships is to use the so-called effect compartment model (8). Thereby, it is implicitly assumed that the transport of drug between plasma and target occurs by passive diffusion. In this model, the distribution of drug to a hypothetical effect site is described by the following differential equation:

$$\frac{dC_e}{dt} = k_{1e} \cdot C_p - k_{e0} \cdot C_e, \qquad 1.$$

where k_{1e} and k_{e0} represent the first-order rate constants for distribution into and out of the hypothetical effect compartment, and C_p and C_e are the drug concentrations in plasma and the hypothetical effect compartment, respectively. In this model the amount of drug entering the effect compartment is considered negligible, reflecting

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the commonly encountered observation that drug distribution to the site of action does not significantly influence the overall pharmacokinetics. As a result, the values of the parameters k_{1e} and k_{e0} are assumed to be identical, whereby it is intrinsically assumed that at steady state, the drug concentration in the biophase is identical to the free concentration in plasma. In their seminal paper, Sheiner et al. (8) demonstrated that for drugs that distribute to the site of action by passive diffusion, this can be a reasonable assumption.

A number of semiparametric and nonparametric approaches of modeling effect compartment distribution kinetics have been proposed. These approaches differ mainly with regard to the prior information required and the technique used for minimalization of the hysteresis between change in plasma concentration and change in effect (9–12). At the same time, the effect compartment model has been successfully applied in numerous investigations to derive in vivo steady-state concentration-effect relationships from non-steady-state data (13).

As discussed for the compartmental PK models, a limitation of the effect compartment model is that it is not truly mechanistic. Specifically, the distribution of drugs between plasma and tissue depends on multiple factors related to the perfusion of the target tissue and the distribution process. For d-tubocurarine, it has been demonstrated that the value of the biophase equilibration rate constant k_{e0} is lower under halothane anesthesia relative to nitrous oxide anesthesia, which could be explained by the reduction in skeletal blood flow (14).

For drugs acting at extracellular targets, physicochemical properties (e.g., molecular size) and binding to plasma proteins and other blood constituents can restrict distribution to the biophase. Moreover, for drugs acting at intracellular targets and at targets in tissues that are protected by specific barriers (e.g., the brain), the distribution to the biophase can be influenced by the functionality of transporters. At present, these mechanisms are typically not taken into consideration when modeling biophase distribution kinetics. Yet, these mechanisms are important because complexities at the level of biophase distribution may affect the derived shape of the concentration-effect relationship (15, 16). Moreover, it may complicate the in vitro to in vivo extrapolation of parameters characterizing the binding affinity of a drug to a specific target (17).

An important question in relation to biophase distribution is whether it is indeed the free drug concentration that drives the intensity of the pharmacological response. For a number of drugs (i.e., benzodiazepines, synthetic opioids), available evidence indicates that this is indeed the case (18, 19). However, there is still limited experimental evidence that the free drug hypothesis is valid under all circumstances. Particularly for drugs with a high affinity for their biological target and for drugs that are transported by active transport mechanisms to the site of action, the biophase distribution might be nonrestrictive (4).

Recently, several specific transporters have been identified that may influence the distribution of drugs to their site of action in the CNS (20–23). However, very few PK-PD investigations have considered the functional role of these transporters in the biophase distribution. An interesting example is the investigation by Letrent et al. (24) of the PK-PD correlation of the antinociceptive effect of morphine, in which the functional role of active extrusion at the blood-brain barrier was determined on the

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basis of the interaction with the selective Pgp inhibitor GF120918. A novel technique to obtain pertinent information on the kinetics of the target site distribution in the CNS is by intracerebral microdialysis (25–28), which has been successfully applied to the characterization of biophase distribution kinetics in a number of investigations of the PK/PD correlation of morphine (29). Ultimately, this may lead to the development of novel mechanism-based biophase distribution modeling concepts.

Target Binding and Activation

The objective of the modeling of target binding and target activation in PK-PD analyses is the prediction of in vivo drug concentration-effect relationships. In PK-PD modeling, steady-state drug concentration effect relationships are commonly described using a hyperbolic function (i.e., the Hill equation):

$$E = \frac{\alpha \cdot [A]^{n_H}}{EC_{50}^{n_H} + [A]^{n_H}}, \qquad 2.$$

where E is the observed drug effect intensity; α is the observed maximum effect; $[A]$ is the drug concentration; EC_{50} is the drug concentration at half-maximal effect; and n_H is the Hill factor, which is the parameter denoting the steepness of the concentration-effect curve. The usefulness of the Hill equation to describe in vivo drug concentration-effect relationships is well established. However, a limitation is that it is not mechanistic. Specifically, the Hill equation does not provide insight into the factors that determine the shape and the location of the concentration-effect relationship. In theory, the relationship between the concentration of a drug and the intensity of the biological response depends on several factors related to the drug and the biological system (**Figure 1**). Specifically, according to receptor theory, the potency (i.e., EC_{50}) and intrinsic activity (i.e., α) are dependent on properties of the drug (i.e., the receptor affinity and the intrinsic efficacy) and the biological system (i.e., the receptor density and the transducer function, relating receptor activation to pharmacological response). Therefore, the prediction of in vivo drug concentration-effect relationships requires the distinction between drug-specific and biological system-specific parameters (30). Recently, PK-PD modeling strategy has been developed based on concepts from receptor theory and that constitutes a scientific basis for the prediction of in vivo drug concentration-effect relationships.

Semiparametric approach to the incorporation of receptor theory. Classical receptor theory combines two independent parts to describe drug actions: (*a*) an agonist-dependent component, which describes the interaction between the drug and the biological system in terms of target affinity and activation, and (*b*) a biological system-dependent component, which is determined by receptor concentration and nature of the stimulus-response relationship. In receptor theory, binding of the drug to the target is described by a hyperbolic function:

$$[AR] = \frac{[R_0] \cdot [A]}{K_A + [A]}, \qquad 3.$$

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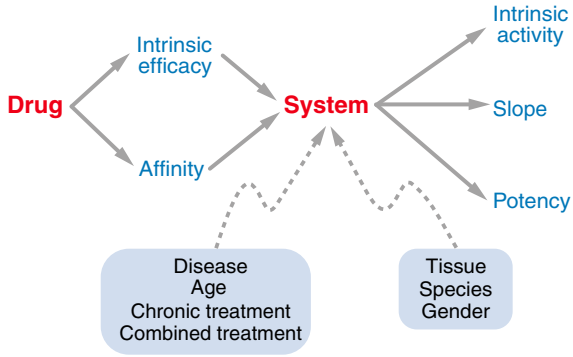

Figure 1

The shape and location of in vivo drug concentration-effect relationships is determined by drug-specific (affinity, intrinsic efficacy) and biological system-specific (transducer function relating receptor activation to effect) properties. Reproduced from Van der Graaf & Danhof (30).

where $[AR]$ is the concentration of agonist-receptor complex, $[R_0]$ is the total receptor concentration, $[A]$ is the concentration of the agonist A, and K_A is the dissociation equilibrium constant of AR. Receptor activation is incorporated in the model on the basis of Stephenson's concept of a stimulus to the biological system, which results from the drug-receptor interaction (31). This stimulus is defined as

$$S = \frac{E \cdot [AR]}{[R_0]} = \frac{e \cdot [A]}{[A] + K_A}, \qquad 4.$$

where S is the stimulus to the biological system and e is a dimensionless proportionality factor denoting the power of a drug to produce a response in a tissue. An important feature of the model is that the intensity of the drug response is not directly proportional to the stimulus. Instead, the response is assumed to be a function f of the stimulus that is monotonically increasing and continuous:

$$\frac{E_A}{E_{\max}} = f(S) = f\left[\frac{e \cdot [A]}{[A] + K_A}\right]. \qquad 5.$$

Thus, the introduction of the function f dissociates receptor stimulus and tissue response as directly proportional quantities. This also eliminates the necessity for the assumption that a maximal response requires maximal receptor occupancy. Furchgott (32) further refined this model by defining the concept of intrinsic efficacy ε as

$$\varepsilon = \frac{e}{[R_0]}, \qquad 6.$$

thereby directly incorporating the receptor density R_0 into the model as a major determinant of the effect. In the model, ε characterizes the capacity of a drug to initiate a stimulus per receptor. Thus, ε is strictly a drug-specific parameter. The incorporation of the term ε into Equation 5 results in

$$\frac{E_A}{E_{\max}} = f(S) = f\left[\frac{\varepsilon \cdot [R_0] \cdot [A]}{[A] + K_A}\right]. \qquad 7.$$

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Table 1 In vivo estimates of the relative intrinsic efficacy (e) and receptor affinity (K_A) of benzodiazepines obtained on the basis of a simultaneous analysis of the concentration-EEG effect relationships of flunitrazepam, midazolam, oxazepam, and clobazam on the basis of Equation 5

Benzodiazepine	e	K_A (ng · ml^{-1})	$K_{A,u}$* (ng · ml^{-1})	K_i** (ng · ml^{-1})
Flunitrazepam	1	21 ± 2.1	3.2	7.0
Midazolam	0.87 ± 0.03	43 ± 6.0	1.6	4.9
Oxazepam	0.90 ± 0.04	411 ± 49	36	86
Clobazam	0.79 ± 0.03	782 ± 86	242	350

*The parameter $K_{A,u}$ is the in vivo receptor affinity based on unbound drug concentrations.
**The in vitro estimates of benzodiazepine receptor affinity (K_i) were determined in a GABA-enriched receptor preparation.
From Tuk et al. (32).

Equations 5 and 7 constitute the scientific basis for the semiparametric approach to the incorporation of receptor theory in PK-PD modeling. Specifically, the semiparametric approach uses a parametric (i.e., hyperbolic) function to describe the receptor activation process in combination with a nonparametric function to describe transduction.

Application to $GABA_A$ receptor agonists. The semiparametric approach to the incorporation of receptor theory has been successfully applied in the analysis of the PK/PD correlations of $GABA_A$ receptor agonists using quantitative electroencephalogram (EEG) parameters as pharmacodynamic endpoints (33). Simultaneous analysis of the in vivo concentration effect relationships of flunitrazepam, midazolam, oxazepam, and clobazam within the nonlinear mixed effects modeling (NONMEM) software has been instrumental in the identification of the system-specific transducer function. This analysis yielded independent estimates of the in vivo receptor dissociation constant K_A for each of the benzodiazepines as well as estimates of the intrinsic efficacy relative to the full agonist flunitrazepam (**Table 1**). The system-specific transducer function was nonlinear, with no saturation at higher stimulus intensities (**Figure 2**). Interestingly, a highly significant correlation was observed between the estimates of the in vivo receptor dissociation constant K_A and the K_i values in an in vitro bioassay in a GABA-enriched membrane preparation (**Table 1**), confirming the validity of the model.

Full-parametric approach to the incorporation of receptor theory: the operational model of agonism. The full-parametric approach incorporating receptor theory differs from the semiparametric approach in that it contains a specific expression for the transducer function relating receptor activation and effect. The most well-known example of a full parametric receptor model (FPRM) is Black & Leff's operational model of agonism (OMA) (34). To allow for receptor reserve in biological systems, this model contains a hyperbolic transducer function, which can be

FPRM: full parametric receptor model

OMA: operational model of agonism

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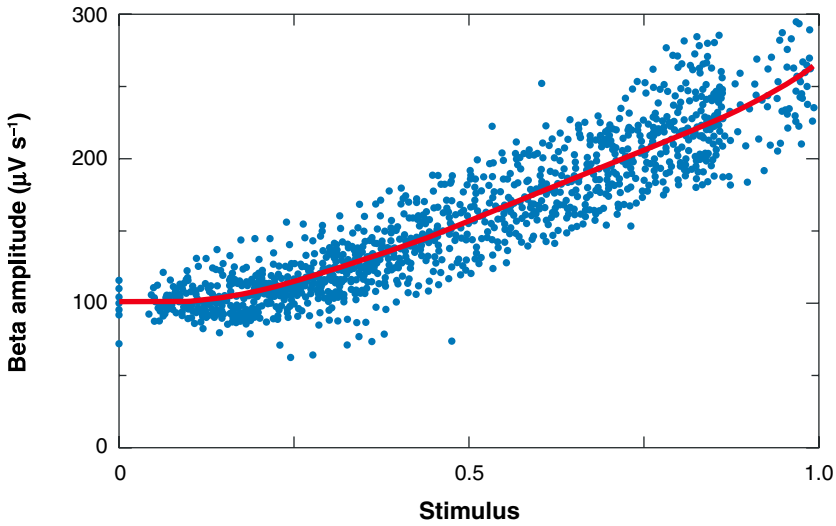

Figure 2

Transducer function of benzodiazepines describing the relationship between the $GABA_A$ receptor activation (= stimulus) and the EEG response. The transducer function was derived by simultaneous analysis of the concentration-EEG effect relationships of flunitrazepam, midazolam, oxazepam, and clobazam on the basis of a semiparametric receptor model. Reproduced from Tuk et al. (32).

represented as follows:

$$\frac{E}{E_m} = \frac{[AR]^n}{K_E^n + [AR]^n}, \qquad 8.$$

where E is the response; E_m is the maximum system response; K_E is the value midpoint location of the transducer function, that is $[AR]$, which elicits half-maximal effect; and n is the slope of the transducer function. Combining Equations 3 and 8 yields an explicit model of agonism describing the pharmacological effect in terms of agonist concentration:

$$E = \frac{E_m \cdot \tau^n \cdot [A]^n}{(K_A + [A])^n + \tau^n \cdot [A]^n}, \qquad 9.$$

where the transducer ratio τ, defined as R_0/K_E, is a measure of the efficiency of the receptor activation into pharmacological effect, and E_m is the system maximum (i.e., the maximum effect that can be observed in the biological system).

The OMA can be employed to obtain estimates of the affinity and intrinsic efficacy of partial agonists by comparison with a full agonist (35). This so-called comparative method (36) is based on the idea that for a full agonist, the Hill equation parameters, intrinsic activity (α) and Hill slope (n_H), are identical to the operational model parameters, E_m and n, respectively. When the values of E_m and n are constrained to the values of α and n_H of a full agonist, the values of K_A and τ can be estimated by fitting the concentration-effect data to the OMA (Equation 9).

An important feature of the OMA is that it can be used to predict the shape and location of the in vivo concentration-effect relationship using a combination of the values of the drug-specific and biological system-specific parameters according to

$$\alpha = \frac{E_m \cdot \tau^n}{\tau^n + 1} \qquad 10.$$

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and

$$EC_{50} = \frac{K_A}{(2 + \tau^n)^{1/n} - 1}, \qquad 11.$$

where α is intrinsic activity, E_m is the system maximum, τ is the efficacy parameter, n is the slope of the hyperbolic transducer function, EC_{50} is the potency, and K_A is the receptor dissociation constant. As such, the model constitutes a theoretical basis for the prediction of in vivo drug concentration-effect relationships that is based on information from in vitro bioassays and for the understanding of differences in drug concentration-effect relationships between different biological systems.

The OMA has been successfully applied in a series of in vivo investigations of the PK-PD correlations of A_1 adenosine receptor agonists (4, 37), μ opioid (MOP) receptor agonists (38, 39), and 5-HT_{1A} receptor agonists (17). The most recent application is in the analysis of drug effects on QTc interval prolongation (40). The application of the OMA in mechanism-based PK-PD modeling of A_1 receptor agonists and MOP receptor agonists is described in detail below, illustrating a number of important features of this model.

Application to A_1 adenosine receptor agonists. The objective of the research on A_1 receptor agonists was to explore the potential of a series of deoxyribose and 8-alkylamino analogs of N^6-cyclopentyladenosine (CPA) as antilipolytic agents for the treatment of noninsulin-dependent diabetes mellitus. Specifically, this research was aimed at the development of compounds that inhibit lipolysis but are devoid of cardiovascular side effects.

A key step in this research was the development of a chronically instrumented animal model and sensitive analytical assays for detailed simultaneous characterization of the pharmacokinetics and the effects on hemodynamic variables and lipolysis (42, 43). This is important because drug-induced bradycardia and hypotension are potentially serious side effects of A_1 receptor agonists.

The PK-PD correlations of various synthetic CPA analogs were determined following intravenous administration in these animal models. Briefly, by simultaneous analysis of the time course of the hemodynamic response in conjunction with plasma concentrations, assuming a direct link between plasma concentration and effect, drug concentration-effect relationships for the effect on heart rate could be established in individual rats. Wide differences in potency (as reflected in the value of EC_{50}) and in intrinsic activity (as reflected in the value of α) were observed between the different CPA analogs (44, 45). Thus, the deoxyribose and 8-alkylamino analogs behaved functionally as partial agonists relative to the reference compound CPA. The next step was the application of receptor theory to make a strict distinction between drug-specific and biological system-specific properties governing the observed concentration-effect relationships. Simultaneous analysis of the cardiovascular data for 10 analogs using the OMA (Equation 9) and the comparative method (36) yielded in vivo affinity constant K_A and efficacy τ values that were highly consistent with results from in vitro receptor assays (**Figure 3**). Specifically, the values of in vivo K_A correlated well with the in vitro estimates of K_i. Moreover, in vivo estimates of τ correlated with the in vitro estimates of the GTP shift as an in vitro measure of

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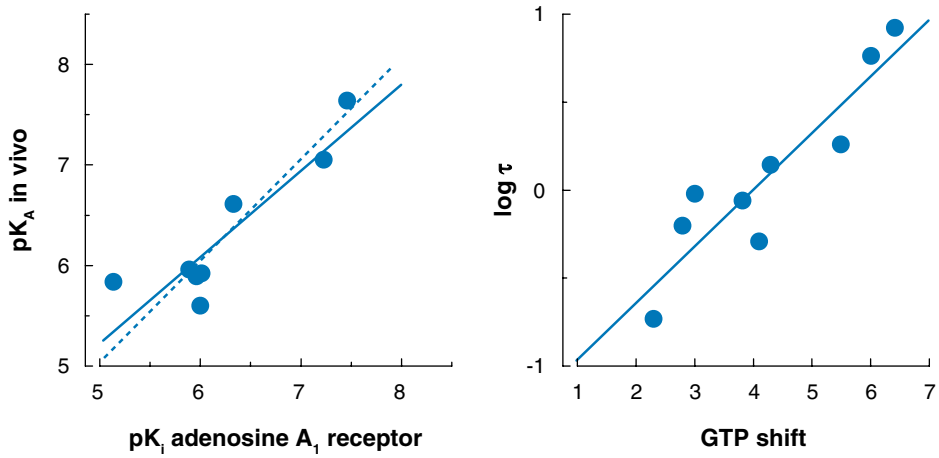

Figure 3

In vitro–in vivo correlation of the receptor affinity (*left panel*) and intrinsic efficacy (*right panel*) of A_1 adenosine receptor agonists for their effect on heart rate. The in vivo receptor affinity (pK_a) and intrinsic efficacy (log τ) were determined by simultaneous analysis of the concentration–heart rate relationships of 10 selective A_1 adenosine receptor agonists on the basis of the operational model of agonism. Reproduced from Van der Graaf et al. (4).

intrinsic efficacy (4). This provided the first proof-of-principle for this mechanism-based PK-PD modeling approach.

The next step in the PK-PD modeling of the effects of A_1 receptor agonists was the analysis of the PK-PD correlation for the effect on lipolysis. The objective here was to validate the hypothesis that partial agonists (i.e., compounds with a reduced intrinsic efficacy) have an enhanced selectivity of action with respect to the cardiovascular side effects. In these investigations, a delay between the plasma concentration and the effect on plasma nonesterified fatty acids (NEFAs) was observed, which was accounted for by the incorporation of an indirect effect model. This yielded concentration-effect relationships for the inhibition of lipolysis (43, 46). An interesting observation during these investigations was that several CPA analogs, which displayed profoundly reduced cardiovascular effects (i.e., behaved as partial agonists with regard to the hemodynamic effect), still produced near maximal inhibition of NEFAs in the rat model (47). This was remarkable because the same adenosine receptor subtype mediates both effects. The OMA (Equation 9) was employed to simultaneously analyze the NEFA effects of all ligands. This yielded estimates of in vivo efficacy and affinity for the adenosine A_1 receptor-mediated effect on NEFAs that could be compared directly with those obtained for the effect on heart rate (**Figure 4**). The main outcome of this analysis was that, on average, all compounds displayed an ~38-fold higher efficacy (as reflected in the value of the parameter τ in Equation 9) for the NEFA effect compared with the cardiovascular effect. This is consistent with independent findings that the density of adenosine A_1 receptors is ~25-fold higher in adipocytes compared with cardiac tissue (37). **Figure 4** also shows the relationship between the

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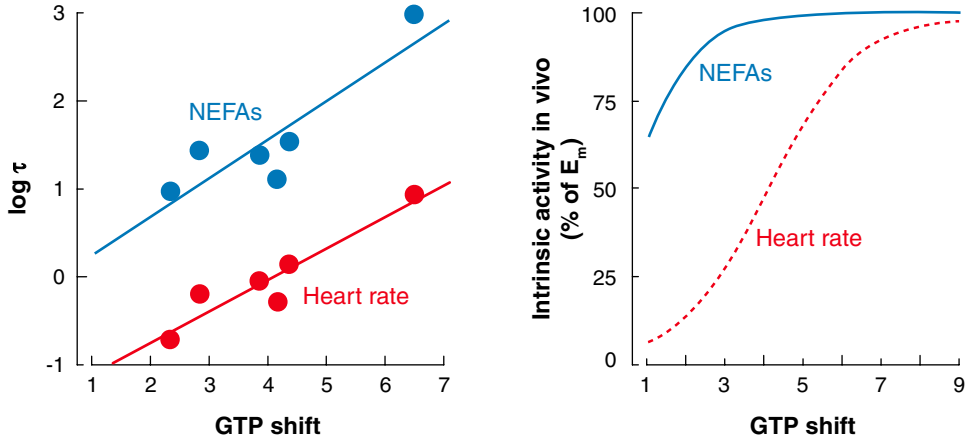

Figure 4

Left panel: Relationship between intrinsic efficacy in an in vitro (GTP-shift) and in vivo (log τ) bioassay for the effect of a series of A_1 receptor agonists on heart rate and lipolysis, respectively. Right panel: relationship between intrinsic efficacy in an in vitro bioassay (GTP shift) and in vivo intrinsic activity (α) for the effects on heart rate and lipolysis, respectively. The graphs show that partial agonists with GTP shift values between 1 and 5 display the highest selectivity of action for the effect lipolysis versus heart rate. Reproduced from Van der Graaf et al. (37).

in vitro GTP shift and the observed in vivo intrinsic activity α of the various compounds. This relationship is nonlinear because at higher values of the GTP shift, the intrinsic activity reaches the system maximum E_m. An important conclusion from this analysis is that compounds with a GTP shift ranging between 1 to ~5 display the highest selectivity of action. Specifically, drugs with a GTP shift close to unity can still produce significant inhibition of lipolysis in vivo, whereas they are virtually devoid of cardiodepressant side effects.

Application to μ opioid receptor agonists. A series of investigations on MOP receptor agonists emphasized the interspecies extrapolation of the PK-PD relationship and the development of a mechanism-based PK-PD model to describe, explain, and predict opioid tolerance development.

Quantitative EEG analysis was used as a biomarker for MOP receptor activity in both preclinical animal models and man. Using the synthetic opioid alfentanil as a reference compound, a rat model was developed in which the amplitudes in the 0.5–4.5 Hz frequency band of the EEG spectrum were used to describe the time course of effect and to derive PK-PD correlations (48). As the first step in the development of the mechanism-based PK/PD model, alfentanil and the related 4-anilidopiperidine analogs, fentanyl and sufentanil, were studied. These compounds were selected as model drugs because of their high selectivity for the MOP receptor. Moreover, in vitro studies had demonstrated that these three ligands display very different levels of intrinsic efficacy, as judged by the sodium shift, which is defined

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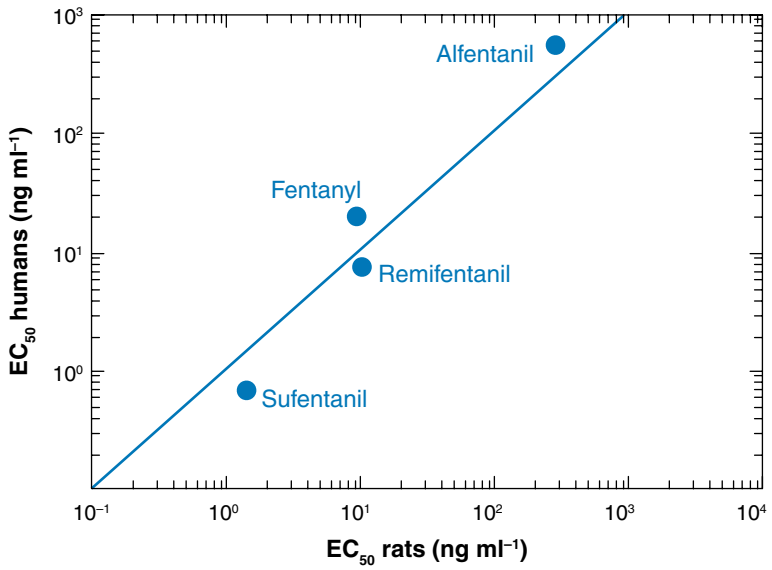
as the ratio between a ligand's MOP receptor affinity in the presence and absence of high concentrations of Na^+ (19). This is important because simultaneous analysis of the concentration-effect relationships of compounds with different receptor affinities and intrinsic efficacies enables identification of the OMA parameter estimates, as was shown above for A_1 adenosine receptor agonists (4). Despite the fact that in vitro sufentanil behaved as a low-efficacy agonist (sodium shift = 2.8) relative to fentanyl and alfentanil (sodium shift = 13.3 and 19.1, respectively), the concentration-effect relationships for the EEG effect in vivo displayed the same maximal response (intrinsic activity). To explain this finding, the OMA (Equation 9) was employed to integrate the in vitro and in vivo data (19). This analysis showed that the sodium shift in vitro provides for an accurate prediction of the expression of agonism in vivo. Specifically, it was shown that the in vivo efficacy parameter τ could be expressed as the product of the sodium shift and an agonist-independent constant with a value of 4.3. This indicates that functionally, the MOP receptor operates with a high receptor reserve and that the observed maximal effect of fentanyl, alfentanil, and sufentanil is equal to the system maximum E_m in the OMA (Equation 9).

The PK-PD correlation for the effect on the 0.5–4.5 Hz frequency band of the EEG has also been determined for fentanyl, alfentanil, and sufentanil in humans (49, 50). Interestingly, for the various synthetic opioids, nearly identical values of EC_{50} values were observed between rats and humans, indicating that the MOP receptor functions in a very similar manner in both species (**Figure 5**). This constitutes a basis for the interspecies extrapolation concentration-effect relationships. The mechanism-based PK-PD model for MOP receptor agonists has been successfully applied to predict the in vivo potency and intrinsic activity of the novel synthetic

Figure 5

Synthetic opioids have similar EC_{50} values in rats and humans, indicating that the MOP receptor functions in a nearly identical manner in these species. This enables the prediction of the in vivo potency (EC_{50}) and intrinsic activity (α) of synthetic opioids in man based on preclinical investigations in rats. Reproduced from Cox et al. (52).



opioid remifentanil and its active metabolite GR90291 in humans on the basis of the results of preclinical investigations in rats (51, 52).

The mechanism-based PK-PD model of MOP receptor agonists has also been successfully applied to explain the development of rapid functional tolerance to alfentanil upon repeated administration. Briefly, upon repeated administration of alfentanil in rats, a parallel shift in the concentration-EEG effect relationship was observed, with an almost twofold decrease in potency (EC_{50}) and without a significant change in the intrinsic activity (α). Analysis of these observations based on the OMA showed that this shift can be explained by a high receptor reserve in combination with a decrease in the value of the efficacy parameter τ, reflecting an approximately 40% loss of functional MOP receptors (53). This model-derived estimate of the fractional loss of functional receptors is very similar to experimental values observed following chronic opioid exposure using molecular techniques (54).

Further validation of the mechanism-based PK/PD model was obtained using a novel experimental approach of MOP receptor knockdown with the irreversible MOP antagonist β-funaltrexamine (β-FNA). Pretreatment of rats with β-FNA prior to the PK/PD experiment was able to produce a gradual reduction (40%–60%) in the number of MOP receptors in rat brain without affecting the affinity of alfentanil, as judged by radioligand binding studies (**Figure 6**). Consistent with previous findings,

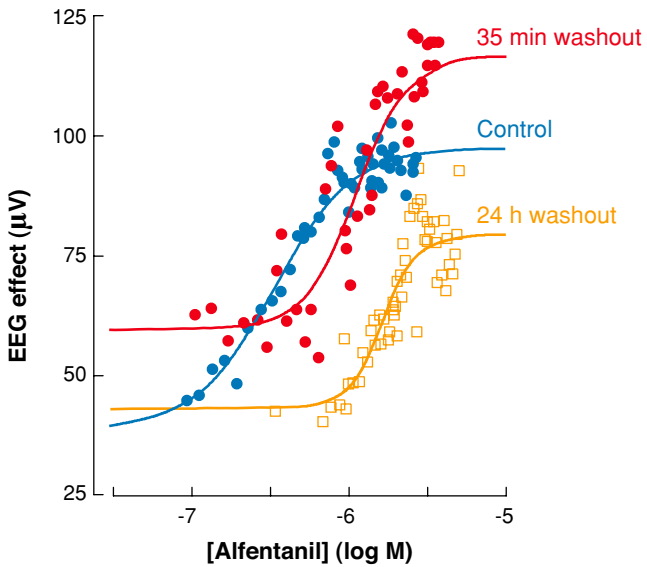


Figure 6

Influence of receptor knockdown with β-flunaltrexamine on the in vivo concentration-EEG effect relationship of alfentanil in rats. Pretreatment with β-flunaltrexamine resulted in an approximately 60% reduction of functional MOP receptors at 35 min and at 24 h post administration. This reduction in functional receptors caused a parallel shift in the concentration-effect relationship without a major change in maximum effect. This is consistent with the observation that the MOP receptor functions with a high receptor reserve. Reproduced from Garrido et al. (39).

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MBM: mechanism-based modeling

which had suggested the presence of a MOP receptor reserve for the EEG effect of opioids in this model, this loss of receptor function did not result in a reduced intrinsic activity of alfentanil, but instead resulted in a two- to threefold loss of potency in β-FNA-treated animals. Again, this finding is in line with expectations of a reduction in τ in the mechanism-based model (MBM) (39). These findings illustrate the utility of mechanism-based PK-PD modeling for understanding, in a strictly quantitative manner, the variability in drug response caused by variability in receptor expression and/or function.

Full parametric approach to the incorporation of receptor theory: A model with a parabolic transducer function. In theory, the transduction function describing the relationship between receptor activation and response can take any shape. The utility of the semiparametric approach to the incorporation of receptor theory in PK-PD modeling is its use in exploratory analyses to obtain pertinent information on the shape of the transducer function in a given biological system. This information can then be used for the design of a FPRM, with an explicit function to describe the stimulus-response relationship. This approach has been successfully applied to the development of a full parametric PK-PD model for $GABA_A$ receptor agonists.

Application to $GABA_A$ receptor agonists. Increases in β activity of the EEG have been used as a biomarkers in several investigations on the concentration-effect relationships of a range of benzodiazepines in experimental laboratory animals (5, 18, 33, 56–60) and in man (61–63). In addition, the change in the β frequency range of the EEG has also been used in investigations of the PK-PD correlations of barbiturates, propofol, and neuro-active steroids (16, 60, 64, 65). The GABA reuptake inhibitor tiagabine gives a characteristic change in the EEG, which is comparable to benzodiazepines (66).

Detailed investigations of the PK-PD correlations of benzodiazepines revealed that benzodiazepines exhibit nonlinear concentration-effect relationships that are readily described by the Hill equation (Equation 2). Between benzodiazepines, wide differences in potency (EC_{50}) and intrinsic activity (α) were observed. Furthermore, inverse agonists were found to display a negative EEG effect. (18, 33, 57, 60). In contrast, neurosteroids demonstrate both qualitatively and quantitatively different concentration-effect relationships. Specifically, neurosteroids exhibit complex biphasic concentration-effect relationships (16, 65): At low concentrations, the EEG effect increases from baseline to a maximum value, which is approximately two to three times higher than the maximum observed for the benzodiazepine displaying the highest intrinsic activity (diazepam), whereas at higher concentrations, the effect decreases below the baseline toward isoelectric EEG. For alphaxalone, the shape of the biphasic concentration-effect relationship was shown to be independent of the rate of administration, indicating that there are no confounding counter-regulatory mechanisms. This confirms that the observed concentration-effect relationships are indeed unique (16). Based on these observations, a novel full-parametric PK-PD model for $GABA_A$ receptor agonists has been proposed (**Figure 7**) featuring a hyperbolic model to describe the receptor activation process in combination with a parameterized

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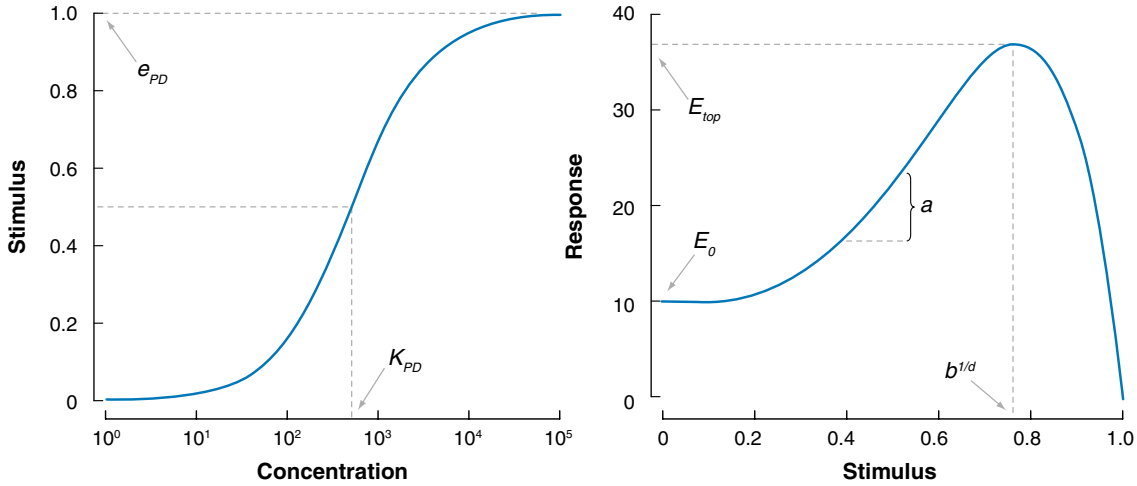

Figure 7

Full-parametric receptor model for characterization of the concentration-EEG effect relationships of $GABA_A$ receptor agonists. The full parametric model features a hyperbolic function to describe the drug-receptor interaction in combination with a parabolic transducer function. Reproduced from Visser et al. (16).

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biphasic transducer function (i.e., stimulus-response relationship) (16). In this model, the transduction f (Equation 7) is described by a parabolic function according to

$$E = E_{top} - a \cdot (S^d - b)^2, \qquad 12.$$

where S represents the stimulus to the biological system resulting from $GABA_A$ receptor activation, E_{top} represents the top of the parabola, and a is a constant reflecting the slope of the parabola. Furthermore, $b^{1/d}$ is the stimulus for which the top of the parabola (i.e., the maximal effect, E_{top}) is reached, and the exponent d determines the asymmetry of the parabola. When no drug is present, the EEG is equal to its baseline value (E_0). Equation 13 then reduces to

$$E_0 = E_{top} - a \cdot b^2. \qquad 13.$$

Substituting Equation 12 in Equation 13 and rearranging yields

$$E = E_0 - a \cdot ((S^d)^2 - 2 \cdot b \cdot S^d). \qquad 14.$$

Thus, the shape and location of the parabolic function is determined by three parameters: a, b, and d. Specifically, the value of parameter a determines the height of the maximal achievable response (E_{top}) as well as the steepness of the increasing and decreasing wing. Parameter b determines the location of E_{top}, and d determines the asymmetry of the parabola.

The model was applied to the analysis of the concentration-effect relationships of neuroactive steroids (65). Simultaneous analysis of the concentration-effect relationships of the neurosteroids alphaxalone, pregnanolone, ORG 20599, and ORG 21465

using the mechanism-based model showed that all observations can be described with a single unique transducer function. This indicates that the obtained transducer function is indeed system-specific and independent of the drug used. With respect to the receptor activation model, it was observed that all neuroactive steroids acted as high-efficacy modulators at the $GABA_A$ receptor, with an intrinsic efficacy equal to that of alphaxalone. Wide differences in in vivo potencies were observed, which were consistent with the differences in affinity in an in vitro bioassay (67).

Subsequently, the model was applied to the concentration-effect relationships of benzodiazepines, imidazopyridines, cyclopyrrolones, and a β-carboline (68). These compounds differ in intrinsic efficacy at the $GABA_A$ receptor, displaying the entire spectrum from full benzodiazepines receptor agonists, partial, and silent to inverse agonists (69, 70). Simultaneous analysis of the benzodiazepine and neurosteroids data using the mechanism-based model allowed estimation of the in vivo efficacy (*e*) and affinity (K_A) for each of the compounds utilizing the single unique transducer function that had previously been identified for neuroactive steroids. This analysis revealed that the $GABA_A$ receptor modulators differ from the neuroactive steroids solely in their in vivo efficacy, and in such a manner that they act as partial agonists relative to neurosteroids (**Figure 8**). A highly significant correlation between the in vitro estimates for efficacy (GABA-shift) and affinity (K_i) and the corresponding in vivo estimates was observed, confirming the validity of the proposed mechanism-based PK-PD model. This model is now applied to analyze mechanisms of drugs resistance in (animal models of) temporal lobe epilepsy (L.C. Liefaard, S.A.G. Visser, M. Danhof, R.A. Voskuyl, unpublished observations).

Pharmacodynamic Interactions

Modeling of pharmacodynamic interactions is an integral part of mechanism-based PK-PD modeling. Specifically, the modeling of pharmacodynamic interactions is not limited to situations in which two drugs are given in combination or where a drug is converted into an (inter) active metabolite. Modeling of pharmacodynamic interactions is also relevant when (*a*) a drug interacts with an endogenous ligand; (*b*) a drug interacts at multiple targets, thereby activating multiple pathways; and (*c*) when homeostatic feedback occurs. Moreover, modeling of the influence of baseline effects is also based on theoretical concepts of interaction modeling.

A number of important papers have been published on the theoretical aspects of pharmacodynamic drug-drug interactions in terms of synergy and antagonism (71–76). In theoretical terms, modeling of pharmacodynamic interactions concerns the prediction of combined drug effects. In this context, synergy occurs when the combined effect is larger than is expected under the assumption of additivity (no interaction) of the two effects separately. In contrast, antagonism occurs when the combined drug effect is smaller.

Response surface analysis of pharmacodynamic interactions. For interpreting pharmacodynamic drug interactions, a comprehensive method for evaluating the combined responses as additive, synergistic, or antagonistic is required. Historically,

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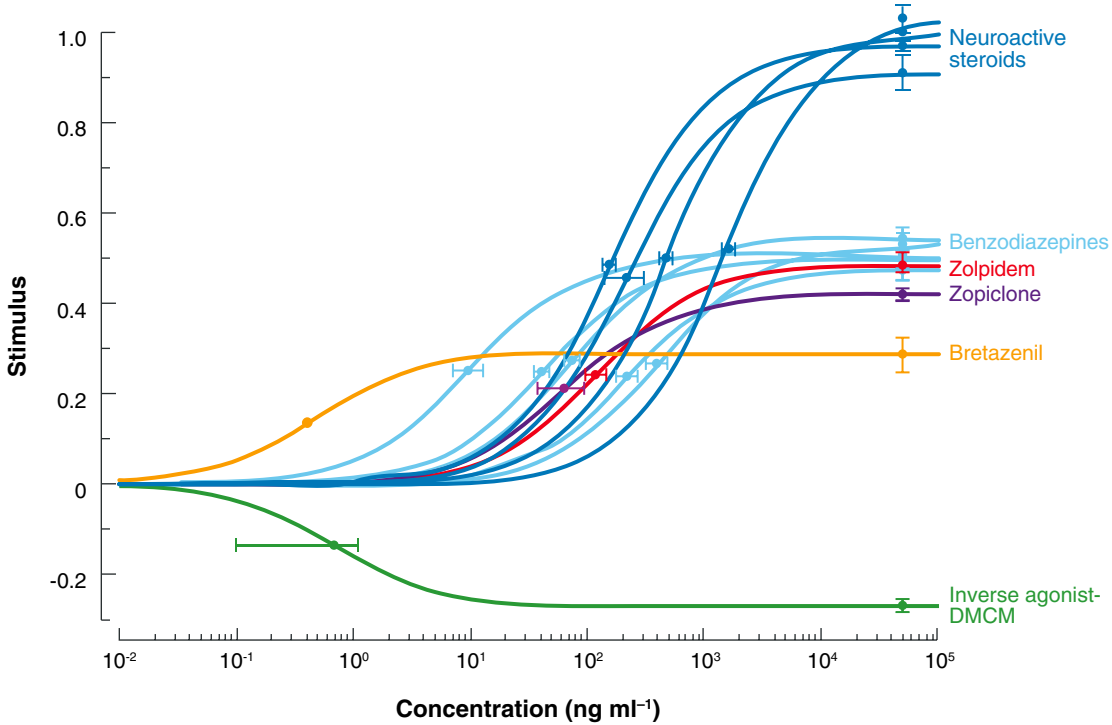

Figure 8

The relationship between drug concentration and stimulus at the $GABA_A$ receptor for the $GABA_A$ receptor modulators. Concentration (ng · ml^{-1}) is depicted on the x-axis in logarithmic scale and the stimulus is depicted on the y-axis. The results of the mechanism-based PK/PD analysis show that functionally, benzodiazepines, imidazopyridines, cyclopyrrolones, and β-carbolines behave as partial agonists relative to neurosteroids. Reproduced from Visser et al. (68).

combined drug responses have been analyzed on the basis of so-called isoboles (i.e., curves of concentration pairs of two drugs that yield the same predefined intensity of the response). A limitation of this approach is that it does not show the relationship of the degree of synergy and/or antagonism to the concentrations of both drugs. For this reason, in recent years, PD interactions have increasingly been evaluated based on response surface analysis (RSA). Within this context, response surfaces are 3-D graphs depicting the intensity of the effect versus two drug concentrations (76) to fully characterize a drug-drug interaction at all concentration pairs. This is important because drug interactions have the potential to be highly dimensional and complex, i.e., synergistic at some concentrations, while antagonistic at others (77). The magnitude and extent of a PD interaction can be visualized by plotting the estimated response relative to the additive response (i.e., the response that is observed when no interaction occurs). In their recent paper on the mechanism-based analysis of pharmacodynamic interactions, Jonker et al. (78) propose the following equations

RSA: response surface analysis

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for the additive response surface of drugs A and B:

$$E_{AB} = E_{A(B)} + E_{B(A)} \qquad 15.$$

in which E_{AB} is the combined drug effect and $E_{A(B)}$ is the response to A in the presence of B and $E_{B(A)}$ is the response to B in the presence of A according to

$$E_{A(B)} = \frac{E_{\max A}}{1 + \left\{ \frac{[A]}{EC_{50A}} + \left(\frac{[B]}{EC_{50B}} \right)^{\frac{n_B}{n_A}} \right\}^{-n_A}} \qquad 16a.$$

$$E_{B(A)} = \frac{E_{\max B}}{1 + \left\{ \frac{[B]}{EC_{50B}} + \left(\frac{[A]}{EC_{50A}} \right)^{\frac{n_A}{n_B}} \right\}^{-n_B}}, \qquad 16b.$$

in which $E_{\max A}$ and $E_{\max B}$ are the maximum effect B, $[A]$ and $[B]$ are the drug concentrations, EC_{50A} and EC_{50B} are the concentrations at half-maximal effect, and n_A and n_B are the slope factors of A and B, respectively. The additive response surface plot for the combination of a full agonist A and a partial agonist B resulting from this method is shown in middle panel of **Figure 9**. This additive response surface serves as reference in the evaluation of PD drug interactions, both in terms of the type of the interaction (synergy, antagonism), the magnitude of the interaction, and the pertinent concentration ranges of the two drugs where the interaction occurs.

The operational model of agonism as a basis for the mechanism-based analysis of pharmacodynamic interactions. Jonker et al. (78) have shown that the OMA (34) constitutes a scientific basis for the mechanism-based analysis of pharmacodynamic drug interactions. For the analysis of the response to a combination of two drugs, two classes of models must be distinguished: (*a*) sequential pathway models for interactions at the level of target binding and (*b*) dual pathway models for interactions at the level of transduction (**Figure 10**).

Within the sequential pathway model, two subtypes of interaction must be distinguished: (*a*) competition, when two drugs competitively bind to a single site, and (*b*) allosterism, when two drugs bind at separate binding sites and allosterically modulate each other's actions. Competitive and allosteric interactions result in a change in the location of the concentration-effect relationship but never in a change in the maximum effect (see Equations 10 and 11). In other words, competitive and allosteric interactions affect the potency of a drug (as reflected in the parameter EC_{50}) but never the intrinsic activity (as reflected in the parameter α). In contrast, interactions at the level of transduction can result in changes of either the potency (EC_{50}) or the intrinsic activity (α) depending on the degree of receptor reserve in the system.

For both competitive and allosteric interactions, comprehensive models have been proposed, often on the basis of investigations in in vitro test systems (79, 80). The implementation of these models in the in vivo situation is still a challenge of mechanism-based PK-PD modeling.

Modeling of competitive drug interactions. In a competitive interaction, where two drugs, A and B, competitively bind at the same site, total receptor occupancy is given

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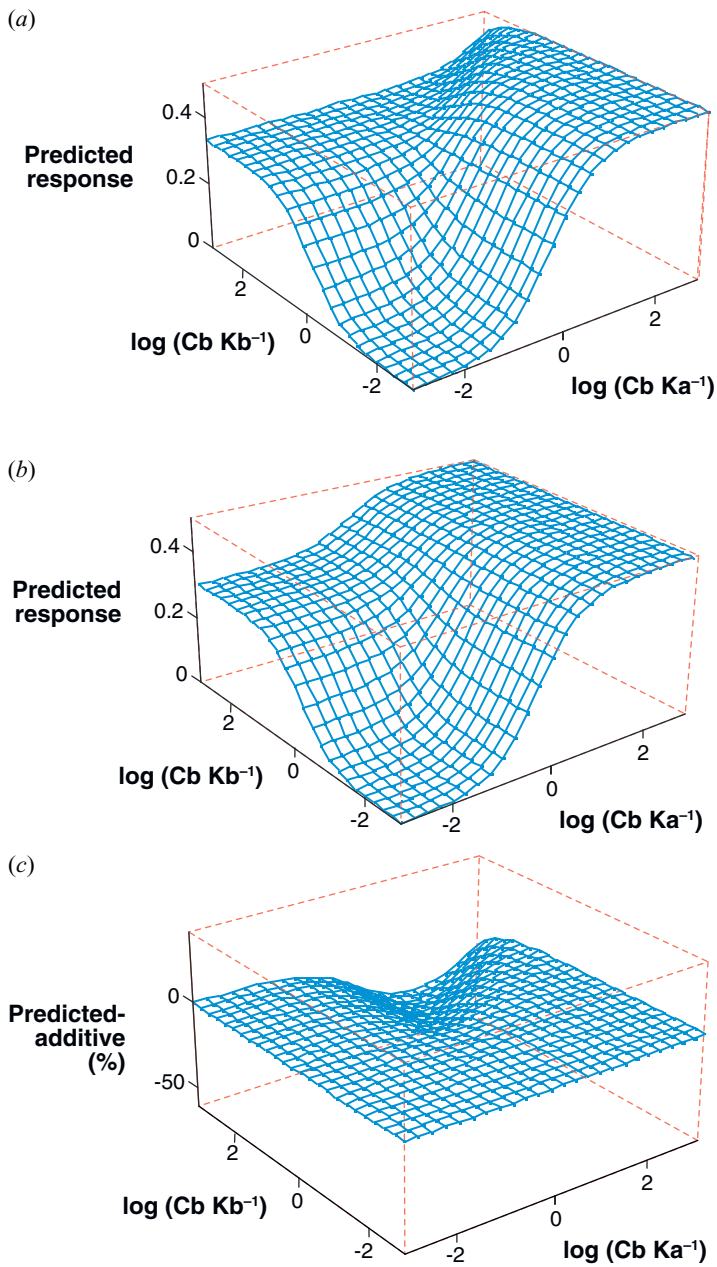

Figure 9

Response surface analysis of a competitive interaction between a full agonist A and a partial agonist B. The upper panel (*a*) shows the response surface for the competitive interaction between drug A and drug B. The middle panel (*b*) shows the additive response surface. Panel *c* shows the net response surface that is obtained by subtraction of panels *a* and *b*. The figure shows that competitive antagonism occurs in a specific concentration range. Reproduced from Jonker et al. (78).

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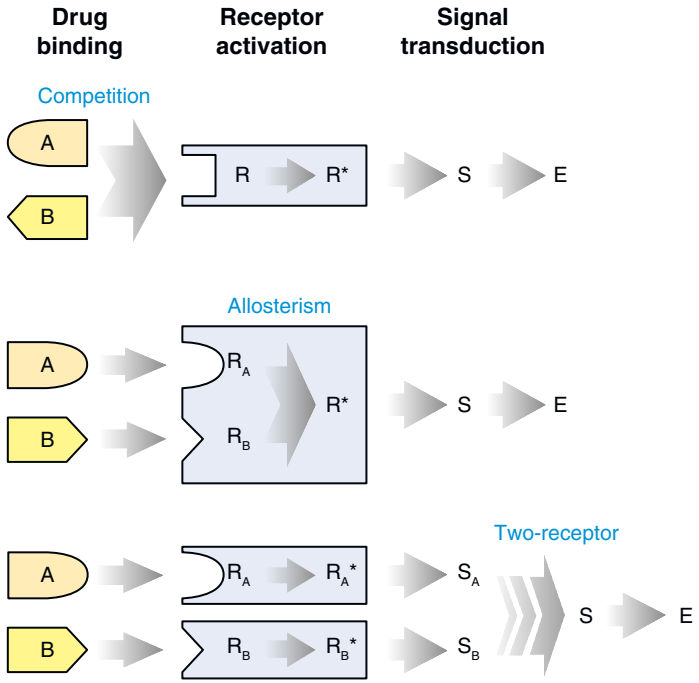

Figure 10

Mechanism-based analysis of pharmacodynamic drug interactions makes a distinction between single-pathway and dual-pathway models. Single-pathway models apply when the interaction occurs at the level of the target binding (i.e., competition and allosterism). Dual-pathway models apply when the interaction occurs at the level of transduction.

by (79)

$$[ABR] = [AR]_B + [BR]_A, \qquad 17.$$

in which $[ABR]$ is the total concentration of occupied receptors by drug A and drug B and $[AR]_B$ and $[BR]_A$ are the concentrations of occupied receptors by drug A in the presence of drug B and by drug B in the presence of drug A, respectively, according to

$$[AR]_B = \frac{[R_0] \cdot [A]}{K_A \cdot \left(1 + {}^{B}/_{K_B}\right) + [A]}, \qquad 18a.$$

$$[BR]_A = \frac{[R_0] \cdot [B]}{K_B \cdot \left(1 + {}^{A}/_{K_A}\right) + [B]}. \qquad 18b.$$

In the latter equations, $[A]$ and $[B]$ are the concentrations of drugs A and B, respectively, and K_A and K_B are the equilibrium dissociation constants of $[AR]$ and $[BR]$, respectively. These equations show that a competitive interaction results in a parallel shift of the concentration receptor occupancy curve to higher concentrations. In other words, a competitive drug interaction results in an apparent shift of the value of the equilibrium dissociation constant to higher concentrations.

The response surface resulting from a competitive interaction between a full agonist A and a partial agonist B is shown in panel *a* of **Figure 9** (78). Subtraction of the corresponding additive response, shown in panel *b*, visualizes the antagonistic nature of this interaction both in terms of the degree of antagonism and the respective concentration ranges of drug A and drug B, respectively (panel *c*).

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The PK-PD modeling of competitive pharmacodynamic interactions in in vivo investigations is well established (58–60, 82–84). Interestingly, competitive drug interactions appear to be readily scalable from experimental animals to humans (85).

Modeling of allosteric drug interactions. Allosteric modulation is defined as the cooperative binding of two agents at distinct sites such that an agent B, which is inactive by itself, modulates the response to agent A. The model for type of interaction is (80)

$$[AR]_B = \frac{R_0 \cdot [A] \cdot (K_B \cdot \gamma + [B])}{\gamma \cdot (K_A \cdot K_{B=} + K_A \cdot [B] + K_B \cdot [B]) + [A] \cdot [B]}, \qquad 19.$$

in which the allosteric constant γ is the cooperativity factor. The cooperativity factor γ is equivalent to the change in dissociation constants of the agonist A and the allosteric modulator B in each other's presence. **Figure 11** shows a simulated response surface for an allosteric interaction between an agonist A and a silent allosteric modulator B. This response surface was obtained by interfacing the allosteric interaction model (Equation 19) with the OMA (Equation 9). The simulation shows that, typically, the allosteric interaction occurs in distinct concentration ranges of the interacting drugs A and B. Moreover, in a series of simulations with different parameter estimates, the degree of synergism was found to depend on the values of the efficacy parameter τ and the slope factor n_E in the OMA (78).

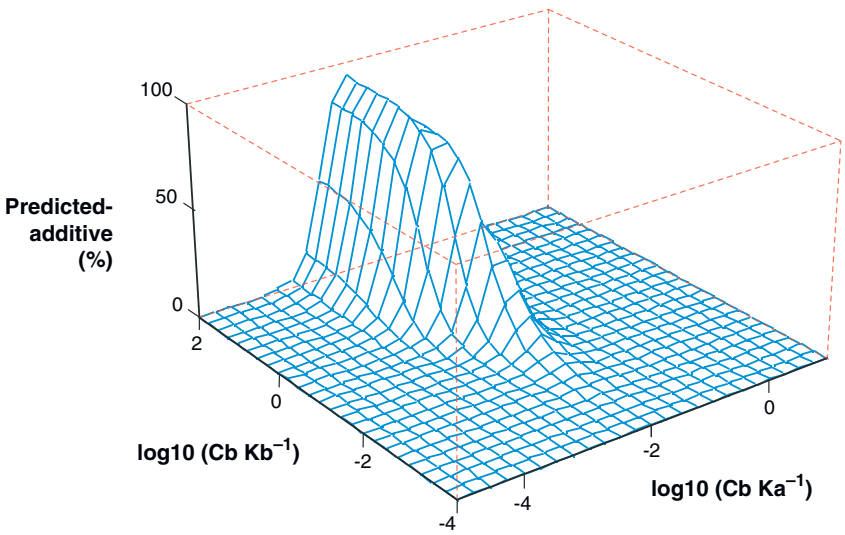

Figure 11

Response surface analysis of an allosteric drug interaction shows that synergism occurs in distinct concentration ranges. Simulations using the operational model of agonism have shown that the degree of synergism depends on the values of the efficacy parameter τ and the slope factor n_E. Reproduced from Jonker et al. (78).

In contrast to competitive interactions, there is limited experience with the modeling of allosteric interactions in in vivo investigations. The best-documented example is the modeling of the allosteric interaction between benzodiazepines and ethanol (86, 87).

Modeling of two-receptor drug interactions. The dual-pathway model (**Figure 10**) serves to describe the interaction between drugs that exert their actions through their interaction with two separate receptor systems. An important feature of this model is that, in contrast to the single pathway model, the interaction occurs at the level of the transduction, which in the OMA is reflected in a change in the value of the parameter τ. Interestingly, according to Equations 10 and 11, interactions at the level of transduction may result in changes in the potency (i.e., the value of the parameter EC_{50}) and/or the intrinsic activity (i.e., the value of the parameter α).

An important aspect of the modeling of two-receptor pharmacodynamic interactions is the point at which the transduction pathways converge and the degree of preamplification that occurs before convergence. Within the OMA, this can be conceptualized by the definition of separate efficacy parameters τ_1 and τ_2 to characterize preamplification and postamplification. Incorporation of this concept in the OMA yields the following equation:

$$E_A = \frac{E_m \cdot \{([A] \cdot \tau_{1A})^{n_A} \cdot \tau_{2A}\}^{n_E}}{\{(K_A + [A])^{n_A} + ([A] \cdot \tau_{1A})^{n_A}\}^{n_E} + \{([A] \cdot \tau_{1A})^{n_A} \cdot \tau_{2A}\}^{n_E}}, \qquad 20.$$

in which the values of the parameters τ_{1A} and τ_{1B} characterize the preamplification and τ_{2A} and τ_{2B} the postamplification for the transduction pathways A and B, respectively. In a series of simulations, it has been shown that the degrees of preamplification of A and B determine the range and the degree of synergy, as well as the concentration ranges in which synergy occurs. A variety of different models have been used to simulate interaction patterns (78). In general, most synergy is observed when the two pathways converge early in the transduction cascade. In addition, most synergy is observed in systems with a low degree of preamplification.

To date, there is limited experience with the mechanism-based modeling of two-receptor pharmacodynamic interactions. Recently, the dual pathway modeling approach has been used successfully to characterize the pharmacodynamic interactions of the antiepileptic drugs tiagabine and lamotrigine in a behavioral animal model (88).

Transduction

Transduction refers to the process of target activation into pharmacological response. Typically, binding of a drug to its target activates a cascade of electrophysiological and/or biochemical events resulting in the observable biological response. For many targets (i.e., G protein–coupled receptors), second messengers, such as 1,4,5 inositol triphosphate, diacylglycerol, and cAMP, serve as messenger molecules. For other receptors (i.e., glucocorticoid receptors), transduction is mediated through their interaction with DNA, thus regulating the expression of second messengers, proteins, or enzymes.

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Within the context of mechanism-based PK-PD modeling, transduction is defined as the cascade of processes that govern the time course of the pharmacological response in vivo following drug-induced target activation. This is therefore a much broader definition than the more traditional definition that is used in biochemical pharmacology.

An important feature of in vivo transduction is that it is often nonlinear. Moreover, there are large differences in the rates at which transduction processes occur in vivo. In many instances, transduction is fast (i.e., operating at rate constants in the range of milliseconds to seconds) relative to the rate constants governing the disposition of the drug (typically minutes to hours). In that situation, transduction is usually described based on a time-independent transducer function, which determines the shape and location of the in vivo concentration-effect relationship, as discussed above. Specifically, the transduction process per se does not cause a delay of the pharmacological effect relative to the time course of the drug concentration. In contrast, transduction in vivo can also be slow, operating with rate constants on the order of hours to days, in which case transduction becomes an important determinant of the time course of drug action.

As an approach to account for delays between the time courses of the drug effect relative to the drug concentration, Dayneka et al. (89) have proposed a family of four turnover models (i.e., indirect physiological response models) that are based on the following differential equation:

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot R, \qquad 21.$$

where R is a physiological entity that is constantly being produced and eliminated in time, k_{in} is the zero-order rate constant for production of the physiological entity, and k_{out} is the first-order rate constant for its loss. In the most basic form of the model, the drug effect is described as stimulation or inhibition on the factors controlling either the input or the dissipation of drug response in a direct concentration-dependent manner. In these models, the rate constants for the input and the dissipation of the drug response are the important system-specific parameters governing the time course of the drug response. In the meantime, numerous useful applications of various forms of the indirect response model have been proposed (90).

The turnover model is conceptually important as it constitutes a scientific basis not only for basic and more complex transduction models but also for disease and disease progression models.

Complex transduction mechanisms can be modeled on the basis of cascading turnover models describing intermediary processes between the pharmacokinetics and the ultimate biological response. In terms of mathematical modeling, the so-called transit compartment model has been proposed. This model relies on a series of differential equations to describe the cascade of events between receptor activation and final response (91). Well-known examples of this modeling are the modeling of the genomic effects of corticosteroids (92) and the modeling of hematological toxicity in cancer (93). The transit compartment model is attractive because of its flexibility, but for it to become fully mechanistic, pertinent information on the processes of the

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causal path is required. This underscores the need for biomarkers to characterize in vivo transduction mechanisms.

Application to corticosteroids. The most well-known example of a mechanism-based transduction model is the so-called fifth generation model for corticosteroid pharmacodynamics (92). This model describes the pharmacodynamics of the receptor/gene-mediated effects of methylprednisolone on the basis of a series of differential equations for the receptor regulation and the turnover of serum tyrosine aminotransferase (TAT) activity as the ultimate pharmacodynamic endpoint (**Figure 12**). The differential equations for the various components of the model controlling the receptor regulation are the following:

$$\frac{dR_m}{dt} = k_{syn\_Rm} \cdot \left(1 - \frac{DR(N)}{IC_{50\_Rm} + DR(N)}\right) - k_{deg\_Rm} \cdot R_m \quad 22.$$

$$\frac{dR}{dt} = k_{syn\_R} \cdot R_m + R_f \cdot k_{re} \cdot DR(N) - k_{on} \cdot D \cdot R - k_{dgr\_R} \cdot R \quad 23.$$

$$\frac{dDR}{dt} = k_{on} \cdot D \cdot R - k_T \cdot DR \quad 24.$$

$$\frac{dDR(N)}{dt} = k_T \cdot DR - k_{re} \cdot DR(N), \quad 25.$$

where R_m represents mRNA for the receptor, R is the free cytosolic receptor concentration, DR is the cytosolic drug-receptor complex concentration, $DR(N)$ is the nuclear activated drug-receptor complex concentration, and k_{on} and k_{dgr} are the first-order rate constants of synthesis and degradation of the response respectively.

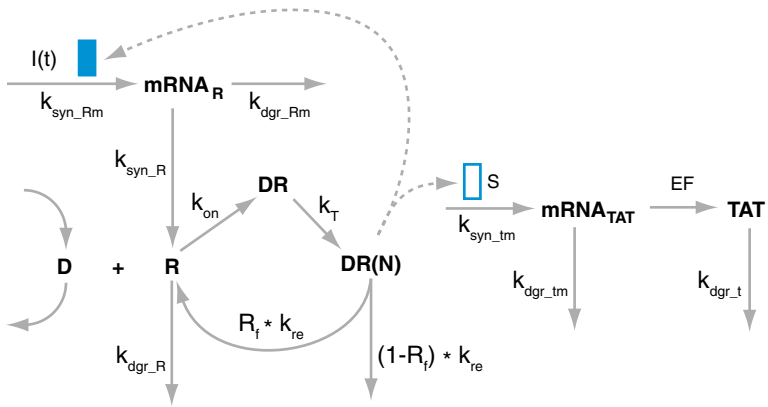

Figure 12

Fifth-generation model of acute corticosteroid receptor/gene-mediated effects. The differential equations for the various components of the model controlling the receptor regulation are described in the text (Equations 21–27). The dotted lines leading to the solid and open rectangles represent inhibition and induction of gene transcription by the drug-receptor complex in the nucleus DR(N) by indirect mechanisms. Reproduced from Ramakrishnan et al. (90).

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The differential equations describing the enzyme dynamics are as follows:

$$\frac{dTAT_m}{dt} = k_{syn\_m} \cdot (1 + S \cdot DR(N)) - k_{dgr\_m} \cdot TAT_m \quad 26.$$

$$\frac{dTAT}{dt} = EF \cdot (TAT_m)^{\gamma} - k_{dgr\_t} \cdot TAT, \quad 27.$$

where TAT_m and TAT are the mRNA for TAT and the TAT enzyme concentrations, respectively; S is the linear constant for the efficiency of TAT gene induction by $DR(N)$; EF is the efficiency of translation of TAT mRNA to TAT enzyme; γ is an amplification component for the translation; k_{syn_m} is the zero-order rate of TAT mRNA synthesis; and k_{dgr_m} and k_{dgr_t} represent the first-order rate constants of degradation of TAT mRNA and TAT, respectively. This kind of modeling of transduction has been applied in a number of animal investigations on the pharmacogenomic effects of corticosteroids (94, 95).

Clearly, the modeling of transduction relies on the availability of biomarkers that characterize processes on the causal path between drug administration and response (3). It is expected that with new advances in pharmacogenomics and imaging techniques, novel biomarkers will become available. In its purest form, modeling of transduction is modeling of the functioning of the biological system in terms of a set of biological system-specific properties. Therefore, this constitutes a unique basis for the prediction of (the time course of) in vivo drug effects.

Homeostatic Feedback

The time course of the pharmacological response is often influenced by in vivo homeostatic feedback mechanisms that may be operative. Such mechanisms may explain observations such as complex pharmacological effect versus time profiles (96), dependency of drug effects on the rate of administration (97), and tolerance development upon chronic treatment (98).

In recent years, important progress has been made in the modeling of physiological counter-regulatory mechanisms based on the seminal work by Ekblad & Licko (99). The most well-known example of the application of dynamical systems analysis in mechanism-based PK-PD modeling concerns the modeling of the effects of organic nitrates in experimental heart failure by Bauer et al. (98). Meanwhile, this type of counter-regulatory effect model has been successfully applied to describe tolerance and rebound to the effects of alfentanil and omeprazole (100–102). A dynamical systems model has also been proposed to account for the complex hemodynamic effects of arterial vasodilators, where the pharmacodynamics has been shown to be critically dependent on the rate of administration (97, 103).

Application to 5-HT1A serotonin receptor agonists. The most recent development in the incorporation of dynamical systems analysis in PK-PD modeling has been the conceptualization of a model to describe oscillatory behavior in pharmacological systems, and more specifically in pharmacodynamics. This particular model was designed to describe the complex effect versus time profiles of the hypothermic

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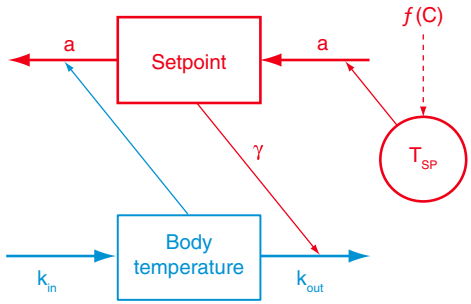

Figure 13

Full model to describe 5-HT_{1A}-receptor-mediated hypothermia. The model is based on the concept of an indirect response model and takes into account rate constants associated with the warming (k_{in}) and the cooling (k_{ou}) of the body. The indirect physiological response model is combined with a thermostat-like regulation of body temperature in which the body temperature (T) is compared with a fixed reference or set point temperature (T_{SP}) at rate a, generating a set point signal X. The extent to which the set point value decreases is a function of the drug concentration $f(C)$, which decreases X by the amplification factor γ. Reproduced from Zuideveld et al. (93).

response following the administration of 5-HT_{1A} receptor agonists to rats (104, 105). To characterize 5-HT_{1A}-agonist-induced hypothermia in a mechanistic manner, a mathematical model has been proposed that describes the hypothermic effect based on the concept of a set point and a general physiological response model (89, 96, 105–107). This model is schematically shown in **Figure 13**. In the general physiological response part of the model (Equation 21), the change in temperature (T) is described as an indirect response to either the inhibition of the production of body heat or the stimulation of its loss. In the model, k_{in} represents the zero-order fractional turnover rate constant associated with the warming of the body, and k_{out} represents the first-order rate constant associated with the cooling of the body. The thermostat-like regulation of body temperature is implemented as a continuous process in which the body temperature is compared with a reference or set point temperature (T_{SP}). It is well established that 5-HT_{1A} agonists elicit hypothermia by decreasing the value of the set point temperature T_{SP}, and hence T_{SP} depends on the drug concentration C: $T_{SP} = T_{SP}(C)$. It is assumed that T_{SP} is controlled by the drug concentration C through Equation 28:

$$T_{SP} = T_0\,[1 - f\,(C)]\,, \qquad 28.$$

where T_0 is the set point value in the absence of any drug, $T_0 = T_{SP}(0)$, and $f(C)$ is a function describing the nonlinear relationship between the drug concentration and the target activation (i.e., Equation 2). Combining the indirect physiological response model with the thermostat-like regulation then yields

$$\begin{cases} \dfrac{dT}{dt} = k_{in} - k_{out} \cdot T \cdot X^{-\gamma} \\ \dfrac{dX}{dt} = a(T_0 \cdot [1 - f(C)] - T) \end{cases}, \qquad 29.$$

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in which X denotes the thermostat signal. In this model, the change in X is driven by the difference between the body temperature T and the set point temperature T_{SP} on a timescale that is governed by a. Hence, when the set point value is lowered, the body temperature is perceived as too high and X is lowered. To relate this decreasing signal to the drop in body temperature, an effector function $X^{-\gamma}$ was designed in which γ determines the amplification. Raising this function to the loss term $k_{out} \cdot T$ therefore facilitates the loss of heat.

Interestingly, in Equation 29, body temperature and set point temperature are interdependent, and as a result, a feedback loop is created that can give rise to oscillatory behavior (96). This model is able to reproduce the complex effect versus time profiles, which are typically observed upon the administration of 5-HT_{1A} receptor agonists.

A population approach was utilized to quantify both the pharmacokinetics and pharmacodynamics of the 5-HT_{1A} receptor agonists (108). This enabled the successful characterization of the time course of the hypothermic effect. Moreover, it also enabled identification of the values of the various (biological system-specific) physiological parameters describing the regulation of body temperature and the drug-specific parameters characterizing the target binding and activation (83, 96, 109).

Toward a full mechanistic model of 5-HT1A serotonin receptor-mediated hypothermia: Interfacing with a receptor model. In the initial version of the model, the sigmoid-E_{max} model (Equation 2) was used to describe the concentration effect relationships of the 5-HT_{1A} receptor agonists at the receptor in terms of potency and intrinsic activity. In a subsequent step, aiming at the development of a fully mechanistic model, the OMA (Equation 9) was used instead of the sigmoid-E_{max} model (34). In this analysis, the value of the system maximum E_m was constrained to the observed maximum effect for a full agonist, R-8-OH-DPAT. Subsequently, the values of K_A and τ for the various partial agonists were estimated by directly fitting the OMA to the combined concentration-effect data. The values of K_A and τ that were obtained in this manner are shown in **Table 2** together with the corresponding estimates of affinity (K_i) and intrinsic efficacy (log agonist ratio) in a receptor binding assay.

The observed correlation between the model-derived values of pK_A and the experimentally observed values (pK_i) in an in vitro [^{3}H]-WAY-100635 binding assay was rather poor ($P > 0.05$) compared to similar in vivo–in vitro correlations observed for A_1 adenosine receptor agonists, synthetic opiates, and $GABA_A$ receptor agonists (4, 19, 37, 68). Close inspection of this correlation showed that flesinoxan deviated from the line of identity. In fact, the correlation between the pK_A and pK_i became statistically significant when flesinoxan was excluded from the analysis ($P < 0.05$). Presumably, this can be explained by complexities at the level of the brain distribution. Recently, Van der Sandt et al. (110) have shown that active transport mechanisms (i.e., P-glycoprotein) at the blood-brain barrier are important determinants of the brain distribution for flesinoxan. Thus, it appears that complexities at the level of blood-brain distribution of flesinoxan explain the observed lack of correlation between in vitro and in vivo receptor affinity estimates (17). This underscores

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Table 2 In vivo estimates of the receptor affinity (pK_A) and intrinsic efficacy ($Log\ \tau$) of 5-HT_{1A} serotonin receptor agonists for the effect on body temperature in rats obtained on the basis of a simultaneous analysis of the concentration-effect relationships on the basis of the operational model of agonism (Equation 9)

	[^{3}H]-R-OH-DPAT [^{3}H]-WAY-100635				
Drug	pK_A	$Log\ \tau$	pK_i*	pK_i	Agonist ratio**
R-8-OH-DPAT	7.35	0.62	8.36	7.35	10.13
S-8-OH-DPAT	6.68	0.0523	7.95	7.22	5.34
Flesinoxan	5.67	0.206	7.91	7.15	4.14
Buspirone	7.03	−0.0684	7.42	6.40	10.53
1-PP	5.68	−0.291	5.38	4.76	5.33
WAY-100135	7.74	−1.25	7.30	7.03	1.88
WAY-100635	8.63	n.a.	8.73	8.94	0.61

*The in vitro estimates of the receptor affinity (pK_i) were determined in the presence of [^{3}H]-R-OH-DPAT and [^{3}H]-WAY-100635.

**The ratio between the two K_i values (agonist ratio) serves as a measure of intrinsic efficacy.

the importance of modeling the biophase distribution kinetics in mechanism-based PK-PD modeling, particularly for drugs with a site of action in the CNS.

With regard to the prediction of the in vivo intrinsic activity it is notable that a significant correlation between the in vivo and the in vitro efficacy parameters (*Log* τ and *Log[agonist ratio]*) was found ($P < 0.05$). The correlation between *Log* τ and *Log[agonist ratio]* showed further that the in vivo test assay was considerably more sensitive to detect 5-HT_{1A} activity then the *agonist ratio*. For example, the significant in vivo agonist activity demonstrated for WAY-100135 was not detected in vitro. This may have important implications for the development of so-called near-silent agonists at the 5-HT_{1A} serotonin receptor. Thus, by combining the semimechanistic PK/PD model for the hypothermic effect of 5-HT_{1A} agonists with the OMA, a full mechanistic PK/PD model was obtained, which proved to be highly predictive of the in vivo intrinsic activity of ligands at this receptor.

Recently, the modeling complex homeostatic feedback mechanisms have been extended to include the modeling of long-lasting tolerance (111) and asymmetrical circadian baselines (112).

Modeling of Disease Processes and Disease Progression

The latest development in mechanism-based PK-PD modeling concerns the modeling of disease processes and disease progression. The use of disease (progression) models is particularly important for drugs that interact in a highly specific manner with a disease and hence have no directly observable effects in normal subjects. Moreover, modeling of disease progression is imperative when drug treatment is specifically intended to modify disease progression. The same applies to investigations that aim to demonstrate the absence of an adverse effect of symptomatic drug treatment on disease progression.

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The modeling of disease progression closely follows the modeling of transduction and homeostatic feedback mechanisms, as it is based on the principles of dynamical systems analysis. However, the modeling of disease progression adds a new dimension of time-variant changes in the status of the biological system to the discipline of mechanism-based PK-PD modeling. Briefly, in conventional PK-PD analyses, the status of the biological system at baseline (i.e., in the absence of drug) is considered constant. For chronic progressive disorders, however, this is not a realistic description, as biological function will deteriorate over time.

Disease system analysis. Chan & Holford (113) and Holford & Peace (114) were the first to propose disease progression models for clinical rating scales. In these models, the signs and/or symptoms of disease and their response to treatment are modeled directly, without consideration of the underlying biological system. However, a theoretical framework for mechanism-based disease progression modeling has been proposed. A pertinent feature of these models is the strict distinction between drug effects on the disease status versus the disease process (115). In this approach, disease progression is described based on a turnover model according to

$$\frac{dS}{dt} = k_{in} - k_{out} \cdot S, \qquad 30.$$

where dS/dt is the change of the measured status S of the biological system over time, which is controlled by a zero-order synthesis process (k_{in}) and a constant first-order elimination process (k_{out}). The structure of the disease progression model is schematically represented in **Figure 14**. In a healthy biological system, the values of the biological system parameters k_{in} and k_{out} are constant. In the case of chronic progressive disorders, however, homeostasis is perturbed by a time-dependent change in either the process of synthesis or elimination, resulting in an ongoing deterioration of the status of the system. Depending on the site of degeneration, two types of models can be distinguished: type I (decrease in synthesis) and type II (decrease in elimination). **Figure 14** shows the natural course of the disease progression in these disease progression models and the potential target sites for treatment. In these models, the degenerative processes affecting synthesis can be described by substituting

$$\frac{dk_{in}}{dt} = f_{dp}(k_{in}, t) \qquad 31a.$$

in Equation 30, where, the change in synthesis (k_{in}) over time is a function of disease state (f_{dp}). In a first-order process, this becomes

$$f_{dp}(k_{in}, t) = -R_{dp} \cdot k_{in}, \qquad 31b.$$

where R_{dp} is the first-order disease progression-rate constant.

Similarly, a degenerative process affecting elimination can be described as

$$\frac{dk_{out}}{dt} = f_{dp}(k_{out}, t), \qquad 31c.$$

with

$$f_{dp}(k_{out}, t) = -R_{dp} \cdot k_{out}, \qquad 31d.$$

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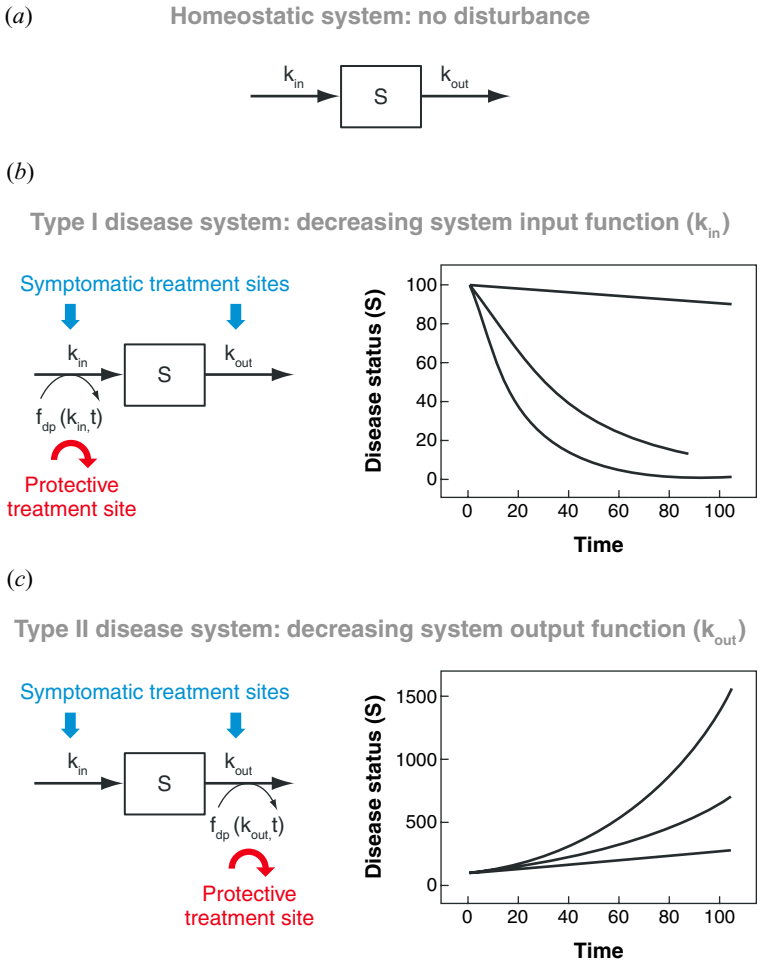
Figure 14

Models of disease progression resulting from a decline in either the synthesis or elimination process controlling the homeostatic system. For each type of disease progression model, three rates of disease progression are presented, visualizing possible progression curvatures (Type I (R_{dp}); [0.001;0.05], Type II (R_{dp}); [0.01;0.03]). Blue block arrows represent target sites for symptomatic effects. Red curved block arrows represent target sites for protective effects. (*a*) Indirect physiological response (IPR) model without disturbance in homeostasis. (*b*) Disturbance in homeostasis owing to an exponentially decreasing synthesis process (Type I). (*c*) Disturbance in homeostasis owing to an exponentially decreasing elimination process (Type II). Reproduced from Post et al. (112).



where the change in elimination (k_{out}) over time is a function of disease state (f_{dp}).

Within the context of disease system analysis (DSA), different types of drug effects can be distinguished. Briefly, drug effects can be divided into (*a*) symptomatic and (*b*) protective effects. In this context, symptomatic effects concern an improvement in the disease status without a change in the underlying process of natural disease progression (110). Symptomatic drug effects can be subdivided into disease-dependent and disease-independent effects. A disease-independent drug effect is described by incorporating an additive term to the status of a system parameter according to

$$\frac{dS}{dt} = \{k_{in}(t) + f_s(D)\} - \{k_{out}(t) + f_s(D)\} \cdot S, \qquad 32a.$$

DSA: disease system analysis

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where $f_s(D)$ is the drug effect as a function of dose or concentration. In contrast, a disease-dependent drug effect is incorporated into the model as a multiplicative term to the value of the affected system parameter according to

$$\frac{dS}{dt} = \{k_{in}(t) \cdot f_s(D)\} - \{k_{out}(t) \cdot f_s(D)\} \cdot S, \qquad 32b.$$

where the drug affect $f_s(D)$ proportionally modulates the status of the system parameter. A protective drug effect concerns the improvement of disease status resulting from modification of the disease process (113). Protective treatment effects are always incorporated on the parameter that determines the disease progression as an additive term for disease-independent modification,

$$\frac{d(k_{in}, k_{out})}{dt} = f_{dp}(k_{in}, k_{out}, t) + f_p(D), \qquad 32c.$$

or as a multiplicative term for disease-dependent modification,

$$\frac{d(k_{in}, k_{out})}{dt} = f_{dp}(k_{in}, k_{out}, t) \cdot f_p(D), \qquad 32d.$$

in which $f_p(D)$ is the parameter characterizing the protective drug effect on disease progression (Equations 31a or 31c) as a function of exposure in terms of dose or concentration.

Using a series of simulation experiments, it has been shown that these mechanism-based disease progression models display distinctly different signature profiles. These models therefore constitute a scientific basis for the distinction between symptomatic versus protective drug effects, as well as the identification of exposure-response relationships (115).

Application to type-2 diabetes mellitus. The concept of disease system analysis has been successfully applied in an analysis of the effects of pioglitazone, metformin, and glyclazide on the disease processes underlying type 2 diabetes mellitus (116). The specific aim was to describe and quantify the effects of drug treatment on the time course of the progressive loss of β cell function and insulin sensitivity in treatment-naïve type 2 diabetes mellitus patients.

The mechanism-based model was based on the analysis of the homeostatic feedback relationship between fasting serum insulin (FSI) and fasting plasma glucose (FPG) concentrations and the feed-forward relationship between FPG and glycosylated hemoglobin A_{1c} (HbA_{1c}) in the following system of interrelated differential equations:

$$\frac{d\mathrm{FSI}}{dt} = EF_B \cdot B \cdot (\mathrm{FPG} - 3.5) \cdot k_{in_{\mathrm{FSI}}} - \mathrm{FSI} \cdot k_{out_{\mathrm{FSI}}} \qquad 33a.$$

$$\frac{d\mathrm{FPG}}{dt} = \frac{k_{in_{\mathrm{FPG}}}}{EF_S \cdot S \cdot \mathrm{FSI}} - \mathrm{FPG} \cdot k_{out_{\mathrm{FPG}}} \qquad 33b.$$

$$\frac{d\mathrm{HbA_{1c}}}{dt} = \mathrm{FPG} \cdot k_{in_{\mathrm{HbA1c}}} - \mathrm{HbA_{1c}} \cdot k_{out_{\mathrm{HbA1c0}}} \qquad 33c.$$

Here, the various k_{in} parameters are the influx rates and the k_{out} parameters are the efflux rate constants for FSI, FPG, and HbA_{1c} turn-over, respectively. At time t,

the rate of FSI production is proportional to the FPG concentration, taking the empirically determined threshold of 3.5 mmol L^{-1} for FPG-stimulated FSI production (117) into account, while the rate of FPG production is inversely proportional to the FSI concentration. At the same time, the production rate for HbA_{1c} is proportional to the FPG concentration. With a typical rate of increase in HbA_{1c} on the order of 0.2% over a period of one year (118, 119), the fraction of hemoglobin molecules involved in this process is so small that hemoglobin was not considered a limiting factor. The coefficient *B* in Equation 33a represents the fraction of remaining β-cell function relative to normal functionality in healthy persons, and the coefficient *S* in Equation 33b represents the fraction of remaining hepatic insulin-sensitivity relative to normal sensitivity in healthy persons. That is, *B* and *S* are system-specific factors that represent disease status at time *t* and range between 1 (full, normal functionality) and zero (complete loss of functionality). The chronic loss of both β-cell function and insulin sensitivity was modeled by letting the coefficients *B* and *S* decline as asymptotic functions of time that go from 1 to zero as *t* goes from minus infinity to plus infinity. The coefficients EF_B and EF_S in Equations 33a and 33b are treatment-specific factors that, attaining values of 1 (in untreated subjects) or greater, represent the effects of different pharmacological agents at their specific site of action. Hence, values for EF_B greater than 1 represent the stimulatory effect of insulin secretogogues, such as gliclazide on the β-cells, and values of *B* smaller than 1 represent counter-acting loss of β-cell function. The parameter EF_S in Equation 33b counteracts loss of hepatic insulin sensitivity reflected in values of *S* between zero and 1, thus representing the suppressing effect on hepatic glucose production of insulin-sensitizers, such as pioglitazone and, purportedly, metformin.

This model allowed the identification of the long-term effects of different treatments on loss of β cell function and insulin sensitivity in a population of 2408 treatment-naïve type-2 diabetes mellitus patients. This model constitutes a promising conceptual advance in the study of drug effects on type 2 diabetes mellitus disease progression.

SUMMARY POINTS

1. Mechanism-based PK-PD models contain specific expressions to characterize in a quantitative manner processes on the causal path between drug administration and response. These processes are target distribution, target activation, pharmacodynamic interactions, transduction, homeostatic feedback, and disease processes. Mechanism-based PK-PD models have much-improved properties for extrapolation and prediction and constitute a scientific basis for integration of the drug discovery/development process
2. Mechanism-based PK-PD models commonly use drug concentrations in plasma as measures of internal exposure. Alternatively, effect-compartment models are used to predict target exposure, assuming passive diffusion as the mechanism for target site distribution. Particularly for drugs with intracellular targets and for drugs that act in tissues protected by specific barriers

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(e.g., the brain), target site distribution can be a factor complicating PK-PD modeling. It is proposed that physiologically-based PK modeling concepts be applied to characterize and predict target-site distribution kinetics in these situations.

3. The Hill equation, or one of its simplifications, is widely used to describe in vivo drug concentration-effect relationships. However, the PD parameters characterizing the potency (i.e., EC_{50}) and intrinsic activity (α) are mixed parameters, of which the values depend on the properties of both the drug and the biological system. This makes the Hill equation the model of limited value for the prediction of in vivo drug concentration-effect relationships.
4. Receptor theory makes a strict distinction between drug-specific and biological system-specific properties as determinants of drug concentration-effect relationships. Receptor theory constitutes, therefore, a scientific basis for the prediction of in vivo drug concentration-effect relationships. Meanwhile, the use of concepts from receptor theory for the prediction of in vivo drug concentration-effect relationships in mechanism-based PK-PD modeling is well established. Both semiparametric and full-parametric approaches to the incorporation of receptor theory have been proposed. The semiparametric approaches are particularly useful for exploratory analysis, aiming at the identification of the shape and location of the transducer function. This then enables the design of a full-parametric model with a specific expression to describe the transducer function.
5. The OMA is a FPRM that features a hyperbolic transducer function and has been successfully applied to characterize the PK-PD correlations of A_1 adenosine receptor agonists, μ opioid receptor agonists, and 5-HT_{1A} serotonin receptor agonists. For $GABA_A$ receptor agonists, a full-parametric PK-PD model featuring a hyperbolic transducer function has been established.
6. Receptor models have been successfully used for the prediction of in vivo concentration-effect relationships of a wide array of drugs, including A_1 adenosine receptor agonists, μ-opioid receptor agonists, 5-HT_{1A} receptor agonists, $GABA_A$ receptor agonists, and drug-induced QT-interval prolongation. Successful applications include in vitro to in vivo extrapolation, animal to human extrapolation, and prediction of interindividual variability in pharmacodynamics.
7. Pharmacodynamic interactions are, in many instances, an important determinant of the time course of drug effect. In conceptual terms, modeling of pharmacodynamic interactions aims at the prediction of the three-dimensional response surface of the concentrations of the two interacting drugs and the intensity of the effect.

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8. Receptor models (i.e., the OMA) constitute a scientific basis for the modeling of pharmacodynamic drug interactions. Two types of pharmacodynamic interaction models must be distinguished: (*a*) single-pathway models (for interactions at the level of the target binding) and (*b*) dual-pathway models (for interactions at the level of transduction). In single-pathway models, interactions can lead to changes in the potency (i.e., EC_{50}) but never in the intrinsic activity (i.e., α). In contrast, in dual-pathway models, interactions may lead to changes in both potency and/or intrinsic activity. Pharmacodynamic interactions have the tendency to be highly dimensional (i.e., synergistic at certain concentration ranges, while antagonistic at others).

9. With regard to the single-pathway interaction models, two subtypes must be distinguished: competition and allosterism. Both types of interaction have in common that the interaction is reflected in an apparent change in the equilibrium dissociation constant *K*. Furthermore, synergism or antagonism is observed only in very specific concentration ranges of the two interacting drugs. Modeling of competitive drug interactions is well established. In contrast, there is only limited experience with the modeling of allosteric interactions.

10. In the dual-pathway interaction model, the maximum achievable synergy is determined by the point at which the two interacting transduction pathways converge and the level of preamplification. Here, the degree of synergism is reflected in the value of the efficacy parameter τ. Again, there is limited experience with the modeling dual-pathway pharmacodynamic interactions.

11. Transduction can be an important determinant of the time course of drug effect in vivo. In mechanism-based PK-PD modeling, transduction is defined as the cascade of processes that govern the time course of the pharmacological response in vivo following drug-induced target activation. There are large differences in the rates at which transduction processes occur in vivo. When transduction is fast (i.e., operating at rate constants in the range of milliseconds to seconds) transduction is best described on the basis of a time-independent transducer function, which determines the shape and location of the in vivo concentration-effect relationship. When transduction is slow, basic turnover models (i.e., indirect physiological response models) can be used to describe delays between drug concentrations in plasma and the effect. For corticosteroids, a mechanism-based transduction model for the gene-mediated effects has been proposed that is based on a characterization of various intermediary steps in the transduction.

12. The time course of the pharmacological response is often influenced by in vivo homeostatic feedback mechanisms. This may explain observations such as complex pharmacological effect versus time profiles, dependency of

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drug effects on the rate of administration, and tolerance development upon chronic treatment.

13. Through the incorporation of concepts from dynamical systems analysis, a novel class of mechanism-based homeostatic feedback models has been proposed. These models have been successfully applied to describe complex effect versus time profiles of drugs such as organic nitrates, fentanyl, omeprazole, and arterial vasodilators. The most recent development in the modeling of homeostatic feedback mechanisms has been the development of a set point model to describe oscillatory behavior of the hypothermic effects of 5-HT_{1A} serotonin receptor agonists.

14. The latest development in mechanism-based PK-PD modeling concerns the modeling of disease processes and disease progression. The use of disease (progression) models is particularly important for drugs that interact in a highly specific manner with a disease and hence have no directly observable effects in normal subjects. Moreover, modeling of disease progression is imperative when drug treatment is specifically intended to modify disease progression or in investigations with the objective to demonstrate the absence of an adverse effect on disease progression of symptomatic treatment.

15. Recently, the concept of disease system analysis has been introduced in mechanism-based PK-PD modeling. In disease system analysis, disease progression is described on the basis of turnover models. A pertinent feature of these models is the strict distinction between drug effects on the disease status versus the disease process. Moreover, a strict distinction is made between symptomatic and protective (i.e., disease modifying) drug effects. Computer simulation has shown that different drug effects yield distinctly different signature profiles of the disease status as a function of time. Disease system analysis has been successfully applied to the modeling of the effects of glyclazide, metformin, and pioglitazone on progression of type-2 diabetes mellitus.

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