Intermittent Adaptation

A Theory of Drug Tolerance, Dependence and Addiction

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Abstract

A mathematical model of drug tolerance and its underlying theory is presented. The model is essentially more complex than the generally used model of homeostasis, which is demonstrated to fail in describing tolerance development to repeated drug administrations. The model assumes the development of tolerance to a repeatedly administered drug to be the result of a regulated adaptive process. The oral detection and analysis of endogenous substances is proposed to be the primary stimulus for the mechanism of drug tolerance. Anticipation and environmental cues are in the model considered secondary stimuli, becoming primary only in dependence and addiction or when the drug administration bypasses the natural – oral – route, as is the case when drugs are administered intravenously. The model considers adaptation to the effect of a drug and adaptation to the interval between drug taking autonomous tolerance processes. Simulations with the mathematical model demonstrate the model's behaviour to be consistent with important characteristics of the development of tolerance to repeatedly administered drugs: the gradual decrease in drug effect when tolerance develops, the high sensitivity to small changes in drug dose, the rebound phenomenon and the large reactions following withdrawal in dependence. Simulations of different ways withdrawal can be accomplished, demonstrates the practical applicability of the model.

Introduction

A living organism is an immensely complex system of interconnected processes. Most of these processes are regulated while they are at the same time dependent on other processes. It is difficult to imagine how a living organism is able to achieve the incomprehensibly complicated task of maintaining a balanced functioning in a continually changing environment. In 1878 Bernard wrote: *"It is the fixity of the 'milieu interieur' which is the condition of free and independent life. All the vital mechanisms however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment*" (Bernard 1878 [7], cited by Cannon 1929 [10]). Cannon translated Bernard's observation into the model of homeostasis [10]. Fundamental in Cannon's theory is the presumption that physiological processes are regulated and that their functioning is in a "steady state": their conditions are stable and held constant through feedback. Homeostasis has been the basis of important theories like Systems Theory of Bertalanffi and Cybernetics of Norbert Wiener, which proposed that physiological processes could be simulated by electronic feedback models [8,9,67]. In the mathematical models of drug tolerance developed on basis of these theories, the effects of drugs are assumed to be counteracted by a feedback mechanism which keeps the processes involved functioning at a preset level, causing tolerance to develop [15,17,21,23,29,39,49,50,52].

This paper demonstrates that the model of homeostasis is not adequate to describe the effect of repeated disturbances on the functioning of living organisms and it argues that, rather than maintaining a steady state as Cannon proposed, living organisms are constantly striving for the best obtainable compromise in their functioning in constantly changing circumstances. In this search for an optimum, the tolerance mechanism plays an important role. When the organism is repeatedly disturbed by a particular drug, it slowly learns to reduce the effect of the drug by

Bibliography
DOI 10.1055/s-0029-1202848
Pharmacopsychiatry 2009;
42 (Suppl. 1): S1–S15

ISSN 0176-3679

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opposing the disturbance at the moment it occurs. In addition to this dynamic action, a lasting shift in functioning develops. In the mathematical model these two activities are modelled with a fast and a slow regulator respectively [32, 33, 36, 37], illustrating the twofold effect of drugs: a drug not only causes a direct, relatively short lasting effect, but it also fundamentally changes the level of functioning of the processes involved.

● The slow build-up of tolerance during repeated drug administrations, combined with a triggered response to those administrations, requires a complex adaptive regulation mechanism which, although incorporating feedback, is essentially different from homeostasis. The model presented in this paper is a general model of drug tolerance and drug dependence where "general" indicates that the model is based on principles which are thought to be more or less applicable to all processes of tolerance development. The model assumes the development of tolerance to a drug to be a process of adaptation to the disturbing effects of the drug: the body slowly learns to counteract these effects [32, 33, 36]. It also assumes that when processes in living organisms are disturbed, they adapt in a way that is fundamentally the same for all processes. Knowledge about adaptation in one process, therefore, teaches us about adaptation in other processes. The latter hypothesis is defended by many writers [24, 27, 39, 50, 61]. It allows us to use our knowledge of the body's adaptation to changing environmental temperature equally well as, for instance, knowledge about adaptation to colour stimuli [50] to solve problems in modelling the organism's adaptation to drugs.

Homeostasis

Homeostasis has made an invaluable contribution to our understanding of how physiological processes function by introducing the concept of the regulated physiological process: the presumption that most processes in a living organism are, one way or another, regulated. Regulation implies that the behaviour of a certain process in the organism ultimately is determined by an aim set by the organism itself, which in a highly simplified process is the process set point or process reference. In a simple regulated process, the output of the process – i.e. what is produced or obtained – is observed by a sensor and compared with a desired value, the process reference. When the output is not at the desired level, the process parameters are changed until the output is – within certain margins of accuracy – equal to the process reference. In this way the process is maintained at the desired level through feedback. There are many forms of feedback. In general, the feedback is negative. Negative feedback of a process in its most simple form means that the deviation of the process output from the desired value – the regulation error – is subtracted from (*negatively* added to) the process input. The effect of negative feedback is that the regulation error is reduced, the remaining error depending on the amplification of the feedback loop. When delay and stability problems can be managed, negative feedback can be very effective in counteracting the effects of disturbances to the process, making the process output less responsive to changes in its environment.

● Homeostasis made clear that physiological processes are regulated, and that regulation implies feedback. This has resulted in numerous models using negative feedback systems as a description of their behaviour. However, the incorporation of negative feedback in itself does not suffice to obtain a model describing the behaviour of adaptive physiological processes like the development of tolerance to drugs, as will be demonstrated with the response of these models to regularly occurring disturbances. The following discussion elucidates the general behaviour of negative feedback systems.

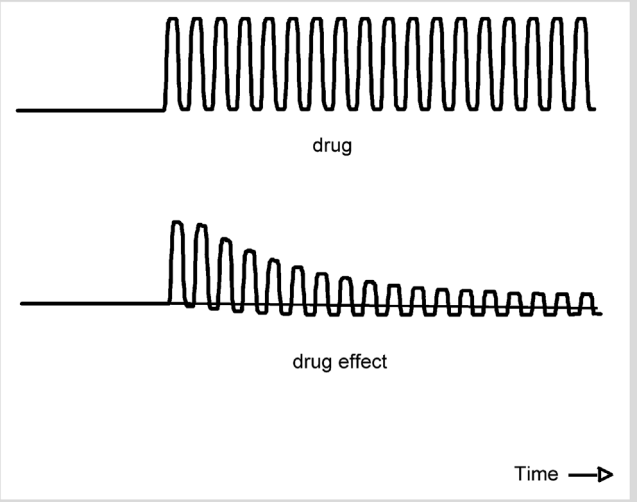

Fig. 1 Drawing of the development of tolerance to the repeated administration of a drug.

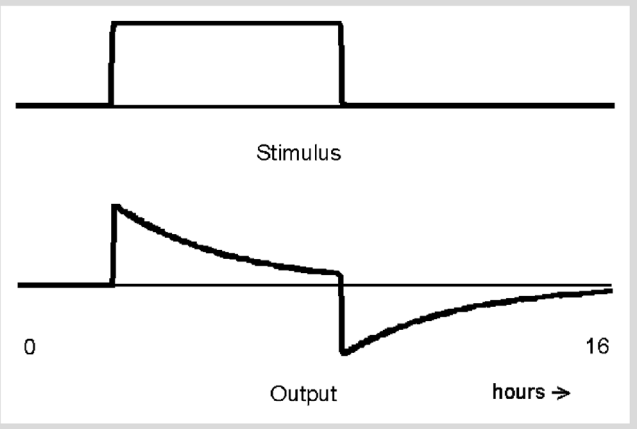

Fig. 2 Computer simulation of the effect of a single disturbance on the process output of a simple linear negative feedback circuit.

● The drawing in **Fig. 1** illustrates the effect of tolerance development on the drug effect when a drug is administered repeatedly. The gradual build-up of tolerance reflects in a gradual decrease in the drug effect. It is accompanied by reactions during the interval between two drug administrations (the signal going below the base line), representing the rebound phenomenon.

Fig. 2 shows a computer simulation of the effect of a disturbance on the output of a simple linear, first order negative feedback circuit. The length of the stimulus and the time constant τ of the circuit are set at 6 and 3 hours respectively. The vertical axes are in arbitrary units. The initially large effect of the stimulus on the output decreases over time at a speed determined by τ. This decrease more or less resembles the development of acute tolerance: tolerance to the effect of a single administration of a drug. When the stimulus ends, there is an effect in the opposite direction, which could be regarded as representing the rebound mechanism.

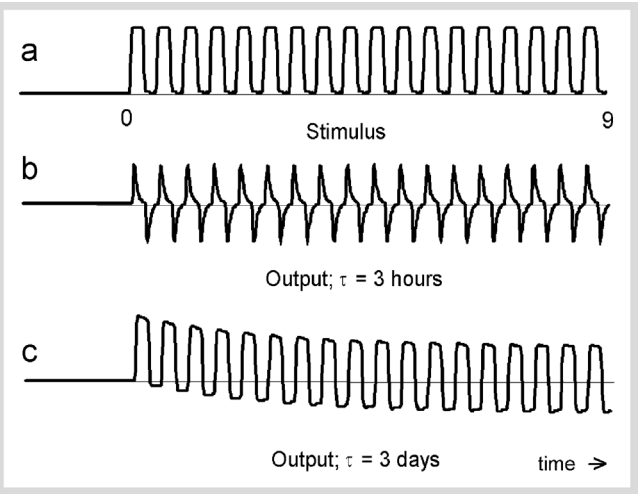

Fig. 3 Effect of a repeatedly applied stimulus on a simple feedback circuit.

If the same stimulus is applied repeatedly to this simple regulated system, the model's response does not resemble the development of tolerance shown in **Fig. 1**. This is demonstrated in the simulation shown in **Fig. 3**, where the stimulus is applied twice a day. Every time the stimulus is applied, the effect of the stimulus on the output (**Fig. 3b**) appears to be the same as shown in **Fig. 2**. This disagrees with the way in which the drug effect decreases over time as the organism develops tolerance. If the time constant of the regulation is increased from 3 h to 3 days, the sole effect of the regulation is that the average value of the signal drifts towards the base line (**Fig. 3c**). Although this example of a simple regulated process shows some qualities of tolerance development and might give an acceptable description of acute tolerance, it apparently lacks the capacity to adapt to recurring disturbances. The above example uses a simple, linear first-order negative feedback circuit. When a mathematical model combines systems to form complex, higher-order feedback circuits, they will generate a response which differs from that of **Fig. 2b**. However, the effect of repeatedly applied stimuli will always give the pattern shown in **Fig. 3**. Apparently, feedback does not suffice to describe the development of tolerance to repeatedly applied disturbances and, consequently, the model of homeostasis cannot describe drug tolerance.

Adaptation in regulated processes

The model presented in the present paper, proposes the development of drug tolerance to be an expression of the general process of adaptation to environmental disturbances. Homeostasis and adaptive regulation are often assumed to be synonymous. In reality these concepts are very different. The basis of homeostasis is that processes continue functioning at a preset level during changing environmental conditions, the "equilibrium" or "steady state" of Cannon. Adaptive processes, on the other hand, change their functioning in response to changes in their environment to continue functioning optimally, which in a changed environment can imply functioning at a different level or even in a different way [5,63]. In addition, because environmental changes in many cases affect the functioning of the entire organism, the level of functioning of individual processes may have to change significantly to allow the organism to find a new optimum for its functioning.

Adaptation and habituation, too, are often used interchangeably. In reality they are essentially different concepts too. Habituation is a multiplicative mechanism: the response to the stimulus is attenuated to reduce the effect of the stimulus. Adaptation, on the other hand, is an additive process: the disturbance is counteracted by a compensating mechanism. The applicability of additive and multiplicative mechanisms to the description of tolerance development has been discussed in a previous paper [33].

Adaptation is often considered a relatively slow, continuous learning process. Drug tolerance, however, usually manifests itself as a relatively short lasting, but recurrent and triggered process and may therefore be seen as an intermittent learning process of the organism: it learns how to deal with recurrent changes in its environment to keep functioning optimally. If a drug is administered, the organism "remembers" the effect of the drug during previous administrations and takes measures to lessen its effect this time. When full tolerance is established, the organism has learned to deal with the disturbance as effectively as possible in the given circumstances. The organism's learning process during adaptation in response to the repeated administration of a drug inevitably presumes memory over an extended period of time: memory for the properties of the particular drug, memory for the effects exerted by the drug on previous occasions and memory for the measures it has to take to oppose the effect of the drug.

- In the general process of adaptation, it is postulated that the organism remembers as separate facts changes in its functioning when these are caused by different changes in its environment.

This seems obvious: different drugs elicit different adaptation processes. However, the implications of such specificity are far-reaching as is demonstrated with a simplified example of how the body's thermogenesis reacts to temperature changes.

When one leaves a warm room to stay in the cold outside for a few minutes, the warm room feels normal on returning. After a day in the cold outside, the warm room feels hot on entering. Apparently, an increased adaptation to the cold necessitates an increase of adaptation to the warm room. This adaptation to the warm room could be interpreted as the transition phase back to the normal situation. However, when the length of the disturbance is increased, the concept of "normal situation" becomes ambiguous. For somebody who has lived rough on the street over a prolonged period, the cold outside has become the normal situation and entering a warm room a disturbance: there has been a shift in the normal situation from the high temperature in the room to the low temperature outside. This shift is only comprehensible when it is accepted that for an adaptive process there is no normal situation: every change in environmental condition results in a new situation to which the process adapts by seeking a new level of functioning (see also: Peper et al., 1987 [32]).

When this analysis of how the organism adapts to temperature changes is translated to the administration of drugs, it implies that for the organism the beginning of the drug action and its ending constitute different disturbances because they are the beginning of different (opposite) events: the drug effect and the interval between drug taking. In existing models of drug tolerance, the interval between drug taking is assumed to be the base line, the situation identical to the undisturbed situation before the first dose. In the model proposed, the organism's adaptation

to the effect of a drug and its adaptation to the interval between drug taking are regarded autonomous processes.

The detection of exogenous substances

The effects of drugs are for an important part determined by their disturbing effect on the information transfer within the organism's regulated processes. Consider a process which sends information about its level of functioning to the regulator of that process (this is detailed below in ◦ **Fig. 4**). The messenger used to transfer this information – a number of molecules of a certain substance – is detected by a sensor – receptors sensitive to that particular substance – which relays the information to the process regulator. If a drug interferes with the transport of this messenger, for instance by binding to the receptors, changing their affinity for the messenger, or simply by adding to the amount of the messenger substance, the information from the sensor will change and the effect will be a change in the output level of the process.

● The disturbing effect of a drug on the regulation of a physiological process decreases when tolerance develops: the process regulator learns to counteract the effect of the drug on the information transfer. This antagonistic action of the regulator is operative mainly during the time the drug is present. This can be deduced from the fact that when a drug to which the organism is tolerant is given infrequently, the effect during the intervals is very small (this subject is treated extensively in Peper et al., 1988 [33]). When tolerance to a drug is a mechanism which is active only during the time the drug is present, an important conclusion can be drawn: when a process is disturbed by a drug, its regulator must at that moment "know" that the change in the output of the sensor is due to the presence of the drug and not to a normal fluctuation in the process it regulates. From the output signal of the sensor alone the regulator will not be able to determine whether the receptors are bound to an endogenous or an exogenous substance or whether a drug has changed the sensitivity of the sensor to the messenger substance. It can distinguish between the various ways in which a drug may interfere only by acquiring additional information about the situation. If, for instance, the exogenous substance differs from substances usually found at the location of the sensor, the regulator might be able to acquire this information from the receptor site. If, however, the exogenous substance is of the same chemical composition as an endogenous messenger substance, this information cannot be acquired other than from the fact that the organism has detected the substance somewhere in the organism where it is normally not present or from oral or environmental information about the substance entering the body. The organism has several ways to detect a drug. If administered orally, there are gustatory and olfactory mechanisms to record the presence of a drug and its chemical characteristics. At a later stage, when the drug is within the organism or if the drug is administered intravenously, there are other ways in which a process regulator may obtain information about its presence and characteristics: from chemical sensors which are sensitive to the drug, from information originating from processes in the organism which themselves are disturbed by the drug or from environmental cues which it has learned to associate with the presence of the drug. However, to enable a process regulation to take measures to reduce the effect of an exogenous substance upon the process, information about the presence of the drug should reach the regulator at an early stage, before the drug actually reaches the receptor site. This implies that the regulator will attach greater value to oral information about the presence of the drug than to information from the surrounding tissue [18, 57]. Given, furthermore, that the natural route into the body is through the mouth, it can be assumed that the organism will regard the detection of exogenous substances in the mouth as the fundamental source of information about the presence of a drug.

The nature of the drug effect

When tolerance to a certain drug has developed, the organism apparently has enough information about the drug to reduce its disturbing effect. That information may include the chemical characteristics of the drug, the exact processes disturbed by the drug, the nature and the extent of the disturbance, the time taken by the drug to reach the receptor site, its effect on the sensor characteristics, and so on. In contrast, when a drug enters the organism for the first time, the organism may be assumed not yet to have gathered this information and it is important to examine the consequences of such a situation.

● The organism must establish the relationship between the taking of a certain – unknown – drug and subsequent disturbances in the organism. To enable the organism to relate changes in the functioning of processes to the drug, it must receive information about the drug's properties at an early stage, before the changes have taken place. Once a change has occurred, it becomes much more difficult or even impossible for the organism to determine the nature of the drug that caused the disturbance. In other words, the organism must analyse and classify a new drug before it produces an effect. However, if the organism is able to detect and analyse a drug which it has never seen before and relate the knowledge it gathers in this way to processes which are disturbed later, the question then arises why it does not readjust these processes at the moment of detection to prevent the disturbances from occurring at all. The answer to this question has several facets: If the above chain of thought is correct, it will not make much difference to the organism whether a drug is new or whether there already exists a certain degree of tolerance to the drug: every drug entering the organism will be analysed anyway. It is, moreover, quite conceivable that the organism has a built-in degree of tolerance to all (or most) substances in nature, in which case there are no "new" drugs and it is not a matter of analysis but of recognition. Every drug entering the organism is "recognised" and the organism "remembers" what the consequences for its functioning were on previous occasions when it detected that particular drug, where "previous" includes the possibility of inheritance.

● The question then remains why it takes the organism such a long time to develop tolerance to a drug when it has all the information about the drug's chemical characteristics even when it enters the body the first time. The answer to this question derives from the observation that, while it are a drug's chemical characteristics which determine which processes are disturbed, it is its quantity which determines how much those processes are disturbed and hence the extent of the measures the organism must take to reduce the drug effect. This quantity, however, cannot be determined at an early stage. The organism is, for example, unable to determine the quantity of a medication before it is dissolved completely, or whether a cup of coffee is

followed by a second or a third one. Such information becomes available only after a relatively long time, which is (or may be) too long for the processes involved to counteract the drug's disturbing effect.

It then becomes clear that when the organism has developed tolerance to a certain drug that does not merely mean that the organism knows how to cope with that particular drug, but that the organism knows how to cope with a certain *quantity* of that drug. And because the organism is not able to determine the quantity of a drug at an early stage, the tolerance level is based on the dose it expects, the dose it is accustomed to. A change in the quantity of the drug – a change in the habitual drug dose – will therefore result in a period of incomplete tolerance during which the effect of the drug on the organism differs substantially from the tolerant situation. The functioning of the organism will then remain disturbed until it has learned to cope with the new drug level and has become tolerant to the new drug dose.

Modelling tolerance development in physiological processes

The effect of a disturbance upon a regulated physiological process will now be elucidated with a simplified model. **Fig. 4** shows a model of a simple regulated physiological process and the way in which a drug may disturb its functioning. In the normal, undisturbed functioning of the process, an endogenous substance in the blood, *e*, which is a measure of the level of the substance in the bloodstream produced by the process, *E*, is detected by the sensor, receptors which have affinity with the substance in question. The binding of this substance with the receptors ultimately results in a signal from the sensor to the process regulator, S_{sens}. The magnitude of S_{sens} is a measure of the number of bound receptors and thus of the amount of the substance in the bloodstream. The process regulator compares the level of S_{sens} with the level of the process reference, R_p, and regulates the process in such a way that S_{sens} and R_p are about equal. In this way the level of the substance in the bloodstream is kept at the desired level through negative feedback. If an exogenous substance, *e′*, with which the receptors also show affinity (this may, but need not, be the same substance as the endogenous substance) is introduced into the bloodstream, the subsequent binding of this exogenous substance to the receptors will raise the level of S_{sens}. However, the negative feedback will keep S_{sens} at

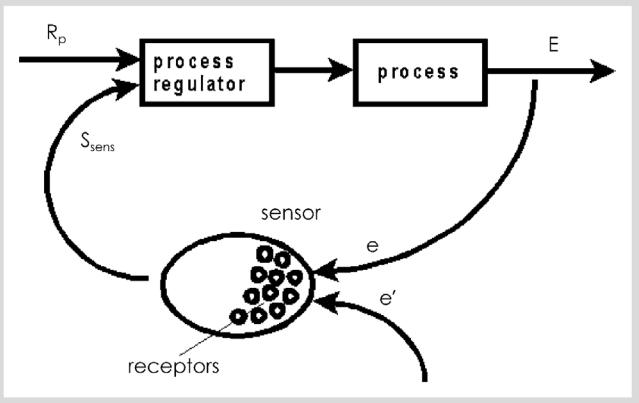

Fig. 4 Example of a simple regulated physiological process and the way in which a drug may disturb its functioning.

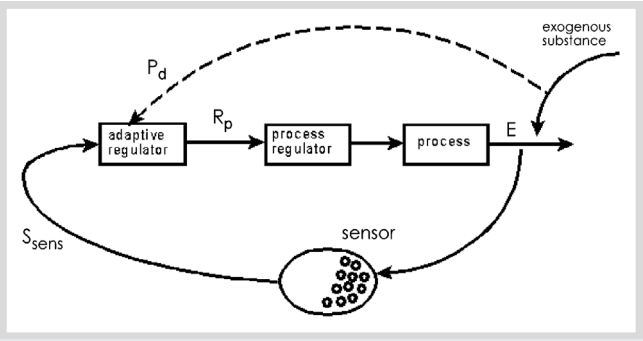

Fig. 5 Adaptive regulator added to the regulated process of **Fig. 4**.

about the level of the reference. To achieve this, the process output, *E*, and consequently the level of the messenger substance, *e*, will be reduced until the number of bound receptors is about the same as before the intervention.

- It was demonstrated above that the development of drug tolerance cannot be described adequately in terms of simple feedback regulation. The responsible mechanism in the organism is fundamentally more complex and, consequently, even a model which describes only the main characteristics of drug tolerance will be more complex. An adequate model of the tolerance process should possess the following characteristics:
  - When a drug is administered repeatedly, the process should gradually learn how to readjust its functioning to oppose the effect of the drug.
  - This adaptation process should be active mainly during the time the drug is present and should be activated upon the detection of the drug or associated cues.
  - The drug's presence and the intervals between drug administrations should be considered different disturbances and should consequently initiate their own adaptation process.
- In **Fig. 5** an "adaptive regulator" is added to the model of the regulated process in **Fig. 4** which is assumed to provide the qualities described above. During successive drug administrations it learns to change the process reference, R_p, during the presence of the exogenous substance in such a way that the effect of the disturbance is reduced. The adaptive regulator bases its action on information it receives from the sensor about the level of the regulated substance in the bloodstream, *E*, and on information about the drug administration, P_d. The dashed line indicates that P_d is information about the moment of administration of the drug only.
- A distinction has to be made between two fundamental different ways drugs may disturb physiological processes:

Case 1: a drug changes the level of a regulated substance in the organism, increasing it by its presence – when it is similar to the substance in question – or decreasing it, for instance by neutralisation.

Case 2: a drug disturbs the information transfer in the organism.

These two possible effects of drugs have essentially different implications. If a drug increases the level of an endogenous substance of the same chemical composition, the long term effect will be a decrease in the production of that substance by the organism. When the low level of insulin in the blood of a diabetic is increased via the administration of exogenous insulin, the organism develops tolerance by gradually decreasing the insufficient insulin production of the pancreas even further,

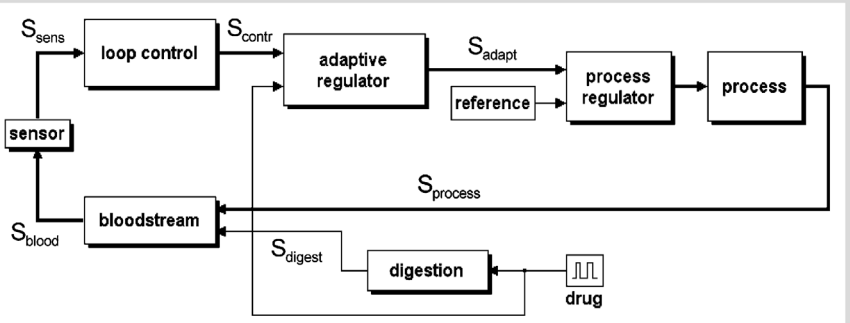

Fig. 6 Block diagram of the mathematical implementation of the regulated adaptive process in ○ **Fig. 5**.

necessitating a gradual increase in the dose of the exogenous insulin [20, 30]. If a drug interferes with the information transfer by affecting messenger-receptor interactions, or in general, the sensitivity of a sensor to an endogenous substance, the organism will learn to counteract the effect and will after a while more or less regain its normal functioning.

● The adaptive regulator treated above minimises the direct effect of a drug on the regulation. If it could suppress the drug effect completely, it would do all that is required. However, in general the effects of drugs are only partially suppressed and in most cases substantial effects remain (see Peper et al., 1987 [32]). Therefore, an important additional function of an adequate regulator is minimising the effect of the remaining disturbance. The model achieves this by combining the fast regulator, which reduces the immediate effect of the disturbance, with a slow regulator, which minimises the magnitude of the error in the long run and which anticipates frequently occurring stimuli. After tolerance has been established, this slow adaptation is responsible for the opposite effect following the disturbance: the initial rise in the output level during the stimulus is followed by a drop in the output level to below normal. The magnitude of these negative reactions in the tolerant situation depends on the interval between drug administrations. When a drug is taken infrequently the organism is not much affected during the intervals; when the frequency of administration is high, the rebound can become considerable [32]. The fast regulator is a complex system and determines to a large extent how tolerance develops. The slow regulator has a small effect by comparison but is an essential component of the adaptive regulator. Slow regulation can have very different forms. For a human moving to a hot climate it may imply a permanent increase of sweat evaporation. The thermo-regulation in animals moved to a colder climate may adapt by slowly increasing the grow of their fur. The time constant of the slow regulator may be weeks to month or even years.

Simulations with the mathematical model

A previous paper discusses the mathematical implementation of the model (see Peper 2004b [37]). The mathematical model is a nonlinear, learning feedback system, fully satisfying the principles of control theory. It accepts any form of the stimulus – the drug intake – and describes how the physiological processes involved affect the distribution of the drug through the body. The 2004b paper addresses the complex structure of the components of the regulation loop and derives the equations describing them. The control-theoretical basis of the complete regulation loop is discussed as well as the conditions for its stability.

● In the following simulations with the mathematical model, the parameters have been chosen to obtain a clear picture of the effects. Because in practice the stimulus – the drug intake – is extremely short in terms of the repetition time, its duration has been extended for clarity. As the model is a general model of tolerance development and does not describe a specific process, the vertical axes in the figures are in arbitrary units.

● ○ **Fig. 6** shows a block diagram of the mathematical implementation of the regulated adaptive process of ○ **Fig. 5** as it was discussed in a previous paper [37]. The process produces a hypothetical substance. Its regulation is disturbed by an exogenous substance of the same composition. The diagram comprises the digestive tract, the bloodstream, the process, the process regulator and an adaptive regulator. When the exogenous substance changes the level of the substance in the bloodstream the adaptive regulator correct for this disturbance by readjusting the output level of the process. The heavy arrows indicate the main route of the regulation loop. The thin arrows indicate the route of the disturbance: the transfer of the exogenous substance through the digestive tract to the bloodstream and the transfer of the information about the presence of the substance to the adaptive regulator.

● When the exogenous substance enters the body, a series of activities takes place to readjust the processes involved in order to reduce the disturbance created by the substance. ○ **Fig. 7** shows some signals from the block diagram which illustrate this mechanism. The endogenous substance is produced at a normally constant level, $L_{process}$. The resulting blood level is L_{blood}. When a similar substance is administered exogenously, the blood level will be disturbed. When the exogenous substance is administered repeatedly, the regulated process will develop tolerance to the disturbance. Trace (a) shows the exogenous substance, S_{digest}, when it enters the bloodstream. Trace (b) shows the process output: during the disturbances the output level will drop to counteract the induced rise in the level of the substance in the blood. The signal representing this change in process output level, $S_{process}$, represents the compensatory response of the process to the disturbance. In addition to these temporary changes in level, a permanent downward shift in the process output occurs. This downward shift in the functioning of the process – the curve shifting to a level substantially lower than the baseline, $L_{process}$ – represents a fundamental change in the functioning of processes involved in the drug effect. Although this shift is moderate compared to the magnitude of $S_{process}$, it may have important consequences as will be discussed presently. The two signals – S_{digest} and $S_{process}$ – are added when the

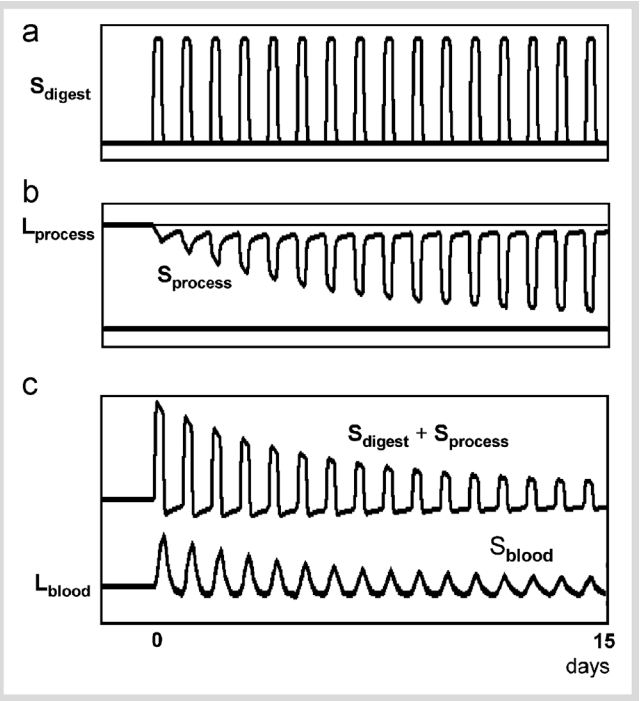

Fig. 7 Some signals from the block diagram of ▶ **Fig. 6** clarifying how tolerance develops. (**a**) The exogenous substance when it enters the bloodstream, S_{digest}. (**b**) Process output during tolerance development, $S_{process}$. (**c**) $S_{process}$ and S_{digest} added in the blood stream and the resulting blood level, S_{blood}. The level of the process output and the resulting blood level before the drug is administered are $L_{process}$ and L_{blood}.

endogenous and exogenous substances mix in the bloodstream. The resulting signal is shown in trace (c) together with the resulting blood level, S_{blood}. The disturbance of the blood level gradually decreases during subsequent administrations when the process regulator adapts to the recurrent disturbance. Recall that all parameter settings in the simulations are arbitrary, as are the axes in the figure.

The effect of changes in drug dose

Tolerance exprɜsses itself in a compensatory response which counteracts the drug action ($S_{process}$ in ▶ **Fig. 7).** Because the magnitude of the compensatory response is not based on the actual drug dose but on the accustomed dose or the anticipated dose, the compensatory response will initially not change when the actual dose is changed. The consequence is that a small change in drug dose will have a disproportionately large effect [33,35,36]. ▶ **Fig. 8** shows a computer simulation with the mathematical model of the effect of a small change in drug dose after tolerance has developed. For a given set of parameters, a 20 percent decrease in the dose results in an initial suppression of the drug effect. When the regulation adapts to the new situation, the magnitude of the drug effect settles at a level reduced proportionally by 20 percent. When the dose is increased to its original magnitude, the drug effect initially increases to about twice the normal level. These large responses to small changes in drug dose are a common feature of the drug effect and are for instance well known in the treatment of addicts. It explains why in slow withdrawal the drug dose has to be gradually tapered off

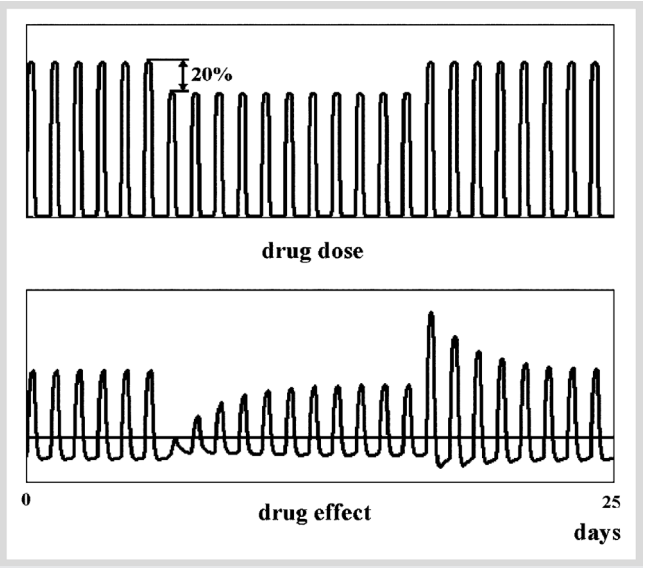

Fig. 8 Simulation of the effect of a small change in drug dose after tolerance has developed. For a given set of parameters, a 20 percent decrease in dose results in an initial suppression of the drug effect. An increase in dose back to the original value causes an initial large increase in the drug effect.

to prevent negative reactions. A decrease of 10% a week is a common value for dependent or addicted subjects as higher values might cause adverse effects [38,41,42,46]. The large positive reaction to a small increase of the drug dose shown in ▶ **Fig. 10**, is not so easy observed. This is due to the fact that, while a negative reaction can cause a reversal of the symptoms which generally is unpleasant or undesired, a positive reaction is of the same nature as the drug effect. Furthermore, many drugs know an upper limit of acting: pain medication, for instance, alleviates the pain and cannot go beyond no pain. In addition, the effect of a larger dose is often reduced by non-linear transfers in the process. These are not incorporated in the general model presented here.

- In ▶ **Fig. 8,** a 20% reduction in the dose results in an initial reduction in the drug effect to zero. This implies that at that moment the drug action and the compensatory response are of equal magnitude (S_{digest} and $S_{process}$ in ▶ **Fig. 7**). When the dose is reduced by more than 20 %, negative reactions occur as the compensatory response then initially exceeds the action of the drug. This is shown in ▶ **Fig. 9**, where the dose is reduced to 50 %.

When the dose is reduced even more, the net result will be approximately the compensatory response alone, as is shown in ▶ **Fig. 10**, where the dose is reduced to 10%. A further reduction in drug dose will give approximately the same negative effect, as the contribution of this small dose to the total drug effect becomes negligible. It should be noted that these large responses to changes in drug dose are a common feature of the drug effect and are not restricted to the dependent state.

- The negative reactions shown in ▶ **Fig. 10** are not fundamentally different from withdrawal reactions in dependence. In withdrawal, however, reactions occur because environmental cues paired to the drug taking continue to trigger the compensatory mechanism after the drug is withdrawn, as will be discussed presently. When the dose is sharply reduced, yet is still detected by the organism, it is basically not the drug which induces these

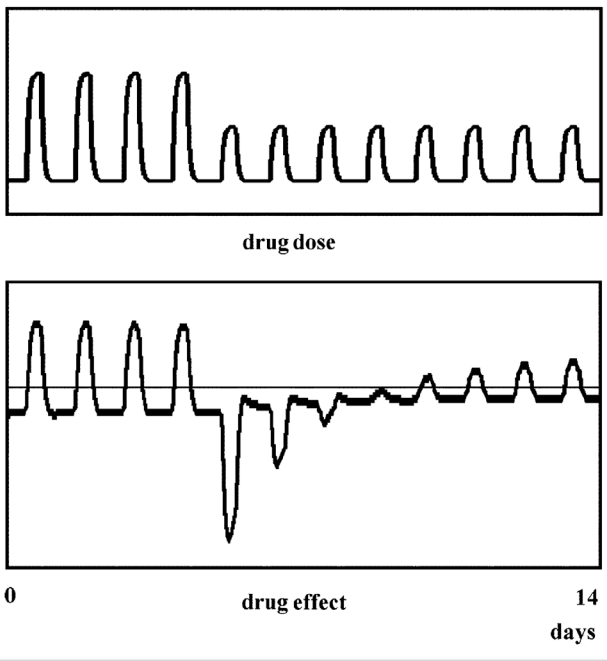

Fig. 9 Effect of reduction in drug dose to 50 %.

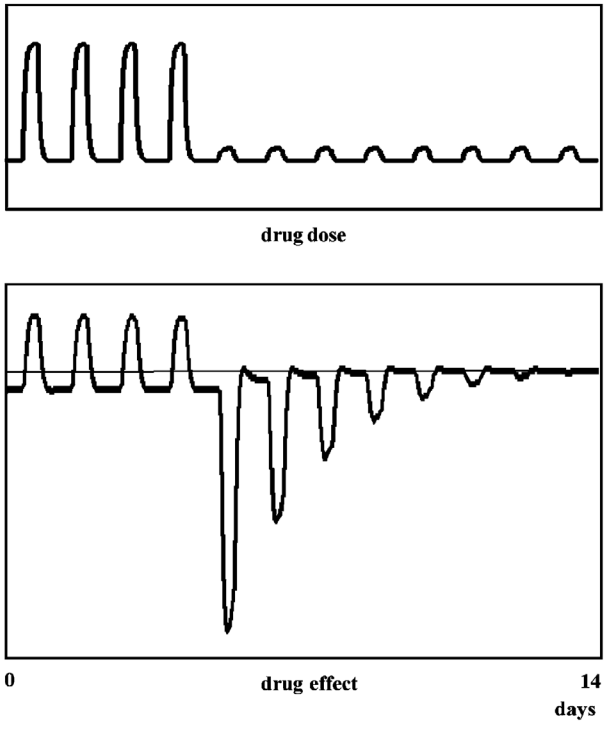

Fig. 10 Effect of reduction in drug dose to 10 %.

reactions but the orally acquired information that the drug is present.

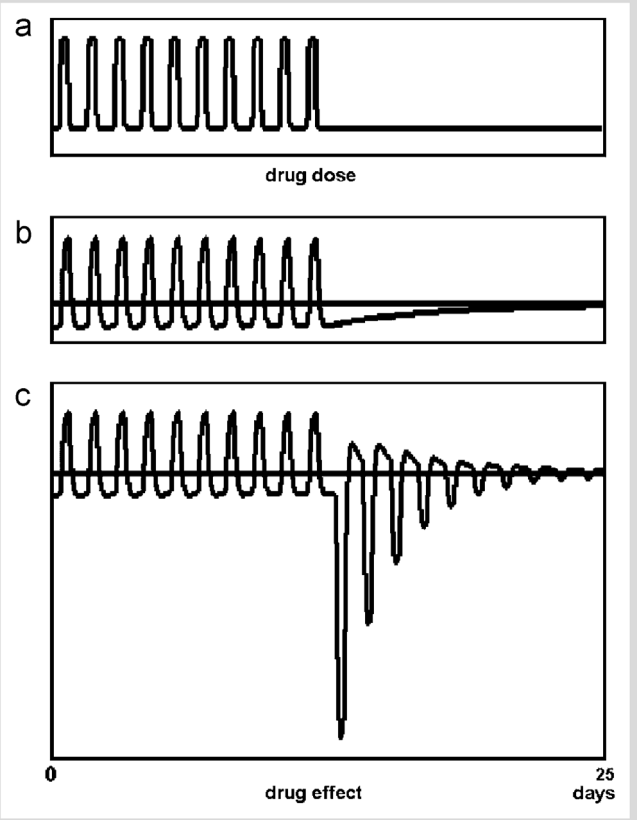

Fig. 11 Simulation of the effect of abrupt drug withdrawal in tolerant (**b**) and dependent (**c**) subjects. The drug is administered once a day.

Anticipation and dependence

When a drug is taken over a longer period, another mechanism will start to play a role: anticipation. When the organism starts to incorporate additional information about the drug's presence, for instance environmental cues or time factors, the nature of the mechanism will change. In simple tolerance the effect of not taking a drug will be that the rebound takes its course. When the organism anticipates a drug which, however, is not applied, strong negative reactions can occur.

Fig. 11 shows a simulation with the model demonstrating what happens when – after tolerance has developed – the administration of a drug is abruptly discontinued. When at withdrawal the triggered compensatory action of the adaptive mechanism also ends, the magnitude of the negative reaction following withdrawal is comparable to the regular rebound (**Fig. 11b).** **Fig. 11c** shows the effect when after withdrawal the adaptive regulator keeps responding, triggered by time factors or environmental cues associated with the administration of the drug. Now, large negative reactions occur at the moment the drug is "expected". In the model, this activation of the compensatory mechanism, independently of the drug's presence, is assumed to be the essential difference between tolerance and dependence. In reality, this difference is of course much more complex and difficult to define. However, in the model domain it provides fundamental insight into the mechanisms playing a role in dependence and addiction. The magnitude of the negative reactions after withdrawal is determined by the dose to which the subject is accustomed, the level of tolerance and the capacity of the organism to suppress disturbances to its func-

tioning. The latter depends, among other factors, on health and age [31–33, 64, 65].

● Compared with the severe reactions in the model to drug withdrawal in a dependent subject, the effect in a tolerant but non-dependent subject is moderate (**Fig. 11b).** Nevertheless, its consequences can be considerable. The negative shift in the process output signal upon drug withdrawal signifies the occurrence of antagonistic symptoms with respect to the drug effect and these are consequently in the "direction" of the disorder the drug was intended to counteract [23]. This implies that the negative reaction after the termination of drug treatment represents a worsening of the disorder in the patient. Although this effect will diminish in time as the organism adapts to the new situation, an initial worsening of the symptoms will be a strong stimulus for the patient to continue drug treatment. In the figure, the reaction declines relatively fast, but the speed of decline is determined for a large part by the slow regulator which can have a long time constant and the shift may remain a long time after a drug is withdrawn. In addition, in the case of a chronic disorder due to a shift in the reference level of a process regulation [64, 65], it is doubtful whether adaptation to zero drug level will occur at all. A permanent shift in the reference level of a process indicates a certain malfunctioning of the regulation and a negative reaction in the process output to interruption of the stimulus represents a further shift in this reference level [32]. Consequently, if a chronic disorder is due to a shift in a reference level, the extra shift after termination of a drug treatment might become permanent too and the effect of drug treatment of limited duration will then be a permanent worsening of the disorder.

Practical application of the model

The large reactions occurring in an addicted subject when a drug is withdrawn, simulated in **Fig. 11c**, are an expression of the tolerance associated with the large dose to which the subject is accustomed. The figure shows that the reactions gradually decrease in time when the body adapts to zero drug level and tolerance decreases accordingly.

Fig. 12 shows a simulation of how withdrawal can be achieved in addicted subjects without negative reactions. The dose is initially decreased by 20% which causes the drug effect to go to zero, as was shown in **Fig. 8** (The 20 % is a consequence of the parameter values used in the simulation. In reality this will be different for different drugs and in different subjects). After this step in drug dose, the dose is gradually tapered off in such a way that the drug effect is kept small, which implies that the decrease in drug action matches the decrease in tolerance. This is a very slow process as the simulation shows, much slower than is the case when the negative reactions are allowed to occur (**Fig. 11c**). The speed of withdrawal can be increased considerably when moderated negative reactions are allowed. This is depicted in **Fig. 13**, where an initial decrease in drug dose of about 50% is followed by a fast decrease in dose of the succeeding drug administrations. The reactions in this approach are considerably smaller than with abrupt withdrawal, while the decrease in drug dose is much faster than is the case in **Fig. 12**. However, moderate responses remain for a long time due to a slow decline in tolerance level. The speed of decline in tolerance can be increased when the frequency of drug administration is increased. This is demonstrated in **Fig. 14** where instead of once a day, the drug

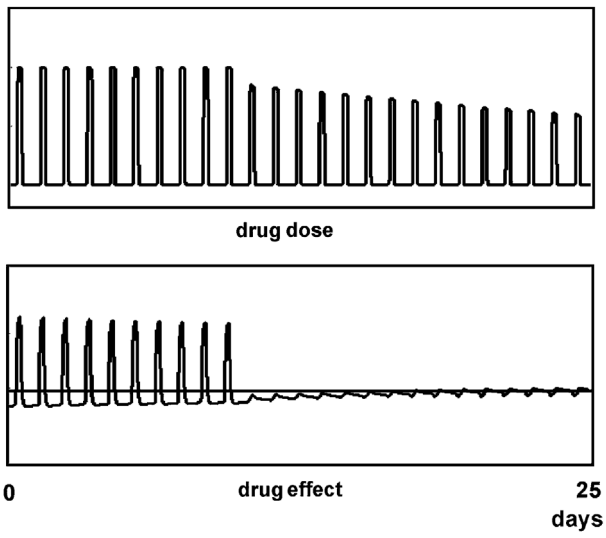

Fig. 12 Simulation of gradual drug withdrawal.

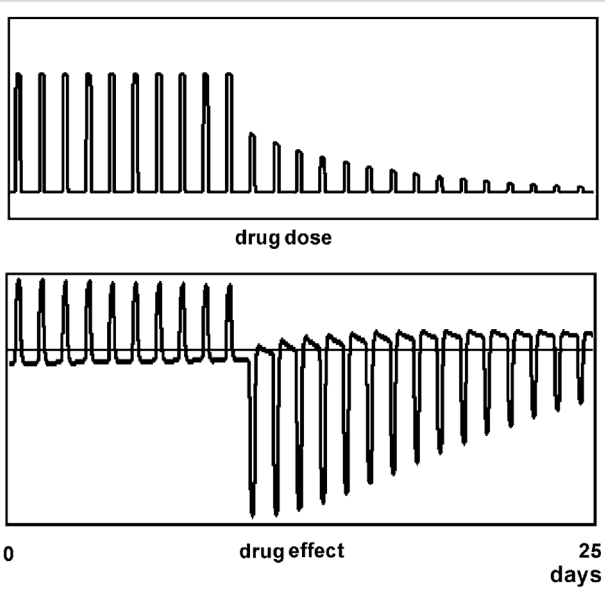

Fig. 13 Gradual drug withdrawal, allowing moderate reactions.

is administered three times a day: the negative effect now declines considerably faster than in **Fig. 13**. This method of reducing tolerance can also be uses when maximal reactions are allowed in withdrawal. If during drug withdrawal the drug dose is reduced to a low rather than zero value, the reactions become almost as large as in complete withdrawal, depicted in **Fig. 11**. When the frequency of application of the small dose is now increased, the speed of decline of the negative effect increases. This is demonstrated in **Fig. 15**, where the drug dose is lowered to 10% of the usual dose and the frequency of administration is increased from one time a day to three times a day. For comparison, abrupt drug withdrawal – as shown in **Fig. 11** – is represented with a dotted line.

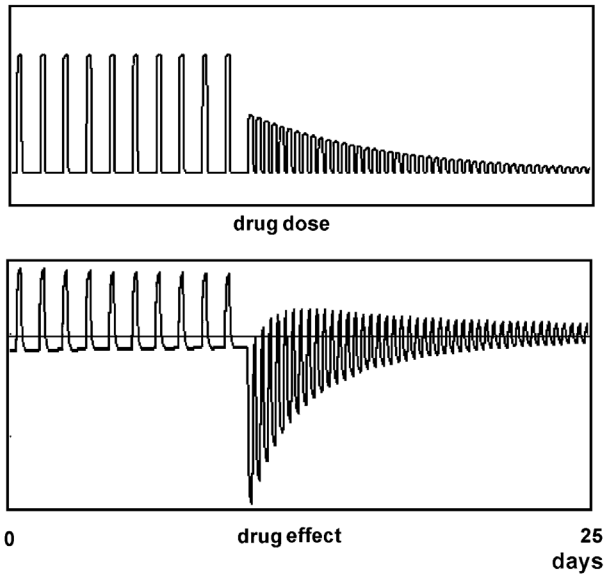

Fig. 14 Withdrawal with increased frequency of drug administration.

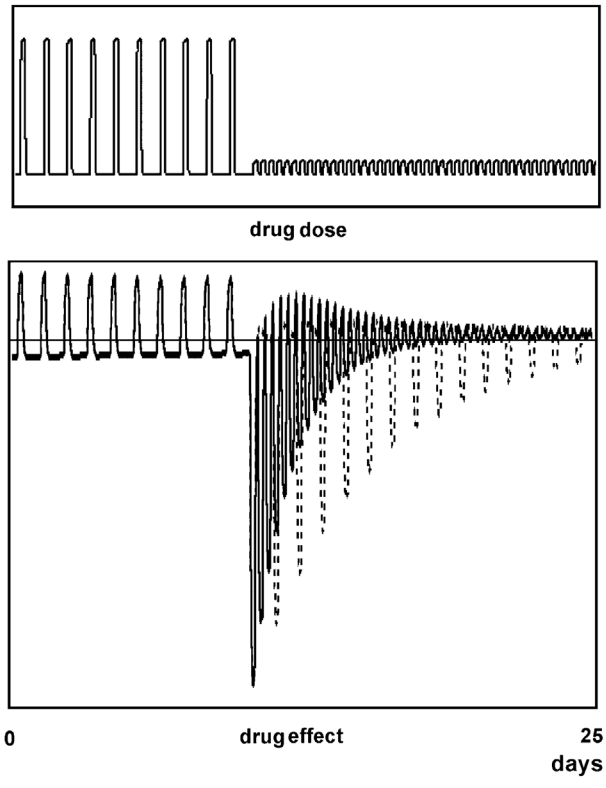

Fig. 15 Abrupt drug withdrawal using a small drug dose and an increased frequency of drug administration.

Discussion

The paper discusses the concept underlying an advanced mathematical model of drug tolerance. Simulations demonstrate the model's behaviour to be consistent with important characteristics of the development of tolerance to repeatedly administered drugs: the gradual decrease in drug effect when tolerance develops, the rebound phenomenon and the large negative reactions following withdrawal in dependence and addiction. Feed forward processes playing a role in many physiological regulations are not considered [44,63] nor the various non-linearities in the process functions present in vivo.

Fundamental in the model is the proposition that the oral detection and analysis of endogenous substances is an integral part of the mechanism of drug tolerance. The substances a living organism uses for its functioning are not unique, they can also occur in its environment and there is a high probability that exogenous substances of the same chemical composition as those used endogenously will invade the organism. If a living organism is to function using substances which are also present everywhere in its environment, it needs a way of protecting its regulations against the disturbing effect of these substances. It is the tolerance mechanism which "isolates" a living organism from the milieu it functions in.

- The analysis of substances in the mouth enables the organism to determine which processes will be disturbed and in which way that will take place: a disturbance of a process level or of the information transfer: case 1 or 2 as discussed above. The organism must make this distinction for tolerance to be able to develop. For instance, if the output level of a process is increased by a drug but the organism would assume that the resulting increase of the sensor signal was due to a disturbance of the information transfer, the organism would try to develop tolerance by decreasing the sensitivity of the sensor. The result would be a further increase of the process output, contrary to the effect of tolerance development.
- The model differs in several important ways from other models of drug tolerance. The basis of the model is that the development of tolerance to a repeatedly administered drug is the result of a regulated and adaptive process. The Opponent-Process theory of Solomon and Corbit [53–56] is not based on the assumption that tolerance development is part of a regulated process. The theory of Rescorla and Wagner [40] is not based on adaptation but on habituation, which was argued to be essentially different from adaptation. The widely supported model of homeostasis was demonstrated not to describe tolerance when a drug is administered repeatedly and it was argued that homeostasis and adaptation are different concepts. In addition, other models of drug tolerance do not make a distinction between adaptation to the effect of a drug and adaptation to the interval between drug taking, which in the proposed model are considered autonomous processes.
- An attempt to modify the model of homeostasis to account for its obvious shortcomings is the model of allostasis [2,25,26,45,58,59]. Allostasis challenges the basis of homeostasis that processes are functioning at a steady state and proposes that the goal of regulation is not constancy, but rather, 'fitness under natural selection' [58,59]. Yet, in spite of its criticism of the homeostatic model, allostasis assumes that while the set points of process regulations are controlled by the organism to meet its overall goal – efficiency – these processes themselves are regulated in a homeostatic manner. 'High-level interventions' in processes undoubtedly can play a significant role in the regulation of processes [59], but these processes also have to adapt to changes in the functioning of the numerous processes they interact with and to disturbances to their functioning, caused for instance by the action of drugs. And it is the latter in particular where homeostasis fails, as discussed above. That processes in the organism interact with other processes, up to

the highest level as allostasis asserts, is indisputable [32–34, 36], but the regulation of processes at any level is necessarily adaptive, from cell level up [34].

The assumption that living organisms function on the basis of efficiency is controversial. This premise is based on the concept of symmorphosis, which postulates that organs are 'designed by nature' to obtain an optimal match of their capacities [60]. The concept of symmorphosis is however highly disputed [3, 4, 6, 12–14, 16, 19, 43]. Allostasis has substituted the goal of homeostasis – a steady state – for optimal efficiency. But neither model can explain the build-up of tolerance during repeatedly administered drugs. Allostasis is predominantly a qualitative model (Ahmed and Koob [2] set out a quantitative model which controls the intravenous administration of cocaine in rats). How the interaction of the different processes in the control hierarchy should be modelled mathematically to meet the goal of efficiency and allow for tolerance development is not made clear and has never been tested quantitatively.

- The proposed theory also differs fundamentally from the theory of Siegel [47–51]. Siegel, like Pavlov, assumes the tolerance mechanism to be triggered by environmental cues which the organism has learned to associate with the drug effect. In Siegel's theory, the drug effect precedes the association with environmental cues while these are thought to be essential for tolerance development.

As is extensively discussed above, the model assumes the adaptive mechanism to be triggered by the oral detection of the drug. The oral analysis of the drug determines the association with the involved processes. This association precedes the drug effect. Anticipation and environmental cues are in the model considered secondary stimuli, becoming primary only in dependence and addiction or when the drug application bypasses the natural – oral – route, as is the case when drugs are applied intravenously.

The addition to the model of a mathematical implementation of the theory also constitutes an essential difference with most other theories of drug tolerance. The mathematical model verifies the proposed theory and provides a basis for the implementation of mathematical models of specific physiological processes. In addition, it establishes a relation between the drug dose at any moment, and the resulting drug effect and relates the magnitude of the reactions following withdrawal to the rate of tolerance and other parameters involved in the tolerance process. In this way, and unlike other theories, the model can predict many characteristics of the tolerance process in vivo.

Model behaviour and the process in vivo

Much confusion has arisen from the attempt to use the model of homeostasis to explain two major phenomena in drug tolerance: 1) the relationship between drug dose and drug effect and 2) the relationship between drug administration and environmental cues. These phenomena have a natural place in the model presented here, while the behaviour of the model clarifies some of their implications:

1. The relationship between drug dose and drug effect

As discussed above, drug tolerance is not just tolerance to a drug but tolerance to a certain level of a drug. The consequence is that even small changes in drug dose may generate large reactions as was shown in the ▶ **Fig. 8,9**. Changes in the drug effect must, therefore, be interpreted with caution as they may be caused by small changes in the drug dose or in the subject's estimation of the dose.

- The magnitude of the reaction to a change in drug dose depends on parameters in the disturbed regulations such as health, age and personal peculiarities of the subject, as was discussed above. In the model domain, the open loop gain of the regulation loop determines this effect. In the example of ▶ **Fig. 8**, the open loop gain is set at 4. This would be a very low figure for a technical feedback system, but is a common value for physiological regulations. The open loop gain also determines the degree in which the drug effect is reduced after tolerance has been established and the magnitude of the reactions after withdrawal, which indicates a link between the reduction of the drug effect and the magnitude of the reactions after withdrawal or changes in the drug dose. The organism apparently has to make a trade-off between a beneficial and an undesirable effect of the regulation, which may partly explain why the reduction of the drug effect when tolerance has developed tends to be relatively low. Another reason why there is a limited reduction in the drug effect in the tolerant situation may be that the organism can not estimate the exact drug dose at the moment of administration and therefore has to be cautious with opposing the effect of the drug. If the organism nevertheless overestimates the dose of the administered drug, its drug-opposing action may outweigh the drug effect itself, resulting in a paradoxical drug effect: an effect with characteristics opposite to the normal drug effect.

2. The relationship between drug administration and environmental cues

In discussions about tolerance development, environmental cues are usually considered more important than the administration of the drug itself. Although environmental cues can dominate completely in certain situations, under closer scrutiny it becomes clear that the oral administration of a drug must be the primary and natural stimulus for the development of tolerance. One rational consideration is that for a living organism there is a relationship between oral drug-taking and the drug effect and that the organism will use this relationship. After all, the natural route of an exogenous substance into the body is through the mouth. The mouth is – so to speak – made for that purpose. As observed earlier, the mouth and nose contain the means needed to detect and analyse exogenous substances. Their primary functions – taste and smell – are there to allow the organism to recognise a substance when it enters the body, enabling it to anticipate its effect and to take appropriate measures in time.

An additional consideration is that, when the organism is able to pair very different kinds of environmental cues with the drug effect as has been demonstrated in the literature, it will certainly relate the drug's presence to the drug effect. In fact, this relation must have been the first to develop in primitive organisms as it also can be observed at cell level where the mere presence of a drug can induce tolerance without the mediation of higher structures like the central nervous system. This has been demonstrated explicitly in isolated cell cultures, where repeated stimulation with toxic substances or changes in temperature induce tolerance [34, 66].

There is ample evidence that the adaptive response – the compensatory action of the organism to the effect of a drug – is triggered by the oral administration of the drug. For instance, the oral administration of glucose almost immediately results in an increased release of insulin into the bloodstream [11, 15, 18, 28, 57]. In fact, the organism will make use of any cue it can find

to anticipate disturbances of its functioning, and oral drug taking seems crucial in this mechanism.

These considerations do not mean that an oral stimulus is always the dominant stimulus for the tolerance process. Indeed, environmental cues become of prime importance when the natural – oral – route is bypassed through the injection of the drug directly into the bloodstream. Since much of the research into drug tolerance has been done with intravenous administered drugs, i.e. without the fundamental – oral – cue being present, care should be taken in interpreting any results. Of course, separating the different cues is important and can provide much insight, but the underlying mechanism must be understood: when the oral cue is not present, the body will have to depend on environmental cues to trigger the tolerance mechanism. This may result in a different behaviour. Also Siegel noted the difference in the degree of tolerance present in subjects accustomed to oral administration when that was changed into transdermal applications (Siegel 1999 [51], referring to Johnson & Faull 1997 [22]). In research into the development of drug tolerance it is therefore essential to understand the natural way in which the organism develops drug tolerance and the consequences of administering drugs directly into the bloodstream.

- The respective trigger functions of oral and environmental stimuli can be demonstrated by manipulating the stimulus to which the subject is accustomed:
  - The stimulation of insulin secretion via the oral administration of glucose, noted above, can be prevented when the glucose is directly introduced into the stomach or the bloodstream. No direct insulin release then occurs because this compensating mechanism is primarily linked to the oral intake of glucose, resulting in a strong hyperglycaemic reaction [57, 62].
  - In heroin addicts, where there is no oral stimulus when the drug is injected directly into the bloodstream, the compensating mechanism is activated mainly by environmental stimuli. When the drug is taken in a different environment, the drug effect can be considerably larger and even lethal because the usual environmental stimulus is not present to activate the compensating mechanism [48, 51].
  - An environmental stimulus which has previously been paired with the administration of a drug can be applied separately, and will trigger the compensating mechanism alone, causing a large reaction (opposite to the drug action). The latter mechanism is well-known from research on heroin addicts, who display craving and withdrawal symptoms when presented with pictures containing drug-related cues [51].

Conclusion

That the mathematical model supports the underlying theory is in contrasts with most other published models of drug tolerance which are qualitative only. The importance of conducting research into the behaviour of regulated physiological systems using control theoretical principles cannot be overemphasised as the behaviour of a regulated system can only be understood from the behaviour of a mathematical model describing it. Even the behaviour of the simplest regulated system cannot be described other than mathematically. The behaviour of more complex regulated systems can only be understood from simulations with computer programs using advanced, iterative methods to solve the differential equations involved. This implies that a model which is qualitative only, may never involve feedback as its behaviour cannot be predicted. It should be noted that the development of a satisfactory mathematical model of a physiological process requires an understanding of the process's behaviour, which provides a check on the investigator's insight into the logic underlying the developed model.

As is true of any mathematical model, the model presented has limitations. For instance, it only describes a single effect of a drug. In reality a drug has numerous different primary and secondary effects so that the total response of the organism to a drug is immensely more complex than can be described by the model. Nevertheless, the simulations show its ability to describe the effects of repeatedly administered drugs during tolerance development and in dependence and the addictive state. In a time when addiction to hard drugs is a huge problem and a growing section of the population is dependent on anti-depressants or sedative drugs, the importance of a model which can describe the effects of repeatedly administrated drugs on the organism and its reaction to withdrawal can hardly be overestimated.

Acknowledgements

The author would like to thank C. A. Grimbergen, R. Jonges, J. Habraken and I. Jans for their critical support and valuable suggestions.

Appendix

In a previous paper, the mathematical implementation of the model and the derivation of the formulae describing its components is extensively discussed [37]. In this appendix, a summary is given of the formulae. For the sake of brevity, the index '(t)' in

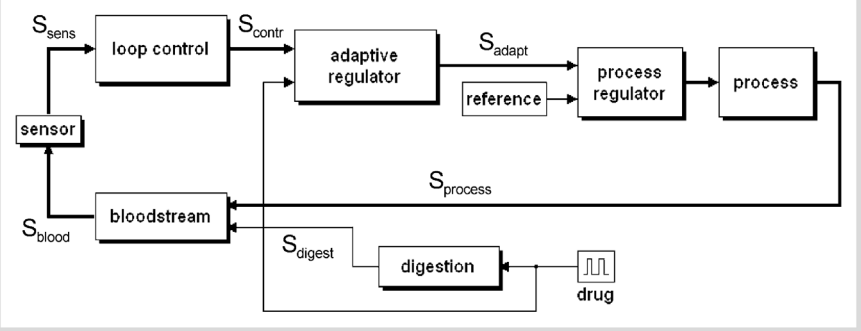

Fig. A1 Block diagram of the mathematical model.

time signals is omitted. ◉ **Fig. A1** shows a block diagram of the mathematical model.

1. The digestive tract

The digestive system plays no role in the regulation loop. Drug transport through the digestive tract is modelled as a first order function:

$$S_{digest} = \int_0^t drug\ dt - \frac{1}{T_{digest}} \int_0^t S_{digest}$$

The input to the block is the drug administration, drug. The input signal is integrated to obtain the drug level when it enters the bloodstream, the output of the block S_{digest}. A fraction $1/T_{digest}$ of the output signal is subtracted from the input to account for the spread in drug distr ibution in the diges tive tract. T_{digest} is the time constant of this process.

2. The bloodstream

After digestion, the drug enters the bloodstream where it is dispersed. In the present configuration of the model, the drug and the substance produced by the process are assumed to be identical in composition and consequently add in the bloodstream. The amount of the total substance in the bloodstream will be reduced by the body's metabolism. The processes are modelled with a first order function:

$$S_{blood} = \int_0^t (S_{process} + S_{digest})dt - \frac{1}{T_{blood}} \int_0^t S_{blood} dt$$

The input signals – the drug as it moves from the digestive tract into the bloodstream, S_{digest}, and the substance produced by the process, $S_{process}$ – are added and integrated, yielding the output of the block, the blood drug level S_{blood}. To account for the body's metabolism, a fraction $1/T_{blood}$ of the output signal is subtracted from the input.

3. The adaptive regulator

The input signals of the adaptive regulator are the drug administration and the sensor signal, processed by the loop control block. The sensor signal provides the information about the drug effect. The adaptive regulator comprises a fast and a slow regulator.

3a. The fast regulator

◉ **Fig. A2** shows a block diagram of the fast regulator. The fast regulator consists of the blocks 'drug regulator', 'interval regulator' and 'model estimation'. ◉ **Fig. A3** shows the implementation of the fast regulator in the mathematical simulation program Simulink. The input signal of the drug regulator S_d is multiplied by M_{drug}, which represents the course of the drug level in the input signal over time. This signal is integrated (1/s) with a time constant T_{drug}, yielding its average. The resulting value is a slowly rising signal, L_{drug}. Multiplying L_{drug} by M_{drug} yields the output signal S_{drug}.
The relation between the signals is:

$$S_{drug} = M_{drug} \cdot \frac{1}{T_{drug}} \int_0^t (S_d - S_{drug}) \cdot M_{drug} dt$$

And

$$S_{drug} = L_{drug} \cdot M_{drug}$$

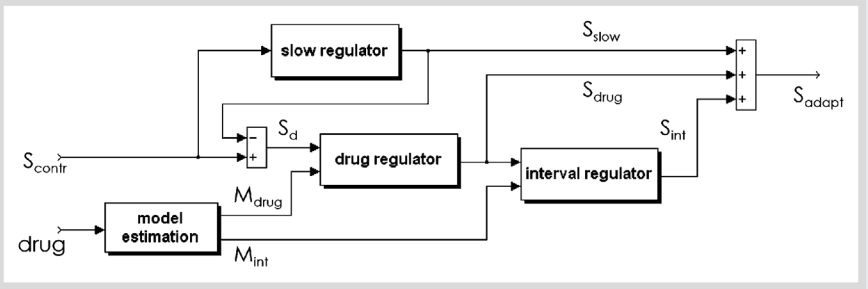

Fig. A2 Block diagram of the adaptive regulator.

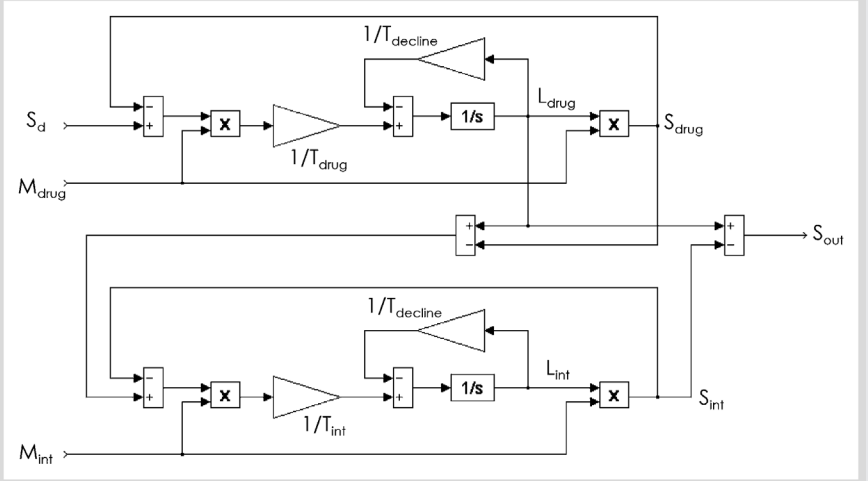

Fig. A3 The fast regulator implemented in Simulink.

The input to the interval regulator is obtained when the output signal of the drug regulator – S_{drug} – is subtracted from its top value L_{drug}. The model of the interval is M_{int}.
The relation between the signals in the fast regulator describing the drug's presence is then:

$$S_{drug} = M_{drug} \cdot \frac{1}{T_{drug}} \int_0^t (S_d - S_{drug}) \cdot M_{drug} dt - M_{drug} \cdot \frac{1}{T_{decline}} \int_0^t \frac{S_{drug}}{M_{drug}} dt$$

and

$$S_{drug} = L_{drug} \cdot M_{drug}$$

Similarly, the equation describing the interval regulator is:

$$S_{int} = M_{int} \cdot \frac{1}{T_{int}} \int_0^t (L_{drug} - S_{drug} - S_{int}) \cdot M_{int} dt - M_{int} \cdot \frac{1}{T_{decline}} \int_0^t \frac{S_{int}}{M_{int}} dt$$

and

$$S_{int} = L_{int} \cdot M_{int}$$

The output of the interval regulator is S_{int}. The output signal of the total fast regulator is obtained by subtracting the interval signal from the top level of the drug signal:

$$S_{out} = L_{drug} - S_{int}$$

3b. Estimation of the drug effect in the adaptive regulator

The model of the course of the drug concentration when it enters the bloodstream – M_{drug} – is computed by calculating the effect of a pulse with a magnitude of 1 on the digestive tract's transfer function. The input of the interval is acquired when the signal "drug" is subtracted from its top value: 1. Multiplying this signal with the transfer of the digestive tract yields the model of the interval M_{int}:

$$M_{drug} = \int_0^t drug\, dt - \frac{1}{T_{digest}} \int_0^t M_{drug} dt$$

And

$$M_{int} = \int_0^t (1 - drug) dt - \frac{1}{T_{digest}} \int_0^t M_{int} dt$$

T_{digest} is the time constant of the digestive system.

3c. The slow regulator

The slow regulator counteracts the disturbance by lowering the level of the process with the average of the drug effect. This is obtained by a low pass filter with a time constant T_{slow}:

$$S_{slow} = \int_0^t S_{contr} dt - \frac{1}{T_{slow}} \int_0^t S_{slow} dt$$

4. The process

The model does not incorporate the characteristics of the process and the process regulator. In a specific model of drug tolerance where the process is included, the effect of the process transfer on loop stability has to be controlled by the "The loop control" block.

5. Loop control

A loop control provides the necessary conditions for stable operation of the negative feedback system. In the present form of the model, the effect of the bloodstream on the regulation loop is counteracted. The relation between the input and the output of the loop control is:

$$S_{sens} = \int_0^t S_{contr} dt - \frac{1}{T_{blood}} \int_0^t S_{sens} dt$$

6. The sensor

The sensor transforms the chemical signal S_{blood} – the blood drug level – into the signal S_{sense}. This transformation is in the present model assumed to be linear and is set at 1. In specific models of physiological processes, this complex mechanism can be described more accurately. Stable operation then requires that the effect of its transfer on loop stability is controlled by the "The loop control" block.

Disclosure: The author declares that there are no financial interests to disclose.

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