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A theory of drug tolerance and dependence I: a conceptual analysis

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Abstract

A mathematical model of drug tolerance and its underlying theory is presented. The model extends a first approach, published previously. 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 exogenous 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 behavior 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. 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. The present paper analyses the concept behind the model. The next paper discusses the mathematical model.

Keywords: Drugs; Drug tolerance; Dependence; Addiction; Adaptation; Homeostasis; Mathematical model

1. Introduction

Drug tolerance manifests itself in the gradual decrease in the effect of a drug when it is administered repeatedly. This decrease in drug effect can be considerable, but a substantial drug effect will nearly always remain. When the effect caused by the administration of a drug has worn off, an opposite effect may follow before the next administration: the rebound phenomenon. In dependent and addicted subjects, the withdrawal of a drug may induce a reaction. This is also an opposite effect, like the rebound, but usually much stronger. A variety of theories and models have been proposed to explain the mechanism relating these aspects of drug taking. Very important has been the concept of homeostasis proposed by Cannon (1929). 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 (Wiener, 1948; Bertalanffi, 1949, 1950). 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 (Goldstein and Goldstein, 1968; Jaffe and Sharpless, 1968; Martin, 1968; Kalant et al., 1971; Snyder, 1977; Poulos and Cappell, 1991; Dworkin, 1993; Siegel, 1996; Siegel and Allan, 1998).

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Besides the theories of drug tolerance based on homeostasis, there are theories which do not regard tolerance development as the result of a regulated process.

An influential theory was developed by Solomon and Corbit, the Opponent-Process theory (Solomon and Corbit, 1973, 1974; Solomon, 1977, 1980). In this theory, the drug is thought to trigger a response known as the A-process. The A-process induces a reaction called the B-process which opposes the A-process and increases in magnitude by repeated elicitation of the A-process. The A-process is fast, while the B-process is delayed and slow. As the difference between the A-process and the (negative) B-process is the ultimate effect of the drug, the drug effect will slowly decrease.

Several theories are based on a model of habituation developed by Rescorla and Wagner, which attribute tolerance to a learned diminution of the response (Rescorla and Wagner, 1972; Wagner, 1978, 1981; Tiffany and Baker, 1981; Baker and Tiffany, 1985; Tiffany and Maude-Griffin, 1988). Dworkin incorporated this theory in a feedback model of drug tolerance (Dworkin, 1993).

Another influential theory was proposed by Siegel (Siegel, 1975–1999). In Siegel's theory, drug tolerance is assumed to be caused by Pavlovian conditioning: the compensatory response of the organism on the administration of a drug is triggered by environmental cues paired to the drug taking. Poulos and Cappell augmented Siegel's theory of drug tolerance by incorporating homeostasis, which was adopted by Siegel (Poulos and Cappell, 1991; Siegel, 1996; Siegel and Allan, 1998).

The present paper presents a model of drug tolerance and dependence which is different from the theories described above. The model is based on the assumption that most processes in a living organism are regulated, which is in accordance with homeostasis. The paper will argue that 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 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 (Peper et al., 1987, 1988). 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 (Thorpe, 1956; Kandel, 1976; Koshland, 1977; Poulos and Cappell, 1991; Siegel and Allan, 1998). 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 color stimuli (Siegel and Allan, 1998) to solve problems in modelling the organism's adaptation to drugs.

2. Properties of adaptive regulated physiological processes

2.1. 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 behavior 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, either from within or from the outside, making the process output less responsive to changing parameter values or changes in its environment.

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

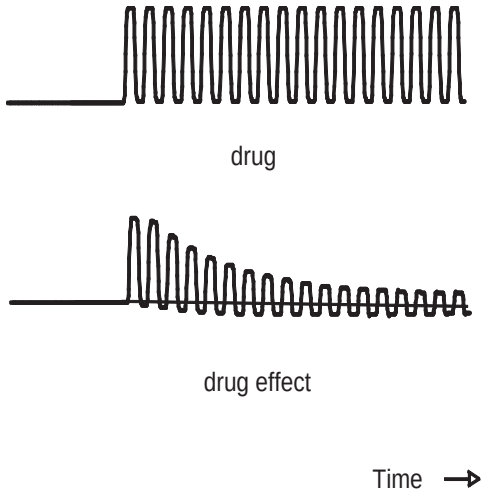

Fig. 1. Drawing of the development of tolerance to the repeated administration of a drug.

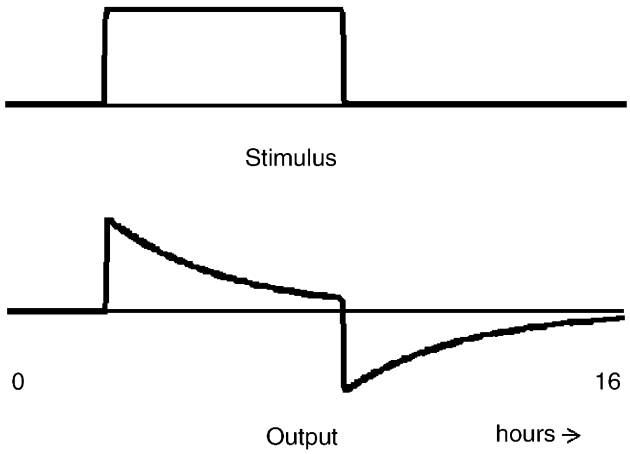

Fig. 2. Computer simulation of the effect of a single disturbance on the output of a simple linear negative feedback circuit.

disturbances. The following discussion elucidates the general behavior of negative feedback systems.

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 h, 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

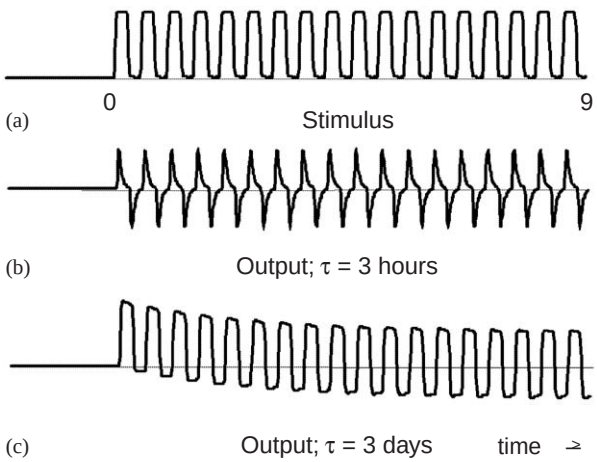

Fig. 3. (a–c) Effect of a repeatedly applied stimulus on a simple feedback circuit.

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.

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. The stimuli are all suppressed to the same degree, which 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 (for a valuable evaluation of the applicability of homeostasis to physiological processes, see Toates, 1979).

2.2. Adaptation in regulated processes

When the development of drug tolerance cannot be described by homeostasis, or in general, by simple

feedback systems, what then is the mechanism which does describe it? 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 (Bell and Griffin, 1969; Toates, 1979). 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 (Peper et al., 1988).

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).

When this analysis of how the organism adapts 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.

Like homeostasis, the model assumes an adaptive process to adapt to a disturbance by opposing its effect. Fig. 4 illustrates how this process of adaptation develops. The level of adaptation at any moment depends on the magnitude and length of the disturbance while it increases with every disturbance. Adaptation to the interval proceeds from the level acquired during the disturbance. In the example of the body's

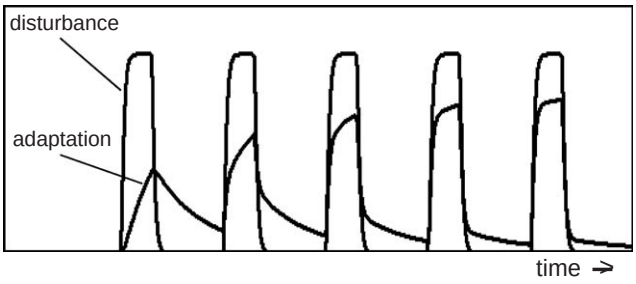

Fig. 4. General outline of the development of adaptation to a repeatedly occurring disturbance in an adaptive process.

thermo-regulation, given above, an increase in thermogenesis on entering the cold outside is the way the body adapts to that disturbance. A return to the warm room will result in a decrease in heat production, if necessary accompanied by cooling, for instance by sweat secretion (for important research into the way the body uses opposite controls, see Saunders et al., 1998). Fig. 4 shows that after the body has learned to cope with this particular disturbance, the increase in thermogenesis on entering the cold and its decrease on return to the room will take place rapidly, while the level of adaptation has increased considerably.

2.3. 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. 5). 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). 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 (Steffens, 1976; Grill, et al., 1984). 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.

2.4. 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 it to relate changes in the functioning of processes to the drug, the organism 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 "recognized" 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 (Snyder, 1977).

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 is 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. A change in that quantity—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.

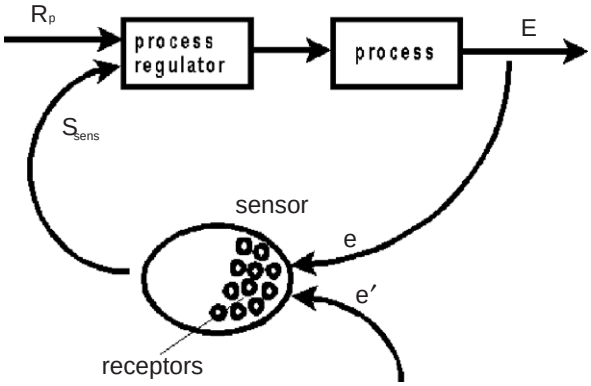

Fig. 5. Example of a simple regulated physiological process and the way in which a drug may disturb its functioning.

It is difficult to find another rationale for the initial large drug effect and the long time it takes the organism to develop tolerance than the assumption that the organism does not determine the quantity of a drug entering the body. Again, if the organism were able to determine the properties and the quantity of the drug at an early stage, it would have all the information needed to rapidly suppress any drug activity. The organism needs a relatively long period to make an approximation of the drug dose it can expect. In practice this approximation will be about the average dose of a number of drug administrations.

3. Modelling tolerance development in physiological processes

The initial effect of a disturbance upon a regulated physiological process will now be elucidated with a simplified model. Subsequently, the model will be extended to describe the complex response of a regulated physiological process to repeated disturbances in its functioning. Fig. 5 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 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 in Section 2 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. 6, an "adaptive regulator" is added to the model of the regulated process in Fig. 5. This adaptive regulator 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 drug in such a way that the effect of the disturbance on the level of the substance in the bloodstream, E, is reduced. To this end, it uses the output signal of the sensor, S_{sens}, and 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. In this model, the sensor output is assumed to be proportional to the sum of the exogenous substance and the endogenous substance. The binding rates of the two substances with the receptors of the sensor are assumed to be equal.

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, necessitating a gradual increase in the dose of the exogenous insulin (Heding and Munkgaard Rasmussen, 1975; Mirel et al., 1980). If a drug interferes with the information transfer in a regulated process in the organism 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 the process will after a while more or less regain its normal functioning.

Fig. 7 shows a model of an adaptive regulated process of which the level of the substance produced by the process is increased by a drug (case 1). The adaptive regulator gradually learns to suppress the effect of the drug during the period the drug is in the bloodstream by lowering the process output. The adaptive regulator bases its action on information it receives from the sensor about the level of the regulated substance in the

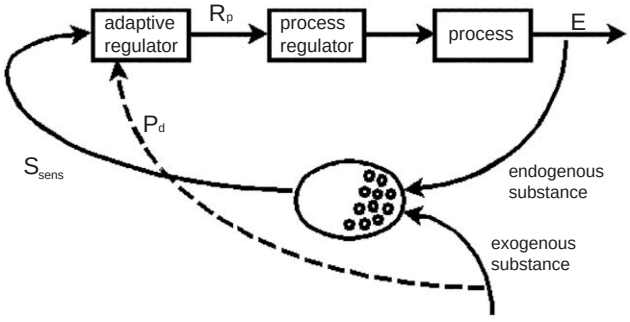

Fig. 6. Adaptive regulator added to the regulated process.

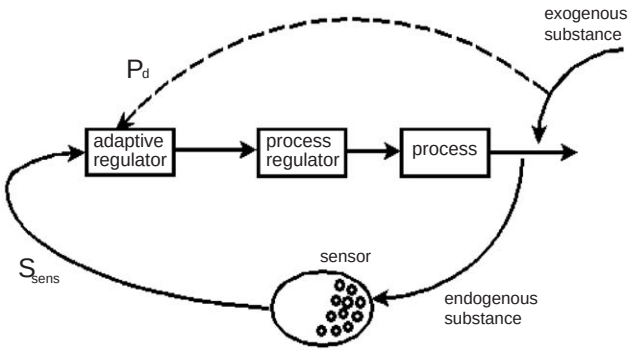

Fig. 7. Model of adaptive regulated process in which a drug increases the level of the produced substance.

bloodstream, E, and on information about the drug administration, P_d. In many models of drug tolerance, adaptation is assumed to be effected at the receptor site. However, if a drug changes the amount of a substance whose level is regulated, this information is crucial for the process regulator and should pass the sensor unaltered. It follows that the transfer function of the sensor (its input–output relation) must be kept constant. Consequently, when a drug changes the amount of a substance which is regulated at a preset level, the organism can be expected to counteract this disturbance primarily by a readjustment of the process parameters.

When a drug interferes with the information transfer in the process regulation (case 2), it is not the level of the process which has to be corrected, but the change of input signal to the process regulator induced by the drug. As the feedback path in the regulation is affected here, the disturbance caused by the drug may be corrected via a change in the transfer function of the sensor, for instance by means of a change in the number of receptors sensitive to the drug. In this configuration, the adaptive regulator learns to change the transfer function of the sensor in a way that counteracts the effect of the drug on the sensor's sensitivity to the messenger.

Fig. 8 shows a model of a regulated process in which the information transfer is disturbed by a drug. The adaptive regulator gradually learns to suppress the effect of the drug on the sensor signal by changing the sensitivity of the sensor. The adaptive regulator bases its action on information it receives from the sensor, S_{sens}, and on information about the drug administration, P_d.

The model in Fig. 7 describes the effect of a drug on the level of an endogenous substance which does not function as a messenger. The model in Fig. 8 describes the effect of a drug on messenger–receptor interactions and is therefore applicable to many of the effects associated with addictive drugs.

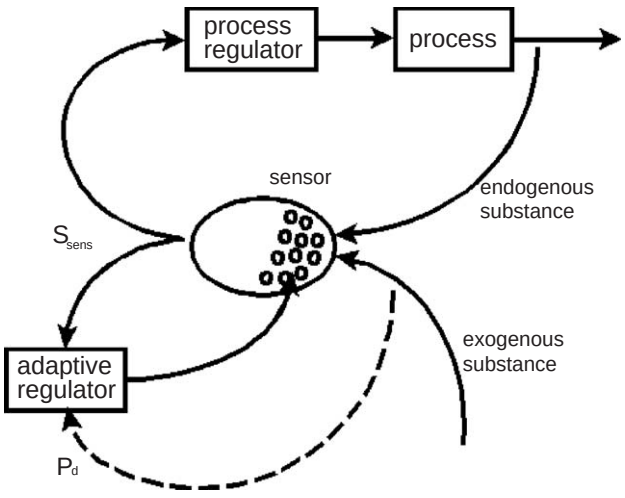

Fig. 8. Model of a regulated process in which the information transfer is disturbed by a drug.

3.1. Fast and slow adaptation

The adaptive regulator treated above minimizes 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). Therefore, an important additional function of an adequate regulator is minimizing 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 minimizes 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 (Peper et al., 1987). 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 (for an interesting approach to slow adaptation, see Dworkin, 1986). 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 thermoregulation in animals moved to a colder climate may adapt by a slow increase of the grow of their fur. The time constant of the slow regulator may be weeks to month or even years.

4. Practical significance of the model

In the subsequent paper, the mathematical implementation of the theory will be discussed. The following section illustrates the value of the mathematical model for reaching a better understanding of how drugs affect physiological processes. The simulations carried out demonstrate the relevance of the model in the development of drug tolerance and in the drug depended and addictive state. In the simulations, the parameters of the model have been chosen to obtain a clear picture of the effects. Because the stimulus—the drug intake—is in reality in most cases extremely short with respect to the repetition time, its duration has been extended for

clarity. As the model does not describe a specific process, the vertical axes in the figures are in arbitrary units.

4.1. Tolerance development to drugs

Fig. 9 shows a simulation with the mathematical model. A hypothetical drug is administered over 20 days, once a day. Whereas in Fig. 1 the drug dose was the same in every administration, in this simulation the dose is increased every day such that the decrease in the drug effect due to tolerance development is compensated, keeping the drug effect more or less constant. This is how drugs are usually administered over longer periods. The figure shows that a rise in the drug effect is followed by a drop to below the base line, representing the rebound mechanism. These negative reactions increase when tolerance to the drug increases. In the simulations, the change in the sensor output caused by the presence of the drug is assumed to be the drug effect.

As discussed above, tolerance to a drug means tolerance to the dose of the drug. A change in drug dose therefore necessitates a relearning by the organism and is followed by a period of imperfect compensation. This manifests itself in large changes in the magnitude of the drug effect on small changes in drug dose. Fig. 10 shows a computer simulation with the mathematical model of the effect of a small change in the 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 itself to the new situation, the magnitude of the drug effect settles at a level reduced proportionally by 20 percent. When the dose is increased

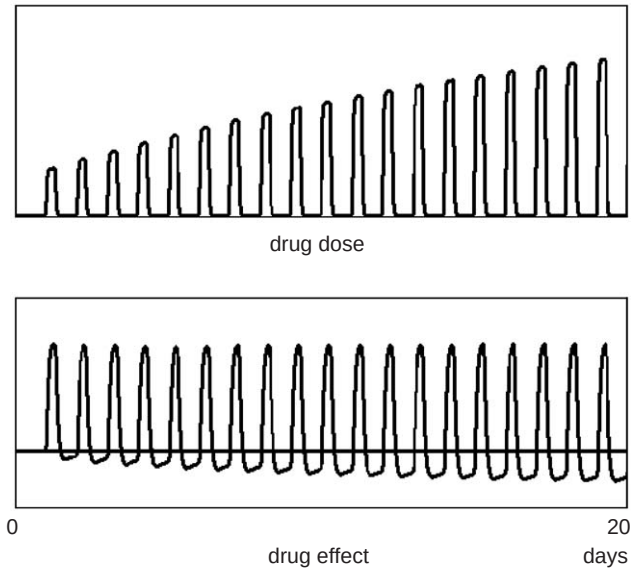

Fig. 9. Gradually increasing drug dose to obtain a constant drug effect. The vertical axes are in arbitrary units in all figures.

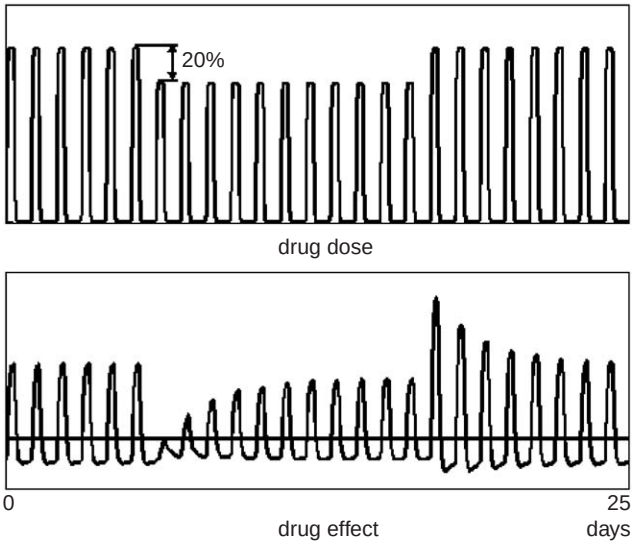

Fig. 10. The effect of a small change in drug dose after tolerance has developed. In the simulation, a 20 percent decrease in the dose results in an initial suppression of the drug effect. An increase in the dose back to the original magnitude causes an initial large increase in the drug effect. The drug is administered once a day.

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 as was discussed in a previous paper (Peper et al., 1988) 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 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 (Perry and Alexander, 1986; Rickels et al., 1993; Schweizer et al., 1998; Rickels et al., 1999). A publication on protocols for optimal drug withdrawal elaborated this sensitivity of the tolerance mechanism to small decreases in drug dose (Peper and Grimbergen, 1999). 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.

4.2. 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 administered, strong negative reactions can occur.

Fig. 11 shows a simulation with the model demonstrating what happens when the administration of a drug is abruptly discontinued after tolerance has developed. 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 functioning. The latter depends, among other factors, on health and age (Mitchell et al., 1870; Verveen 1978, 1983; Peper et al., 1987, 1988).

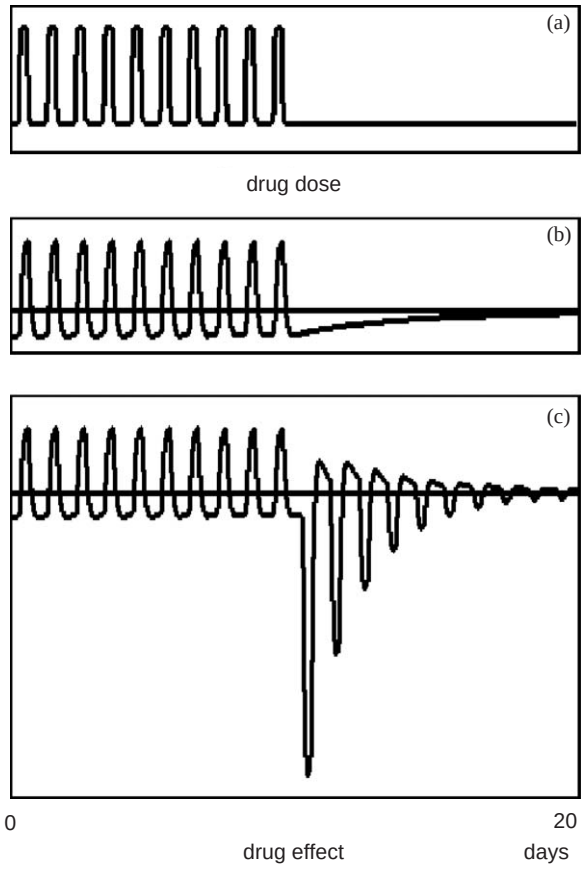

Fig. 11. (a) Model simulation of the effect of abrupt drug withdrawal in tolerant (b) and dependent (c) subjects. The drug is administered once a day.

5. Discussion

The paper discusses the concept underlying an advanced mathematical model which extends the simple model presented previously. Simulations with the mathematical model demonstrate the model's behavior 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. This general model of physiological tolerance development does not take into account psychological factors like motivational effects (Ahmed and Koob, 1999; Ahmed et al., 2000). Also feed forward processes playing a role in many physiological regulations are not considered (see: Toates, 1979; Saunders et al., 1998) nor the various non-linearities in the process functions present in vivo. The effect of feed forward and non-linearities on model behavior will be discussed in future publications. The mathematical implementation of the model will be presented in the subsequent paper. Fundamental in the model is the proposition that the oral detection and analysis of exogenous 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 in Section 3. 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 is not based on the assumption that tolerance development is part of a regulated process. The theory of Rescorla and Wagner 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.

The proposed theory also differs fundamentally from the theory of Siegel. 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 administration bypasses the natural—oral—route, as is the case when drugs are administered 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.

5.1. Model behavior 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 behavior of the model clarifies some of their implications:

5.1.1. 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 Fig. 10. 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. 10, 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 rate of suppression of the drug effect after tolerance has been established and the magnitude of the reactions after withdrawal, which indicates a link between the rate of maximal suppression 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 suppression of the drug effect when tolerance has developed tends to be relatively low. Another reason why there is a limited suppression of the drug effect in the tolerant situation may be that the organism cannot 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.

5.1.2. The relationship between drug administration and environmental cues

In discussions about tolerance development, cues originating from environmental causes 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 recognize a substance when it enters the body, enabling it to anticipate its effect and to take appropriate measures in time.

An additional consideration indicating that oral administration is the fundamental stimulus in the tolerance process 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 (Peper et al., 1998; Wiegant et al., 1998).

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 (Deutsch, 1974; Steffens, 1976; Grill et al., 1984; Dworkin, 1993; Loewy and Haxhiu, 1993). 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 drug cue is not present, the body will have to depend on environmental cues to trigger the tolerance mechanism. This may result in a different behavior. 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 referring to Johnson and Faull, 1997). 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 (Steffens, 1976; Tillil et al., 1988).
- 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 (Siegel et al., 1982; Siegel, 1999).
- 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 (e.g. Siegel, 1999).

6. Conclusion

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.

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