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Abraham Peper
University of Amsterdam, Amsterdam, The Netherlands

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ASPECTS OF THE RELATIONSHIP BETWEEN DRUG DOSE AND DRUG EFFECT

Abraham Peper □ Department of Medical Physics, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

□ It is generally assumed that there exists a well-defined relationship between drug dose and drug effect and that this can be expressed by a dose-response curve. This paper argues that there is no such clear relation and that the dose-response curve provides only limited information about the drug effect. It is demonstrated that tolerance development during the measurement of the dose-response curve may cause major distortion of the curve and it is argued that the curve may only be used to indicate the response to the first administration of a drug, before tolerance has developed. The precise effect of a drug on an individual depends on the dynamic relation between several variables, particularly the level of tolerance, the dose anticipated by the organism and the actual drug dose. Simulations with a previously published mathematical model of drug tolerance demonstrate that the effect of a dose smaller than the dose the organism has developed tolerance to is difficult to predict and may be opposite to the action of the usual dose.

Keywords: Dose-response curve, drug tolerance, mathematical model, hormesis, homeopathy, sensitization

INTRODUCTION

In previous publications, a model of drug tolerance and dependence was presented (Peper *et al.* 1987, 1988; Peper and Grimbergen 1999; Peper 2004a, 2004b). The two 2004 papers present an advanced mathematical model of intermittent adaptation describing the mechanism of tolerance development and elaborate the theory underlying the model (Peper 2004a, 2004b). The model is essentially more complex than the generally supported model of homeostasis, which has been demonstrated to fail in describing tolerance development to repeated drug administrations (Peper *et al.* 1987, Peper 2004a). The papers argue that tolerance to a drug is not just tolerance to the properties of a certain drug, but tolerance to a certain dose of that particular drug, and that the magnitude of the compensatory response is not determined by the actual dose of the administered drug but by the dose the organism anticipates. In addition, the papers argue that the oral recognition of exogenous substances is the natural and primary stimulus for the compensatory response in the tolerance mechanism. Environmental cues are considered primary stimuli only in dependence and addiction or when there is no oral stimulus such as when

Address correspondence to Abraham Peper Ph.D., Milletstraat 48-3, 1077 ZG Amsterdam, The Netherlands; Tel.: +31.20.6751000; E-mail: a.peper@planet.nl; Website:www.abraham-peper.com

a drug is administered intravenously. Siegel's theory of Pavlovian conditioning describes how environmental cues may become associated with the drug effect (Siegel *et al.* 1982; Siegel and Allan 1998; Siegel 1999).

In the present paper, the behaviour of the mathematical model with respect to the dose-response relation will be examined further. The simulations carried out with the model demonstrate that when a level of tolerance has developed the relation between drug dose and drug effect is very different from what is generally assumed.

The paper discusses how the development of tolerance to a drug affects the measurement of the dose response curve and indicates the serious consequences tolerance development has for the applicability of the curve. The effects of small doses are examined with regard to hormesis and homeopathy. Sensitization and other paradoxical effects in the use of drugs are discussed and possible explanations of these phenomena are given, relating them to changes in drug dose, the gain of the regulation loop and the only gradual adaptation of the regulation to changing parameters.

The simulations show the effects of tolerance development on repeated drug administrations. For the tolerance mechanism to function, it must be triggered when the drug is administered. For the behaviour of the mathematical model it is of no relevance whether the triggering takes place orally or by environmental cues and no distinction between different kinds of triggering was made in the simulations. Whenever the paper discusses oral drug administration, the drug is assumed to be gustatorily detectable.

A DYNAMIC MODEL OF THE DOSE-RESPONSE RELATION

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 the functioning of other processes. It is difficult to imagine how living organisms are 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, cited by Cannon, 1929). Cannon translated Bernard's observation into the model of homeostasis, which assumes physiological processes to maintain a steady state through feedback (Cannon 1929). An earlier publication (Peper 2004a) demonstrates that the model of homeostasis is not adequate to describe the effect of repeated disturbances on the functioning of living organisms and 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 disturbing effect of the drug by opposing the disturbance at the moment it occurs. In addition to this dynamic action, a lasting shift in functioning develops. In the mathematical model described previously, these two activities are modelled with a fast and a slow regulator respectively (Peper *et al.* 1987, 1988; Peper 2004a, 2004b), 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.

A previous paper discusses the mathematical implementation of the model (Peper 2004b). 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. 1 shows a block diagram of a regulated adaptive process. The process produces a hypothetical substance. Its regulation is disturbed by

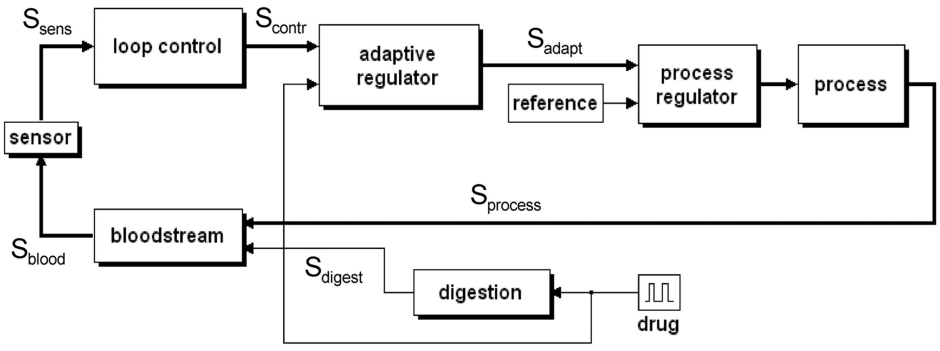

FIG. 1. Block diagram of a regulated adaptive process.

an exogenous substance of the same composition (see Peper 2004b). 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.

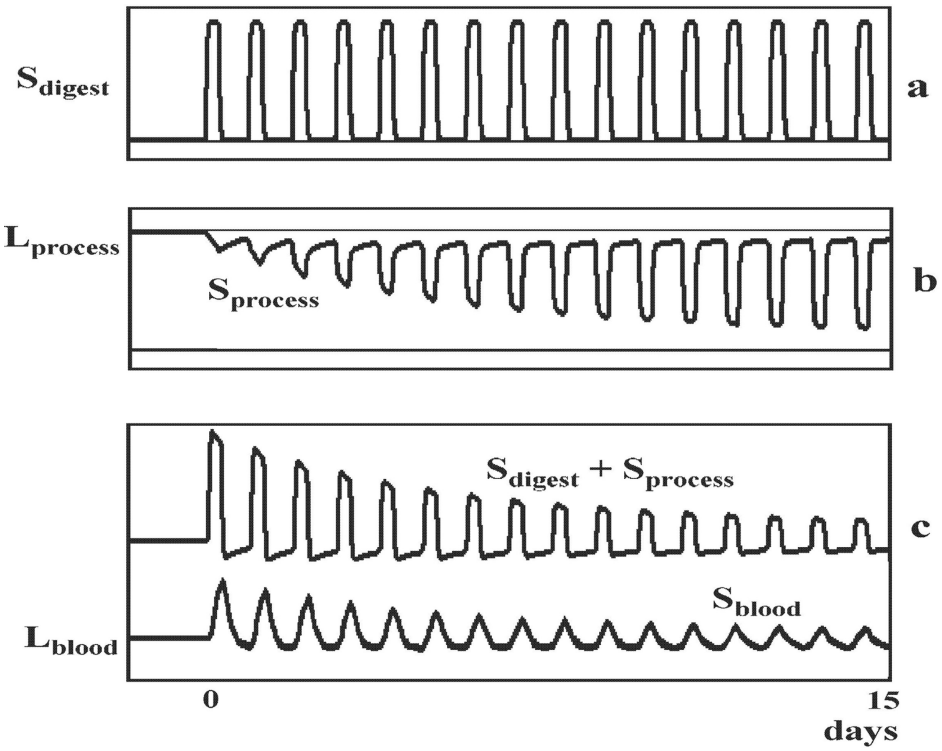

FIG. 2. Some signals from the block diagram of Fig. 1 clarifying how tolerance develops: (a) The exogenous substance when it enters the bloodstream, S_{digest}. (b) Process output during tolerance development, $S_{process}$. (c) $S_{process}$ and S_{digest} added in the blood stream and the resulting 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}.

When the exogenous substance enters the body, a series of activities takes place to readjust the processes involved in order to reduce the disturbance. Fig. 2 shows some signals from the block diagram which illustrate this mechanism (Peper 2004b). 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 shift of the curve to a level substantially lower than the baseline, $L_{process}$, represents a fundamental change in the functioning of the processes involved.[1] The two signals—S_{digest} and $S_{process}$—are added when the 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.

Fig. 2 demonstrates how the adaptive regulator learns to generate a compensatory response when a drug is administered repeatedly. It slowly learns to readjust the process parameters *during the disturbance* to counteract the change in functioning caused by the drug. These readjustments will start at the moment an exogenous substance is detected in the mouth.[2] The mouth analyses the substance and sends the acquired infor-

[1]This downward shift in the functioning of the process represents the drug induced change in the functioning of processes involved in the drug effect, as discussed above. The shift depends mainly on the functioning of the slow regulator which can have a long time constant. Consequently, the shift may remain a long time after a drug is withdrawn. This has important consequences as was first discussed in a previous paper (Peper et al. 1987): *The negative shift of the process output on 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 (Kalant et al. 1971). This implies [...] a worsening of the disorder of the patient after termination of drug treatment.* Apparently, for the body, adaptation to a medicine means a shift in its functioning in the direction of the disease.

[2]As has been discussed extensively in Peper 2004a, the detection of exogenous substances in the mouth is central to the process of tolerance development. The effect of the readjustments of disturbed processes after a drug administration takes time, as most processes in the body have a relatively slow response. If the body were to wait with counteracting the drug action until it gets information from processes themselves that they have been disturbed, the tolerance mechanism would be too late to suppress the disturbance effectively. As the mouth is where, in natural circumstances, exogenous substances enter the body, information from the mouth actuates the readjustment of the involved processes. The mouth is equipped with all the necessary means to detect and analyze exogenous substances. Taste—and, to a lesser extent, smell—exist to provide the organism with the information it needs to organize its defense.

mation to the processes which will be disturbed. This information is, however, restricted to the properties of the substance and does not include its quantity. At the time of detection, the body cannot know how much of the substance is to be administered and it has therefore developed a defence mechanism in which the actual dose does not play a role. Instead, it bases its defence on an assumed dose, the anticipated dose, which in most cases will be approximately the average dose of recent drug deliveries (Peper *et al.* 1988; Peper 2004a).

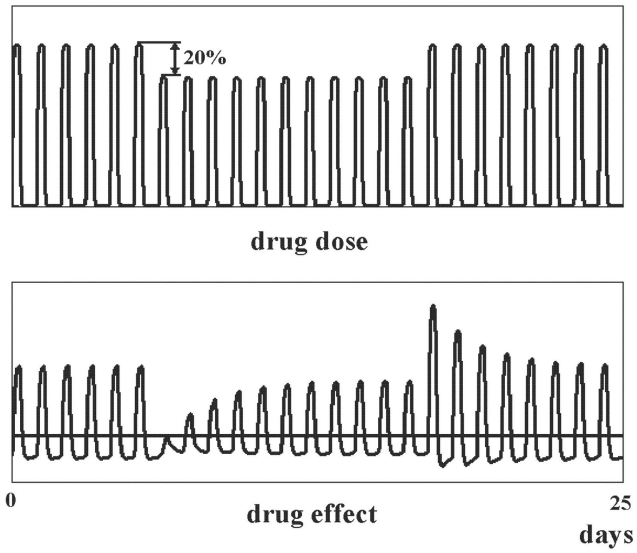

FIG. 3. A simulation of the effect of a small change in drug dose after tolerance has developed. For a given set of parameters, a 20 percent decrease in dose results in an initial suppression of the drug effect. An increase in dose back to the original value causes an initial large increase in the drug effect.

THE EFFECT OF CHANGES IN DRUG DOSE

Because the compensatory response is not based on the actual dose but on the accustomed 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 (Peper *et al.* 1988; Peper and Grimbergen 1999; Peper 2004a). Fig. 3 shows a simulation with the mathematical model of the effect of a small change in drug dose after tolerance has developed. In the simulation, for a given set of parameters, a 20 percent decrease in drug dose results in an initial suppression of the drug effect. When the regulation adapts itself to the new situation—it slowly learns to decrease the compensatory response—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 approximately twice the normal level.

In Fig. 3, with the parameter values selected, 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. 2). 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. 4, where the dose is reduced to 50 %. As was discussed in previous papers, these large responses to small changes in drug dose are a common feature of the drug effect and are not restricted to the dependent state (Peper *et al.* 1988; Peper 2004a).

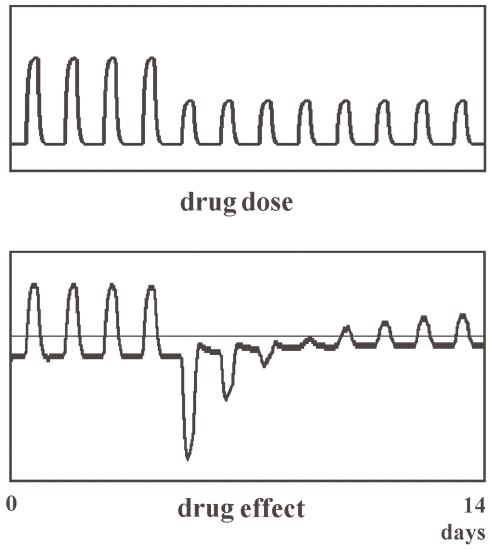

FIG. 4. Effect of reduction in drug dose to 50 %.

THE DOSE-RESPONSE CURVE

Existing conceptualizations of the relationship between drug dose and drug effect display fundamental contradictions. It is undisputed that in dependent subjects a reduction in drug dose may generate large reactions. At the same time, the dose-response curve (Fig. 5)—which postulates that a change in drug dose will produce a proportionate and predictable change in drug effect—is assumed to provide an adequate description of the dose-effect relation. The applicability of the dose-response curve is limited because responses vary widely across subjects (Ramsay and Woods 1997). But it also has other shortcomings. In standard medical practice the initial dose of a drug is selected on basis of the dose-response curve of the drug and the characteristics and peculiarities of the patient. If, after a few days, the effect is not as desired, the dose is adjusted. If the dose-response curve were used to determine the new dose

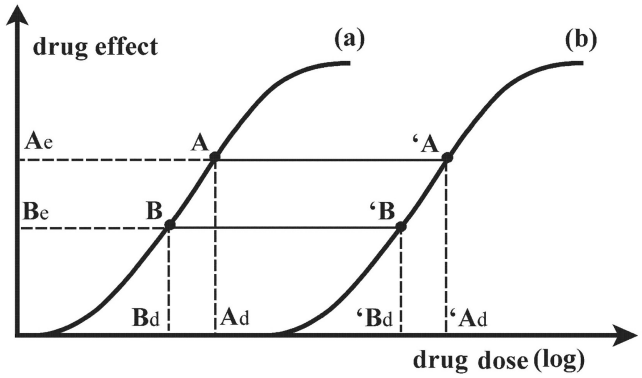

FIG. 5. Drug dose—drug effect relation from the literature (a). Curve (b) shows the relation after tolerance has developed.

a problem would occur. During the administration of the drug, tolerance may have developed and the curve will then have shifted to the right: an increase in dose is required to obtain the same drug effect. In the example given in Fig. 5, dose A_d, which causes drug effect A_e becomes 'A_d for the same drug effect after tolerance has developed. In the figure the shift is arbitrarily large, but in reality the shift can also be substantial after a few administrations of a drug and, due to the shift, curve (a) cannot be used to determine another dose. If tolerance development can be estimated and the curve is shifted to the right by the measured value, another difficulty arises. Whereas from curve (a)—i.e. for the first dose—the drug effect values A_e and B_e can be determined from the drug dose values A_d and B_d, after tolerance development a decrease in dose from 'A_d to 'B_d will cause a decrease in the drug effect larger than curve (b) suggests. As was demonstrated in Fig. 3, a reduction in the dose of a drug to which tolerance has developed may result in a disproportionate reduction in drug effect. Even large reactions may occur as shown in Fig. 4. The latter is generally accepted in dependence. However, this effect in dependence does not fundamentally differ from the effect when only tolerance is present, as observed in earlier research. In dependence the effect is large because tolerance in dependence is high. When tolerance is lower, as will be the case after only a few drug administrations, the disproportionate effect of a reduction in dose is smaller but the decrease in drug effect may initially still be significantly larger than predicted by the dose-response curve. Positive overshoot when the drug dose is increased will be as large and both situations may not be without risk to the patient.

The dose-response curve presumes a static relationship between drug dose and drug effect. Yet, tolerance development—and thus time—is an important factor in measuring the drug effect. This is demonstrated in simulations with the mathematical model shown in Fig. 6, where the dose and

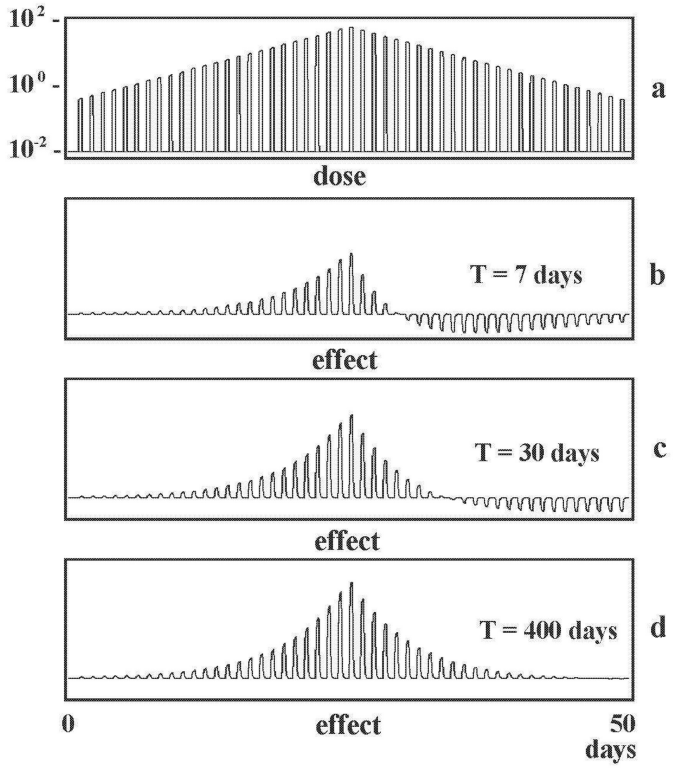

FIG. 6. Simulations with the mathematical model of the relation between dose (a) and drug effect, plotted against time to illustrate the influence of tolerance development on the outcome of dose-response curve measurements. The time constant of the tolerance mechanism in the simulations is respectively 7 days (b), 30 days (c) and 400 days (d).

the drug effect are plotted separately against time to illustrate the influence of tolerance development on dose-response curve measurements.

Usually, the dose-response curve is measured by increasing the dose in logarithmic steps. The tolerance which develops during such a measurement distorts the curve. This effect, however, is not very clear in the curve, partly due to the distortion being gradual and partly due to the logarithmic change in dose.[3] When the curve is determined with a decreasing dose, the effect of tolerance development becomes readily apparent. To demonstrate these effects, in Fig. 6 the dose is first increased and subse-

[3]The bend in the bottom of the dose-response curve is largely caused by the logarithmic scale. In a linear process, a linear change in dose will cause a linear change in drug effect, as long as there is no tolerance development (curve (d)). With a linear scale, distortion of the curve due to tolerance development is easily noticed. However, as the dose-response curve is commonly presented using a logarithmic dose scale, this has also been adopted here.

The saturation in the top of the dose-response curve in Fig. 4 is the natural maximal activity of the processes involved. This effect has been left out in the simulation of Fig. 5 as it has no relevance to the subject discussed.

quently decreased (a). In curve (b), representing the drug effect, a time constant for the tolerance process is chosen of seven days (approximately the time constant used in the simulations shown in previous papers on the subject). The effect of the decrease in drug dose is a dramatic shift towards a negative drug effect with symptoms opposite to the normal drug effect. When the time constant is increased to 30 days (c), this effect is still very strong. When the time constant is increased to 400 days (d), the effect has nearly disappeared, leaving a curve where tolerance development does not take place during measurement and the upward- and downward-sloping portions of the curve have a similar shape.

The distortion of the curve during the increase in dose is significant. The full implication of the effect of tolerance development, however, becomes clear during the decrease in drug dose when the decrease in drug action causes the compensatory response to become dominant and the overall drug effect to turn negative.[4] The dose-response curve is usually measured by increasing the dose, in which case no such reactions are generated. But negative reactions are commonly seen in slow withdrawal when the dose is tapered off too rapidly, a situation comparable to that depicted in the figure. In the simulations, doses are administered once a day, over 50 days in total. Simulations with other settings of the model parameters, such as a different maximal dose, fewer stimuli or stimuli with different time spacing gave a very similar picture.

The static representation of the relationship between drug dose and drug effect suggested by the dose-response curve cannot be reconciled with the dynamic responses of the organism to changes in drug dose characteristic of the mechanism of tolerance development. Unless tolerance to a certain drug develops very slowly, tolerance development will distort the curve when the effect of different drug doses is determined in a single subject. Values for the dose-response curve should therefore be determined from the (averaged) responses to single drug administrations measured in different subjects. Even measured this way, a dose-response curve can only serve one valid purpose: it shows the average relationship between the dose and the *initial* response to a drug.

THE EFFECT OF SMALL DOSES

It was argued above that when the compensatory response exceeds the drug action, negative reactions occur. This was demonstrated in Fig. 4 with

[4]As discussed, the distortion of the curve shown in the figure is caused by the development of tolerance. The way the tolerance mechanism is triggered during this process—whether by oral triggering or by environmental cues—is of no importance.

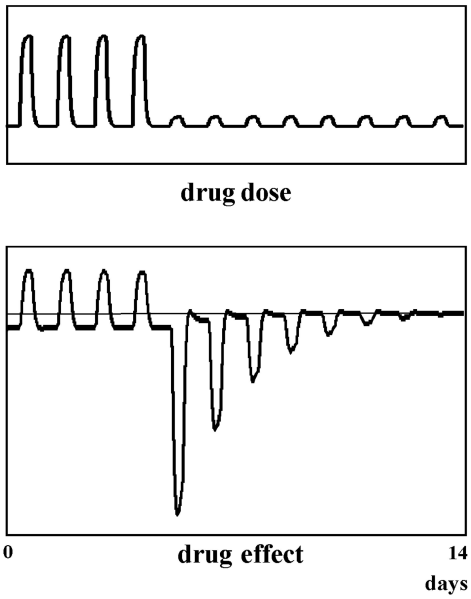

FIG. 7. Effect of reduction in drug dose to 10 %.

a reduction of the dose to 50 %. When the dose is reduced even more, the net result will be approximately the compensatory response alone, as is shown in Fig. 7, 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.

The negative reactions shown in Fig. 7 are not fundamentally different from withdrawal reactions in dependence (Peper and Grimbergen 1999). In withdrawal, however, reactions occur because environmental cues paired to the drug taking continue to trigger the compensatory mechanism after the drug is withdrawn. When an exogenous substance is taken orally and there are no environmental cues paired to the drug taking, the compensatory mechanism is not triggered when the administration of the drug is stopped and no reactions will occur (Peper *et al.* 1988; Peper 2004a). When the administration of the drug is continued but the dose is reduced, however, the compensatory mechanism will keep responding at the moments when the drug is administered, as shown in Figs 4 and 7. When the dose is sharply reduced, yet is still detected by the organism, it is basically not the drug which induces these reactions but the orally acquired information that the drug is present.

Not only oral administrations of small doses can evoke the responses described above. Any stimulus able to trigger the compensatory mechanism—like environmental cues and drug-onset cues (Kim *et al.* 1999;

Sokolowska *et al.* 2002)—can cause reactions such as those shown in Fig. 7. In other words, the tolerance mechanism will respond, whether it is triggered orally or by environmental cues. But, whereas the effects of environmental cues and drug-onset cues can be crude and relatively unpredictable (Siegel *et al.* 1982; Kim *et al.* 1999), the oral detection of exogenous substances and the resulting stimulation of the compensatory response is a highly sensitive and specialized mechanism, able to react to very small doses. How triggering the compensatory response by means of small doses can be used in withdrawal treatment in addiction was discussed in a previous publication (Peper and Grimbergen 1999).

HORMESIS AND HOMEOPATHY

Hormesis has been defined as a bi-phasic dose-response relationship in which the response at low doses is opposite to the effect at high doses. Examples of opposite effects of drugs (and radiation) at low and high doses can be found abundantly in the literature (Calabrese and Baldwin 2001, 2003; Conolly and Lutz 2004; Ali and Rattan 2006). Hormesis is usually explained by assuming a negative part in the dose-response curve at the low dose end. Homeopathy claims a curative reaction from a small dose of a drug of which high doses cause symptoms similar to those from which the patient is suffering. A dose-dependent reverse drug effect is difficult to explain with existing models. In the proposed model this phenomenon is an intrinsic component.

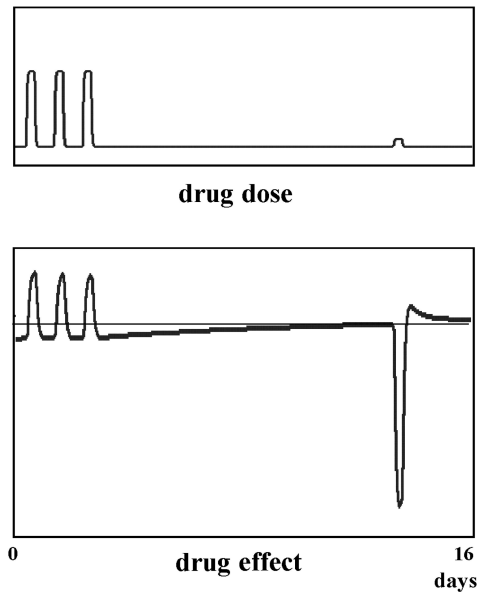

FIG. 8. The drug effect when a small dose is administered at an arbitrary time after the administration of a drug to which tolerance has developed is discontinued.

In Figs 4 and 7, the dose was reduced abruptly. The resulting reactions, however, do not depend on a sudden change in dose, but on the difference between the actual dose and the dose to which the organism has developed tolerance. Tolerance to a drug develops slowly and remains present a long time. Fig. 8 depicts a simulation with the mathematical model describing what happens when a small dose is administered at an arbitrary time after the administration of a drug to which tolerance exists is discontinued. The figure shows that the small dose evokes a reaction in the same way as the sudden reduction in dose simulated in Figs 4 and 7. The drug dose in the figure of 10 % is arbitrary: as the actual dose itself plays only a minor role in the remaining drug effect, any small dose will cause approximately the same reaction as long as the body recognizes the drug. Generally speaking, when there exists tolerance to a substance, the effect of a small dose is limited to triggering the compensatory response, resulting in effects opposite to the normal drug effect.

SENSITIZATION AND OTHER PARADOXICAL EFFECTS

Fig. 3 shows that the large fall in drug effect in response to a decrease in dose is followed by a rise in drug effect during subsequent drug administrations. The reduction in drug dose in this figure has been chosen to obtain a large initial reduction in drug effect. However, any reduction in dose after tolerance has developed will be followed by a rise in drug effect until the organism has readjusted the magnitude of the compensatory response to correspond with the action of the new drug dose. This gradual increase in drug effect may explain cases of sensitization, a phenomenon whereby the drug effect increases during repeated administrations (Robinson and Berridge 1993; Everitt and Wolf 2002). Fig. 3 demonstrates the effect of abrupt changes in drug dose. As noted above, tolerance to a drug remains present for a long time. When a drug has not been administered over a certain period but tolerance has remained, or when innate tolerance exists, a dose different from the dose to which tolerance exists will result in a similar effect and may also be the origin of other paradoxical drug effects reported in the literature (Beasley *et al.*, 1991; Bauer 1996; George *et al.* 1997; Heisler and Tecott 2000; Wilens *et al.* 2003). It should be observed that neither sensitization nor opposite drug effects necessarily require tolerance to the administered drug as cross tolerance to a related drug may cause similar effects.

Besides the drug dose, the magnitude of the compensatory response also depends on other variables. The capacity of the body to suppress disturbances—in the model domain represented by the open loop gain of the regulation loop (Peper *et al.* 1988; Peper 2004b)—is of major importance. The latter parameter is not fixed but depends on health and age (Mitchell *et al.* 1970; Verveen 1978, 1983; Peper *et al.* 1987, 1988; Peper

2004a;). The consequence is that an individual's level of tolerance to a certain drug and the resulting drug effect may appear different in different situations. This may mimic changes in drug dose with the consequences discussed above and may be an additional cause of sensitization. Rather than a loss of tolerance (Miller 2000) this might then constitute a loss of the organism's ability to express an acquired tolerance.

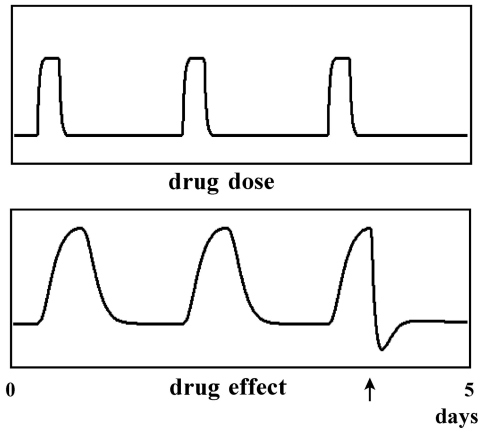

FIG. 9. Decrease in drug effect after the gain of the regulation loop is increased by 20 %.

In addition, the open loop gain may be affected by depressants and stimulants and even by the effect of the administration of the drug itself. Psychological factors, too, such as positive reinforcers may affect the open loop gain, causing changes in the drug effect (Fillmore and Vogel-Sprott 1999; Grattan-Miscio and Vogel-Sprott 2005). As holds for small changes in drug dose, small changes in the open loop gain can have large effects. This is demonstrated in Fig. 9, where at the instant indicated with the arrow, the gain of the regulation loop is increased by 20 %. There is an instant decrease in the drug effect and even an adverse effect temporarily appears. In the physiological regulation process, the gain is a distributed entity and the speed of change in the drug effect depends on where in the regulation loop a change in gain occurs.

DISCUSSION

"*People respond to food in the same way that they respond to exogenous drugs*" observed Woods in 1991 (Woods 1991). Yet the similarity he noticed has not led to a general realization that for the body there is no fundamental difference between food and other exogenous substances such as drugs: they all disturb bodily processes and as a consequence induce tolerance to their effect. In natural circumstances, exogenous substances enter the body through the mouth and the function of the gustatory system must be to recognize and analyse them before they can affect the functioning

of the body (Peper *et al.* 1988; Scott and Verhagen 2000; Peper 2004a). The notion that the gustatory system triggers a compensatory response when an exogenous substance is detected has been well established for glucose (Fischer 1972; Deutsch 1974; Steffens 1976; Louis-Sylvestre 1978; Grill *et al.* 1984; Dworkin 1993; Loewy and Haxhiu 1993).[5] Much of the research into the drug effect has been performed with intravenous drug administrations which bypass the oral detection mechanism. When an oral analysis of the substance is not available, the body uses environmental cues to trigger the tolerance mechanism. Although this has major disadvantages, demonstrated by for instance the potentially lethal consequences of a change in environment in addicted subjects (Siegel *et al.* 1982; Siegel 1999), the body is able to develop tolerance. For the problems identified above concerning the dose-response curve, the way in which the tolerance mechanism is triggered—directly by oral stimuli, or indirectly, by environmental cues—is of no relevance. Tolerance development will influence the dose-response relation, irrespective of how the tolerance mechanism is triggered.

Research into the effect of repeatedly administered drugs has been important and elucidating (Rescorla and Wagner 1972; Solomon and Corbit 1973, 1974; Tiffany and Baker 1981; Wagner 1981; Siegel *et al.* 1982; Baker and Tiffany 1985; Tiffany and Maude-Griffin 1988; Poulos and Cappell 1991; Dworkin 1993; Ramsay and Woods 1997; Heyne *et al.* 2000). Nevertheless, a lack of quantitative studies has meant a commensurate lack of clarity concerning important characteristics of the tolerance mechanism. The magnitude of the compensatory response, in particular, has remained obscure, while it is a major parameter in the overall drug effect. The magnitude of the compensatory response is based on the dose to which the organism is accustomed and not on the actual drug dose. This proposition was defended previously for the oral administration of exogenous substances, but it is also evident for intravenous drug administrations. When there is no oral stimulus, environmental cues remain as a trigger for the compensatory response. Information about the drug dose is not commonly part of a cue paired to a drug administration, nor can the body obtain this information physiologically in time to oppose the drug effect since injected drugs can exert their effect very rapidly. Drug-onset cues, where the body uses the onset of the drug effect as a trigger for the compensatory response, do not contain information about the dose either.

[5]In the reaction of the body to oral glucose, the immediate, orally triggered, insulin secretion is followed by a slow, extended insulin response which is related to the blood glucose level. In the mathematical model this kind of effect is not incorporated.

Consequently, there is no way for the body to acquire information about the actual drug dose and its only option seems to be to base its response on the dose it anticipates.

That the model of homeostasis—or negative feedback—cannot describe the effects of repeatedly administered drugs in a satisfactory way was extensively discussed in a previous paper (Peper 2004a). Feedback systems lack the capacity for learning, which is a vital tool in the development of tolerance to repeated drug administrations (Thorpe 1956, Siegel 1983, Peper *et al.* 1987). Learning is the domain of adaptive processes and in earlier work it was argued that the development of tolerance is an adaptive process (Peper *et al.* 1988; Peper 2004a, 2004b). Although adaptive processes generally also use feedback, they constitute a class of regulated processes essentially different from and much more complex than feedback processes and the two should be kept distinct.

The meaning of the concept of homeostasis often seems so stretched that it has become ambiguous (Toates 1979; Carpenter 2004). Usually it is merely meant to indicate that a certain process is regulated. Many models are based on homeostasis without proof that they will work in the assumed manner, as such models are rarely tested mathematically. Those mathematical models that have been developed commonly investigate a single disturbance only. Sometimes it is assumed that the homeostatic concept will work for repeated disturbances when the model is made up of complex combinations of feedback systems. However, no combination of feedback systems can describe the effects of repeated disturbances. Because feedback systems do not learn, every disturbance will evoke a similar reaction, as was discussed in previous research (Peper 2004a). Often qualities are attributed to homeostasis without proof that they satisfy the principles of control theory (Carpenter 2004; Woods and Ramsey 2007; Siegel 2008). As stated before (Peper 2004b): *'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 hypothesis underlying homeostasis—processes are kept at a steady state by feedback—has widespread support. However, although feedback can help to keep a process at a desired level, the open loop gain of physiological processes is very small (Peper 2004b) and its effect in dynamic forms of regulation will always be limited. In addition, a steady state is difficult to define. It depends on the deviations considered acceptable and on the accuracy of the measurement. When wide margins of accuracy are accepted, the statement is always true but loses significance.

An attempt to modify the model of homeostasis to account for its obvious shortcomings is the model of allostasis (Sterling and Eyer 1988;

Koob and Le Moal 2001; Ahmed *et al.* 2002; Schulkin 2003; Sterling 2004). Allostasis challenges the basis of homeostasis that processes function at a steady state and proposes that the goal of regulation is not constancy, but rather, 'fitness under natural selection' (Sterling and Eyer, 1988; Sterling 2004). 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' undoubtedly can play a significant role in the regulation of processes (Sterling 2004), 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 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 (Peper *et al* 1987, 1988, Peper *et al.* 1998; Peper 2004a), but the regulation of processes at any level is necessarily adaptive, from cell level up (Peper *et al* 1998).

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 (Taylor and Weibel, 1981). The concept of symmorphosis is however highly disputed (Garland and Huey, 1987; Bennet 1988; Dudley and Gans 1991; Diamond and Hammond, 1992; Alexander, 1998; Ricklefs, 1998; Harrison *et al.* 2001; Bacigalupe and Bozinovic 2002; Dudley *et al.* 2006). 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.[6] 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.

With regard to homeopathy, this paper does not go into the assumed curative effect of small doses. However, it does show that a small dose of a substance can cause reactions with symptoms opposite to the action of the drug in high doses, a phenomenon that lies at the basis of homeopathy. The small dose mentioned above does not refer to the infinitesimal dose or high "potency" homeopathic medicines. On the other hand, the

[6]Ahmed and Koob (2005) set out a quantitative model in which considerations are based on allostasis. The model is a homeostatic feedback system which controls the intravenous administration of cocaine in rats.

analysis shows that it is not the dose but the information about the presence of the substance that triggers the compensatory response.

CONCLUSION

On the basis of simulations with a previously published mathematical model of drug tolerance, the paper discusses different aspects of the relationship between drug dose and drug effect. The simulations show that tolerance developing during the measurement of a dose-response curve causes serious distortion of the curve. It is argued, furthermore, that the dose-response curve should not be used after the first dose of a drug as a curve cannot express the dynamic action of the tolerance mechanism.

The effect of a certain dose of a certain drug on an individual is difficult to predict as it depends on several very different parameters, such as the magnitude of the compensatory response, the level of tolerance, the subject's state of health and the history of drug administrations. The simulations show that a dose of a drug smaller than the quantity the body has tolerance to may generate symptoms opposite to the normal drug effect, indicating that a negative drug effect is a natural phenomenon. The only condition required to obtain a negative drug effect is that the drug action is smaller that the compensatory response. This situation can occur at any dose level, demonstrating that the relationship between the drug dose and drug effect is much more complicated than is generally assumed and can be captured in a curve.

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REFERENCES

Ahmed SH, Kenny PJ, Koob GF and Markou A. 2002. Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. Nature Neuroscience 5(7):625-626

Ahmed SH and Koob GF. 2005. Transition to drug addiction: a negative reinforcement model based on an allostatic decrease in reward function. Psychopharmacology 180(3):473-90

Alexander R McN. 1998. Symmorphosis and safety factors. In: Principles of Animal Design. The Optimization and Symmorphosis Debate. Weibel ER, Taylor CR and Bolis L (eds), pp 28-35. Cambridge: Cambridge University Press

Ali RE and Rattan SIS. 2006. Curcumin's biphasic hormetic response on proteasome activity and heat shock protein synthesis in human keratinocytes. Ann New York Acad Sci 1067:394-399

Baker TB and Tiffany ST. 1985. Morphine tolerance as habituation. Psychol Rev 92:78-108

Bacigalupe LD and Bozinovic F. 2002. Design, limitations and sustained metabolic rate: lessons from small mammals. J Exp Biol 205:2963–2970

Bauer J. 1996. Seizure-inducing effects of antiepileptic drugs: a review. Acta Neur Scand 94 (6): 367-77

Beasley Jr CM, Sayler ME, Bosomworth JC and Wernicke JF. 1991. Highdose fluoxetine: efficacy and activating-sedating effects in agitated and retarded. J Clin Psychopharmacol 11:166-174

Bennet AF. 1988. Structural and Functional Determinates of Metabolic Rate. Amer Zool 28:699-708
Bernard C. 1878. Leçons sur les Phénomènes de la Vie Communs aux Animaux et aux Végétaux. Bailliére et Fils, Paris, France
Calabrese EJ and Baldwin LA. 2001. The frequency of U-shaped dose-responses in the toxicological literature. Toxicol Sci 62:330-338
Calabrese EJ and Baldwin LA. 2003. A general classification of U-shaped dose-response relationships in toxicology and their mechanistic foundations. Hum Exp Toxicol 17:353-364
Cannon WB. 1929. Organization for physiological homeostasis. Physiol Rev 9:399-431
Carpenter RHS. 2004. Homeostasis: a plea for a unified approach. Advan Physiol Edu 28:S180-S187
Conolly RB and Lutz WK. 2004. Nonmonotonic Dose-Response Relationships: Mechanistic Basis, Kinetic Modeling, and Implications for Risk Assessment. Toxicol Sci 77:151-157
Deutsch R. 1974. Conditioned hypoglycemia: a mechanism for saccharin-induced sensitivity to insulin in the rat. J Comp Physiol Psychol 86:350-358
Diamond JM and Hammond KA. 1992. The matches, achieved by natural selection, between biological capacities and their natural loads. Experientia 48:51-557
Dudley R and Gans C. 1991. A critique of symmorphosis and optimality models in physiology. Physiol Zool. 64:627-637
Dudley R, Huey RB, and Carrier DR. 2006. Living History of Physiology: Carl Gans. Advan Physiol Educ 30:102-107
Dworkin BR. 1993. Learning and Physiological Regulation. Un of Chicago Press, Chicago
Everitt BJ and Wolf ME. 2002. Psychomotor stimulant addiction: a neural systems perspective. J Neurosci 22:3312-3320
Fillmore MT and Vogel-Sprott M. 1999. An alcohol model of impaired inhibitory control and its treatment in humans. Experimental and Clinical Psychopharmacology, 7, 49–55
Fischer U, Hommel H, Ziegler M and Jutzi E. 1972. The Mechanism of Insulin Secretion after Oral Glucose Administratio. III. Investigations on the Mechanism of a Reflectoric Insulin Mobilization after Oral Stimulation. Diabetologia 8:385-390
Garland T Jr and and Huey RH. 1987. Testing symmorphosis: does structure match functional requirements? Evolution 41:1404-1409
George DT, Benkelfat C, Rawlings RR, Eckardt MJ, Phillips MJ, Nutt DJ, Wynne D, Murphy DL and Linnoila M. 1997. Behavioral and neuroendocrine responses to m-chlorophenylpiperazine in subtypes of alcoholics and in healthy comparison subjects. Am J Psychiatry 154:81-87
Grattan-Miscio K and Vogel-Sprott M. 2005. Effects of alcohol and performance incentives on immediate working memory. Psychopharmacology 81:188-196
Grill HJ, Berridge KC and Ganster DJ. 1984. Oral glucose is the prime elicitor of preabsorptive insulin secretion. Am J Physiol 246:R88-R95
Harrison JF, Camazine S, Marden JH, Kirkton SD, Rozo A and Yang X. 2001. Mite not make it home: tracheal mites reduce the safety margin for oxygen delivery of flying honeybees. J Exp Biol 204(4):805-814
Heisler LK and Tecott LH. 2000. A paradoxical locomotor response in serotonin 5-HT2C receptor mutant mice. J Neurosci 20 RC71:1–5
Heyne A, May T, Goll P and Wolffgramm J. 2000. Persisting consequences of drug intake: towards a memory of addiction. J Neural Transm 107(6):613-638
Kalant H, LeBlanc AE and Gibbins RJ. 1971. Tolerance to, and dependence on, Some Non-Opiate Psychotropic Drugs. Pharmacol Rev 23(3):135-191
Kim JA, Siegel S and Patenall VR. 1999. Drug-onset cues as signals: intraadministration associations and tolerance. J Exp Psychol Anim Behav Process 25:491-504
Koob GF and Le Moal M. 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacol 24:97–129
Loewy AD and Haxhiu MA. 1993. CNS cell groups projecting to pancreatic parasympathetic preganglionic neurons. Brain Res 620:323-330
Louis-Sylvestre J. 1978. Relationship between two stages of prandial insulin release in rats. Am J Physiol Endocrinol Metab 235: E103-E111
Miller CS. 2000. Mechanisms of Action of Addictive Stimuli; Toxicant-induced loss of tolerance. Addiction 96(1):115-139
Mitchell D, Snellen JW and Atkins AR. 1970. Thermoregulation during Fever: Change of Set-Point or Change of Gain. Pflugers Archiv 321(4):393-302

Peper A, Grimbergen CA, Kraal JW and Engelbart JH. 1987. An approach to the modelling of the tolerance mechanism in the drug effect. Part I: The drug effect as a disturbance of regulations. J Theor Biol 127:413-426

Peper A, Grimbergen CA, Kraal JW and Engelbart JH. 1988. An approach to the modelling of the tolerance mechanism in the drug effect. Part II: On the implications of compensatory regulations. J Theor Biol 132:29-41

Peper A, Grimbergen CA, Spaan JAE, Souren JEM, and Van Wijk R. 1998. A mathematical model of the hsp70 regulation in the cell. Int. J. Hyperthermia, 14(1):97-124

Peper A and Grimbergen CA. 1999. Preliminary results of simulations with an improved mathematical model of drug tolerance. J Theor Biol 199:119-123

Peper A. 2004a. A Theory of Drug Tolerance and Dependence I: A conceptual analysis. J Theor Biol 229:477-490

Peper A. 2004b. A Theory of Drug Tolerance and Dependence II: The mathematical model. J Theor Biol 229:491-500

Poulos CX and Cappell H. 1991. Homeostatic theory of drug tolerance: A general model of physiological adaptation. J Abnorm Psychol 98:390-408

Ramsay DS and Woods SC. 1997. Biological Consequences of Drug Administration: Implications for Acute and Chronic Tolerance. Psychol Rev 104:170-193

Rescorla RA and Wager AR. 1972. A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and non-reinforcement. In: Black AH and Prokasy WF (eds), Classical Conditioning II: Current Research and Theory, pp 64-99. Appleton-Century-Crofts, New York

Ricklefs RE. 1998. The concept of symmorphosis applied to growing birds. In: Principles of Animal Design. The Optimization and Symmorphosis Debate. Weibel ER, Taylor CR and Bolis L (eds), pp 56-62. Cambridge: Cambridge University Press

Robinson TE and Berridge KC. 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 18:247–291

Schulkin J. 2003. Rethinking homeostasis: allostatic regulation in physiology and pathophysiology. MIT Press. Cambridge, Mass

Scott TR and Verhagen JV. 2000. Taste as a Factor in the Management of Nutrition. Nutrition 16:874-885

Siegel S, Hinson RE, Krank MD and McCully J. 1982. Heroin "Overdose" Death: Contribution of drug-associated environmental cues. Science 216:436-437

Siegel S. 1983. Classical conditioning, drug tolerance, and drug dependence. In Y Israel, F. B. Glaber, H. Kalant, R. E. Popham, W. Schmidt, & R. G. Smart (eds), Research advances in alcohol and drug problems: (Vol. 7, pp. 207-246). New York: Plenum

Siegel S and Allan LG. 1998. Learning and homeostasis: Drug addiction and the McCollough effect. Psychol Bull 124(2):230-239

Siegel S. 1999. Drug anticipation and drug addiction. The 1998 H. David Archibald lecture. Addiction 94(8):1113-1124

Siegel S. 2008. Learning and the wisdom of the body. Learn Behav 36(3):242-52

Sokolowska M, Siegel S and Kim JA. 2002. Intra-administration associations: Conditional hyperalgesia elicited by morphine onset cues. J Exp Psychol Anim Behav Process 28:309-320

Solomon RL and Corbit JD 1973. An Opponent-Process Theory of Motivation. II: Cigarette Addiction. J Abnormal Psychology 81:158-171

Solomon RL and Corbit JD. 1974. An Opponent-Process Theory of Motivation I: Temporal Dynamics of Affect. Psychol Rev 81:119-145

Steffens AB. 1976. Influence of the oral cavity on insulin release in the rat. Am J Physiol 230:1411-1415

Sterling P and Eyer J. 1988. Allostasis: a new paradigm to explain arousal pathology. In: Handbook of Life Stress, Cogintion and Health. Fisher S, Reason J, (eds), pp 629-649. New York, NY: J. Wiley & Sons.

Sterling P. 2004. Principles of allostasis: optimal design, predictive regulation, pathophysiology and rational therapeutics. In: Allostasis Homeostasis and the Costs of Adaptation. Schulkin J (ed), Cambridge University Press, Cambridge, England

Taylor CR and Weibel ER. 1981. Design of the mammalian respiratory system. I. Problem and strategy. Respir Physiol 44:1-10

Thorpe WH. 1956. Learning and instinct in animals. London: Methuen and Co

Tiffany ST and Baker TB. 1981. Morphine tolerance in rats: Congruence with a Pavlovian paradigm. J Comp Physiol Psychol 95:747-762

Tiffany ST and Maude-Griffin PM. 1988. Tolerance to morphine in the rat: associative and nonassociative effects. Behav Neuroscience 102(4):534-543

Toates FM. 1979. Homeostasis and drinking. Behav and Brain Sci 2:95-136.

Verveen AA. 1978. Silent endocrine tumors. A steady-state analysis of the effects of changes in cell number for biological feedback systems. Biol Cybern 31:49-54

Verveen AA. 1983. Theory of diseases of steady-state proportional control systems. Biol Cybern 47(1):25-31

Wagner AR. 1981. SOP: A model of automatic memory processing in animal behavior. In: Spear NE and Miller RR (eds), Habituation: Perspectives from child development animal behavior and neurophysiology, pp 5-47. Erlbaum, Hillsdale NJ

Wilens TE, Biederman J, Kwon A, Chase R, Greenberg L, Mick E and Spencer TJ. 2003. A systematic chart review of the nature of psychiatric adverse events in children and adolescents treated with selective serotonin reuptake inhibitors. J Child Adolesc Psychopharmacol 13(2):143-152

Woods SC. 1991. The Eating Paradox: How We Tolerate Food. Psychol Rev 98 (4):488-505

Woods SC and Ramsay DS. 2007. Homeostasis: beyond Curt Richter. Appetite 49(2):388-98