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An Approach to the Modeling of the Tolerance Mechanism in the Drug Effect. I: The Drug Effect as a Disturbance of Regulations

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In this paper the disturbing effect of drugs upon regulation in the organism is argued to be an important factor in the total drug effect. It is made plausible that the decrease of the drug effect after prolonged or repeated administration of the drug is caused by the adaptation of the involved regulations to the presence of the drug, the adaptive process being selective for the drug in question. A model based on these assumptions is developed taking into account the specific behaviour of regulated processes. The functioning of the model is investigated by means of computer simulations. The behaviour of the model appears to be well in accordance with the phenomenon of drug tolerance as described in literature.

1. Introduction

Drug tolerance is the decrease in the pharmacological action of a chemical substance (drug) upon a biological system after prolonged or repeated administration of the drug. Processes by which drug tolerance can occur are (Hug, 1972): the decrease of the concentration of the drug at the site of action (altered biological disposition), the decrease of responsiveness of the cells on which the drug acts (cellular mechanisms of tolerance), and the decrease of the response as a result of homeostatic mechanisms counteracting the response without acting on the drug action itself.

Processes which can be responsible for altered biological disposition are absorption, metabolism, excretion and distribution. A large number of drugs have the ability to stimulate the mechanisms responsible for their own metabolism in various tissues of the body (Bush, 1967; Axelrod, 1968) resulting in a decrease of the drug effect. The accelerated metabolism of the drug can be assumed to be caused by a regulating mechanism, tending to neutralize the drug action (Conney, 1967; Mannering, 1968; Watson, 1972).

In cellular mechanisms of drug action, the drug is assumed to act on special drug-sensitive elements on the cell surface called drug receptors. The formation of binding between drug and receptor is thought to trigger a series of events which lead to a pharmacological effect. In the receptor concept, several mechanisms have been proposed as being responsible for a diminished response after prolonged or

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repeated drug administration. Possible mechanisms are: a reduction of the number of active receptors available for interaction with the drug through a continued occupation by previously administered drug molecules (Ariens, 1964; Waud, 1968); a reduced affinity of the receptors for the drug or a reduced ability of the receptors to initiate the response (Rang & Ritter, 1969, 1970); a lowering of the concentration of the active drug by an increased binding to inactive receptors (Colier, 1965, 1969); the occupation of receptors with an antagonistic type of compound (Rang, 1969, 1970); the reduction of the affinity of the receptors for the drug by the action of an antagonistic—endogenous—substance which changes the structure of the receptor site (Ariens, 1964, 1966); a decrease of the number of functional receptors (Raffa & Tallarida, 1985) or, conversely, if the response of the drug is related to the proportion of the total number of receptors occupied by the drug, tolerance could arise from an increase in the total number of active receptors (Ford *et al.*, 1979*a,b*). All of these possible mechanisms except the first—where a passive mechanism is suggested—can be expected to be the outcome of a regulatory action counteracting the drug action (Collier, 1965; Goldstein & Goldstein, 1961, 1968; Kalant *et al.*, 1971; Bar, 1976; Hollenberg, 1985).

It appears that homeostatic regulation plays an important role in the development of drug tolerance and might be the essential factor. This assumption has been the basis of several models of drug tolerance developed in the past (Shuster, 1961; Goldstein & Goldstein, 1968; Martin, 1968; Jaffe, 1968; Kalant, 1971; Snyder, 1977). However, because the consequences of homeostatic regulation are not sufficiently worked out in these models, they are of limited significance. In the present paper, an approach to a more elaborate model of drug tolerance is made. The model is based on two assumptions. The first—discussed above—is that the decrease of drug effect after repeated administration is due to homeostatic regulation counteracting the drug effect. The second is that the development of tolerance to a certain drug is in essence an adaptive process of the organism, adapting itself to changed circumstances.

A feature common to most processes in a living organism is the property of self regulation. Biological processes exist in a continuous exchange of matter and energy with their environment. Because the environmental conditions of a biological process are changing continuously, regulation is essential to maintain the process, or the process output, at the appropriate level. However, although the effects of changes in the external conditions of a biological process on the course of the process are highly reduced in the long run by the process regulation, the short term disturbances they can induce can be considerable, as is demonstrated by the effect drugs can have on living organisms. If a regulated process in an organism has been disturbed by the action of a certain drug, there can be two possible ways this disturbance has come about: either the process is disturbed and the regulation has at that moment not been able to cope with this disturbance, or the regulation itself has been disturbed by the drug action. In either way, the occurrence of the disturbance is made possible by failure of the regulation process. It follows that when after repeated administration the effect of the drug action upon the process output decreases, the process regulation must be assumed to have partially regained its regulating function: it has adapted

itself to the changed conditions by changing the process parameters in such a way as to counteract the disturbance. From the observation that tolerant (but not addicted) subjects are little affected in the periods between drug action, it can be deduced that the adaptation mainly occurs at the time of drug action (this subject is further discussed in sections 2 and 3). Apparently, the process regulation is able to detect the presence of the drug and to time its reaction to the period of drug action; it "learns" to deal with the disturbance without the required adjustments having much consequence for its normal functioning. Seen this way, the development of drug tolerance, or more general habituation, is the learning process of the involved regulations in an organism adapting themselves to the drug action. This appears to be in accordance with the learning behaviour of living organisms as a whole, or as Thorpe puts it: "habituation is a simple learning not to respond to stimuli which tend to be without significance [. . .] which may be said to be one of the fundamental properties of living matter" (Thorpe, 1956). In which "simple" indicates the difference of this fundamental type of learning from the more complex learning behaviour described by Pavlov, Skinner etc., in which the learning behaviour is related to combined stimuli of different kinds. That more complex stimulus combinations can also play a role in drug tolerance will be shown in the subsequent paper. An extensive treatment of the different forms of learning behaviour in man and animal and the related cellular mechanisms in the nervous system is given by Kandel in his study of the nervous system of the marine snail *Aplysia californica* (Kandel, 1976).

2. The Model

A prominent property of a living organism is its capacity to regulate its processes. Regulation means that the effect of a process, the outcome or output, is sensed and compared in magnitude with the "desired" value (the reference value). If a deviation of the process output from the reference value occurs, a regulating or control mechanism is activated in order to change the process parameters in such a way as to decrease the output deviation in magnitude: the output of the process is maintained at the desired value by negative feedback.

Figure 1 shows a block diagram of a possible model of a regulated process. Information about the process output reaches the sensor of the regulating mechanism

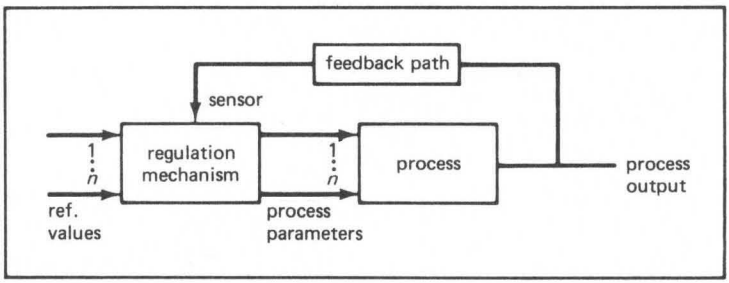

FIG. 1. Block diagram of a simplified model of a regulated process with *n parameters.*

via the feedback transmission path. The process regulator compares this information with the reference values at the reference input and adjusts the process parameters in order to optimize the process output. This model must be regarded as a highly simplified representation of processes in a living organism. The complexity of these processes is indicated to some extent by the number of process parameters and the corresponding reference values. In a further simplified model, of which a block diagram is shown in Fig. 2, the regulation of one single process parameter, based on one reference value, is described. The diagram shows how transport of information concerning the course of a process takes place and how disturbances in the information transfer influence the process regulation and the process output. If the components of the system are assumed to be linear and stationary, which is yet another simplification, the diagram of Fig. 2 can be redrawn as shown in Fig. 3. The output $O(t)$ can now be written as a function of the reference $R(t)$ and the transfer functions of the regulator C, the process P and the feedback element F

$$O(t)=\frac{R(t)CP}{1+FCP} \tag{1}$$

which equals

$$O(t)=\frac{R(t)}{F}\left[1-\frac{1}{1+FCP}\right]. \tag{2}$$

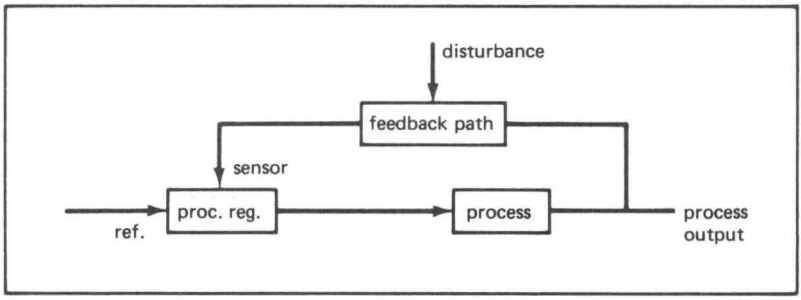

FIG. 2. Block diagram of the regulation of one process parameter showing how the transport of information concerning the course of a process takes place and how disturbances of the information transfer influence the process regulation.

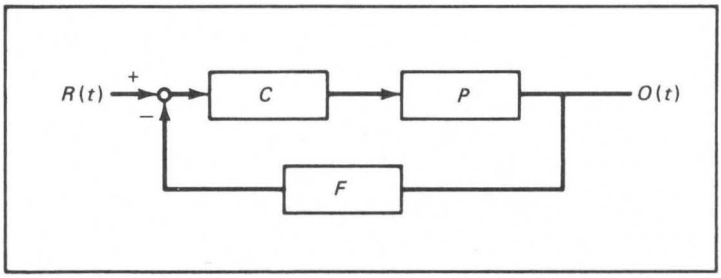

FIG. 3. The block diagram of Fig. 2 rearranged; the elements are assumed to be linear and stationary.

When CP is large, as is the case in most technical feedback systems, F directly determines the relation between $R(t)$ and $O(t)$. But also, when CP is small, which as we will see later is to be expected in many biological processes, F largely influences the process output.

In many regulations of biological processes, the path between the process output and the sensor input of the regulator is indirect, in the sense that information about the effect of the regulation is derived from other processes—the outputs of which are influenced by the output of the process in question. The feedback path in Fig. 2 may therefore be a complex of interconnected processes, in which the output of each process is a function of the output of the previous process (Verveen, 1978). Changes in these processes directly change the information transfer from the output of the process under investigation to the sensor input of its regulation mechanism. Expression (2) shows that the effect of disturbances in the direct path of the regulation loop (C and P) upon the process output is counteracted by the regulation, but that disturbances in the feedback path of the regulation (F) affect the process output directly, which means that the latter effect is the most prominent (Chestnut & Mayer, 1951). In the following, only disturbances in the feedback path will therefore be considered.

An obvious cause of disturbance of body function is drugs. The model developed so far suggests that it is not the direct action of drugs which necessarily causes these disturbances, but that a slight change in the feedback path between a certain process output and the sensor input of its regulation can cause major disturbances due to the disturbed process itself being a chain in the feedback path of other processes.

The severity of disturbances caused by drug action decreases when the administration of the drug is repeated (drug tolerance). To account for this phenomenon, we will base the further development of the model on an assumed learning faculty in the process regulation. Learning behaviour necessarily implies the detection of a "cause" and an "effect", and a memory for their nature and their characteristics. In the case of a biological process, it infers that the disturbing stimulus (the drug action) and the resulting disturbance in the process output are detected by the regulating system of the process and that, when the stimulus occurs again, measures are taken by the process regulation to reduce the effect of the stimulus on the process output.

Learning abilities are difficult to incorporate in a model like the one described above. Our approach will be to furnish an adaptive regulator with the desired qualities and then describe its behaviour as accurately as possible in its separate functions. It is assumed that the adaptive regulator determines the level of the reference for the primary process regulation as shown in Fig. 4. The adaptive regulator bases the instantaneous value of this reference on information it obtains about the process output and the disturbing stimulus. The dotted line between the disturbance and the adaptive regulator indicates that it is only information concerning the presence and the nature of the disturbing stimulus which is transmitted here (this point is further discussed in the subsequent paper). The adaptive regulator will link the information about the presence of the disturbing stimulus with the resulting disturbance in the output of the process and "memorize" the fact that they

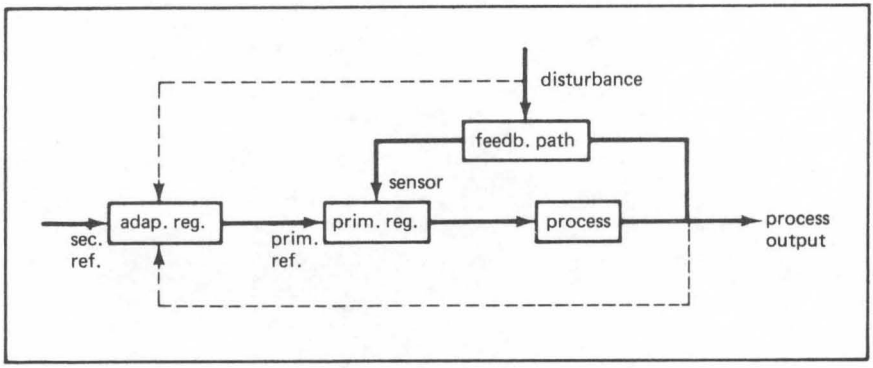

FIG. 4. Adaptive regulation added to the regulated process. The adaptive regulation determines the value of the primary reference. It bases its regulation on information from the process output and the disturbing stimulus.

are related for future use. When the same stimulus occurs again, the adaptive regulator will react by adjusting the reference value of the disturbed process to lessen the disturbance in the process output. From eqn (2) it can be seen that the effect on the process output of a disturbance in the feedback path can be compensated by an adjustment of the reference value. For the detection of a disturbance in the process output, the adaptive regulator needs its own "model" of the course of the process, which is here provided by a second reference. The information path between the process output and the adaptive regulator is represented by a dotted line which indicates that its nature is not discussed here.

When the stimulus is repeated regularly, the adaptive regulator will gradually learn to adjust the process reference in such a way as to minimize the total disturbance of the process output. It is assumed that the activity of the adaptive regulator can be divided into two components: a fast component which reduces the immediate effect of the disturbance in the output of the process, and a slow component which minimizes the magnitude of the error in the process output in the long run and which anticipates frequently occurring stimuli.

3. Regulation Error

In Fig. 5, the result of a computer simulation of the effect of a periodically recurring disturbance in the feedback path of the model is shown. The computer program used for the simulation is discussed in the appendix. Figure 5 shows that the disturbance at the sensor input is compensated by an increasingly accurate adjustment of the primary reference value, resulting in a decrease of the disturbance in the process output. An additive stimulus at the sensor input of the process regulator is used as a disturbing cause. In reality, the stimulus may occur everywhere in the feedback path, and may be additive as well as multiplicative. The compensation of the change in the transfer function of the feedback path by a correction of the reference value is a choice. Compensation could also have been effected in the

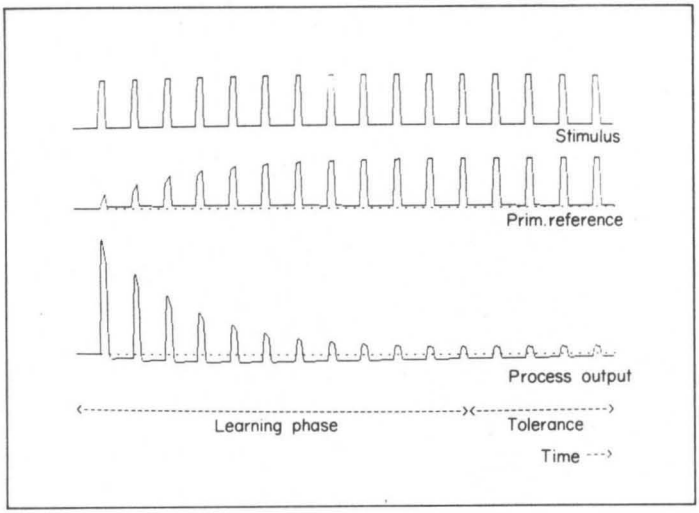

FIG. 5. The result of a computer simulation of the effect of a periodic recurring disturbance in the feedback path of the model. The disturbance at the sensor input is compensated by an increasingly accurate adjustment of the reference value, resulting in a decrease of the disturbance in the process output.

feedback path itself (Verveen, 1978), as is the case in those models of receptor theory where the effect of a disturbance is counteracted at the site of action. The present form of the model is chosen because it shows more distinctly the different properties of the regulating components and because implementation in a computer program is straightforward. Figure 5 shows that although the suppression of the disturbance in the process output increases in time, it does not become complete. This is due to the regulation error of the fast regulation. A regulation error is present in every regulated system. Its magnitude depends largely on the open loop gain of the regulation loop (*FCP* in eqn (1)). Because the open loop gain directly affects the stability of the regulation, it can be expected to be small in fast biological processes where a high number of processes are coupled and interlinked. Fast high-order regulation loops can be kept stable only when the open loop gain is kept small because of the different delays in the individual parts of the system. A small open loop gain has as a consequence that the error in the regulated process is large. Although these considerations are derived from linear system theory, they can not be expected to be essentially different in the case of biological processes. The error of the slow regulation can be assumed to be small because stability is much less involved here than in the fast regulation.

In Fig. 5 it can also be seen that the gradually improving suppression of the disturbance in the process output is accompanied by an effect in the opposite direction following the remainder of the disturbance: the initial rise of the output level during the stimulus is followed by a drop of the level to below normal after the stimulus. This effect agrees with the "reaction" following the action of a drug: the drug effect is followed by symptoms showing opposite chracteristics (Jaffe &

Sharpless, 1968; Seevers & Deneau, 1968; Kalant, 1971; Snyder, 1977). This effect can be clearly observed in drug dependence where the reaction is so dominating that the drug effect is used to counteract its symptoms (Seevers, 1968). In the model the reaction is caused by a shift of the base line of the signal at the adaptive regulators output. This shift is a consequence of the, especially initially, imperfect regulation of the fast regulation component, by which only a limited compensation of the disturbance in the process output is obtained and which at the same time prevents a complete return to the pre-disturbance level. In the long run, the shift is determined by the slow regulation component which minimizes the output error by regulating the average of the output signal equal to the level of the secondary reference. This is illustrated in Fig. 6(a), which shows the part of the signal of Fig. 5 in which tolerance has been effected, and the signal which evolves if the stimulus repetition

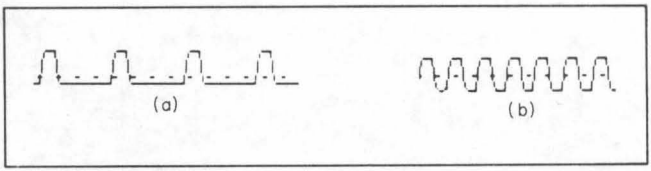

FIG. 6. The output signal after tolerance has been effected. The disturbances at the process output are followed by reactions (the part of the signal under the base line) of which the magnitude is determined by the repetition rate of the stimulus. (a) A low stimulus repetition rate causes low reactions. (b) A high stimulus repetition rate induces large reactions.

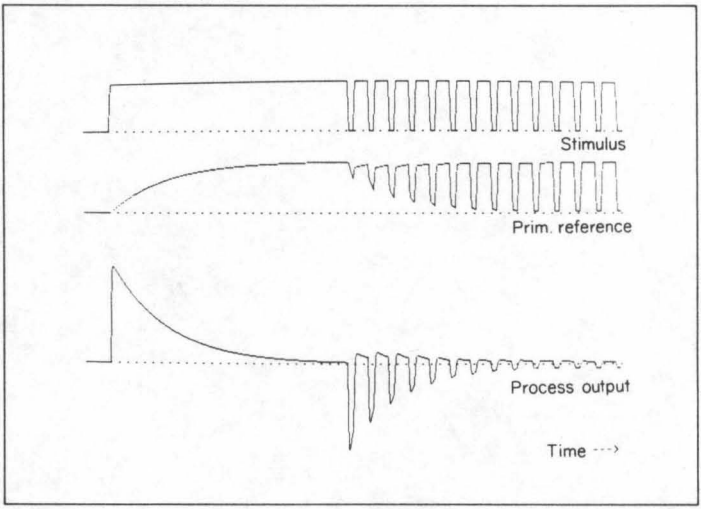

FIG. 7. Illustrations of the consequences of adaptive regulation: in the case of a long lasting stimulus the primary reference signal will after a while approach the new signal level at the sensor input. This level then becomes the base line for the regulation. Interruptions of the permanent stimulus are now new, negative, stimuli, the suppression of which will increase in time.

rate is increased (Fig. 6(b)). The repetition rate of the stimulus appears to determine the magnitude of the reaction.

The consequences of adaptive regulation are further elucidated with the result of the computer simulation of Fig. 7. It shows that in case of a long lasting stimulus the primary reference signal will, after a while, approach the signal level at the sensor input. This level then becomes the new base line for the regulation. Interruptions of the permanent stimulus are now new—negative—stimuli, the suppression of which will increase in time as described above. Figure 7 demonstrates that negative reactions are inherent to adaptive regulation. Adaptive regulation implies that there exists no fixed reference. A repeated stimulus will cause the process reference to shift in the direction of the stimulus, with the consequence that part of the stimulus will become negative with respect to the reference level, resulting in a negative effect in the process output.

4. Discussion

A model of drug tolerance has been developed which is in accordance with the behaviour of regulated processes and which covers important features of the effect of drug action upon processes in living organisms. It describes the decreasing effect of a recurring stimulus (drug administration) on biological processes. Its functioning is "drug selective" in that it suppresses the effect of recurring stimuli without the involved processes being much affected in the periods between the stimuli if the repetition rate of the stimulus is low, and it shows a marked reaction in the periods between the stimuli in case of a high stimulus repetition rate.

The essence of the model is that it combines a fast selective regulation component which minimizes the effect of disturbing stimuli of short duration, with an integrative slow regulation component which minimizes the disturbances over a long period. The combination of these two, in essence simple regulations, must be regarded as the minimum configuration able to describe the basic characteristics of the process of drug tolerance as described above. That the selective regulation is essential for the model is demonstrated in the result of the computer simulation shown in Fig. 8(a) in which the fast regulation component is omitted from the model. The effect of the remaining slow regulation, which resembles a normal homeostatic process regulation, is not the suppression of the disturbance in the output signal, but a drift of the baseline of the output signal to the average level. Reduction of the time constant of the regulation does improve the suppression of the stimulus, but lowers the after effect with the consequence that all stimuli are suppressed to the same degree (Fig. 8(b)), which is not in agreement with the phenomenon of drug tolerance. The effect of omitting the slow regulation component from the present model is that, when tolerance has been accomplished, the magnitude of the reaction after the stimulus will equal the magnitude of the stimulus component in the output signal, irrespective of the repetition rate of the stimulus (Goldstein, 1968; Martin, 1968; Kalant, 1971; Snyder, 1977). In reality, the reaction of the organism after the drug action is highly dependent on the frequency of administration: sporadic use of drugs will not give large reactions in tolerant subjects, while a high repetition

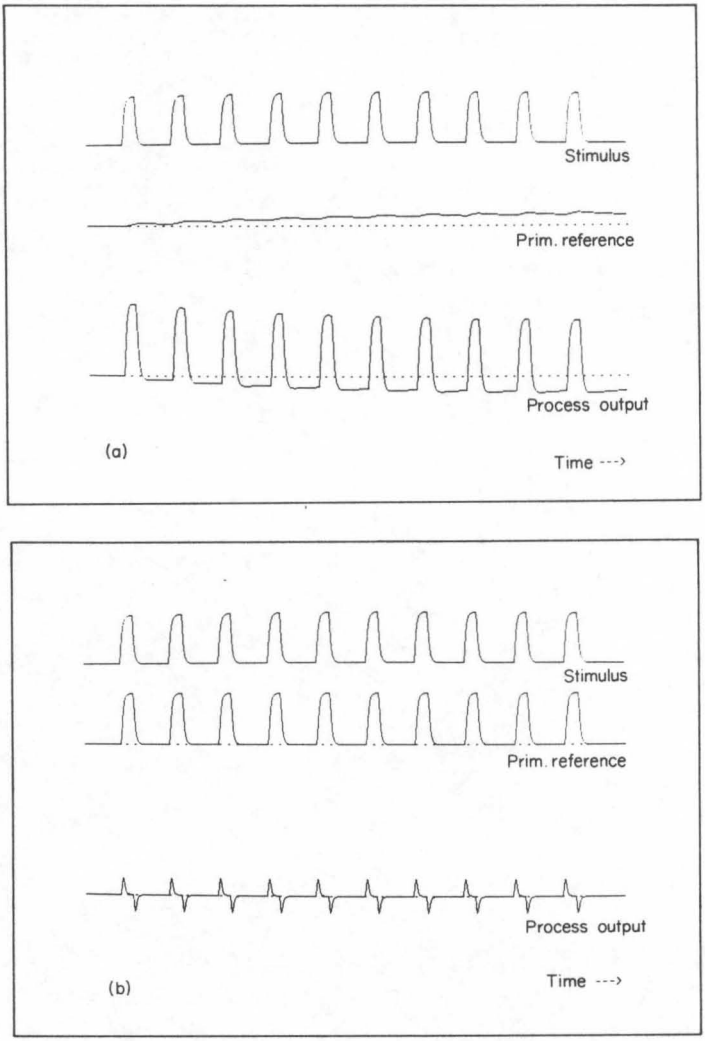

FIG. 8. The resulting signals if the fast adaptive regulation is omitted from the model. The effect of the remaining slow regulation, which resembles a normal homeostatic process regulation, is not the suppression of the disturbance in the output signal, but a drift of the baseline of the output signal to the average level (a). Reduction of the time constant of the regulation does improve the suppression of the stimulus, but lowers the after effect with the consequence that all stimuli are suppressed in the same degree (b), which is not in agreement with the phenomenon of drug tolerance.

rate leads to drug dependence with marked reactions. In the subsequent paper, drug dependence will be further discussed, as well as the dose-response relation and mechanisms underlying the initiation of the stimulus selective fast regulation. Of the latter subject, the relation with withdrawal symptoms and other reactions of the organism will be established.

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APPENDIX

Figure A1 shows a block diagram of the model as it is implemented in the computer program. D is the disturbance (stimulus), R_1 is the primary reference, R_2 is the secondary reference and O_p is the process output (see Fig. 4). The elements of the diagram are expressed as functions of the complex Laplace operator s (Chestnut & Mayer, 1951; Truxal, 1955; Tompkins & Webster, 1981). The primary process is simulated by an integrator: K_p/s. If the feedback loop is closed via the transmission

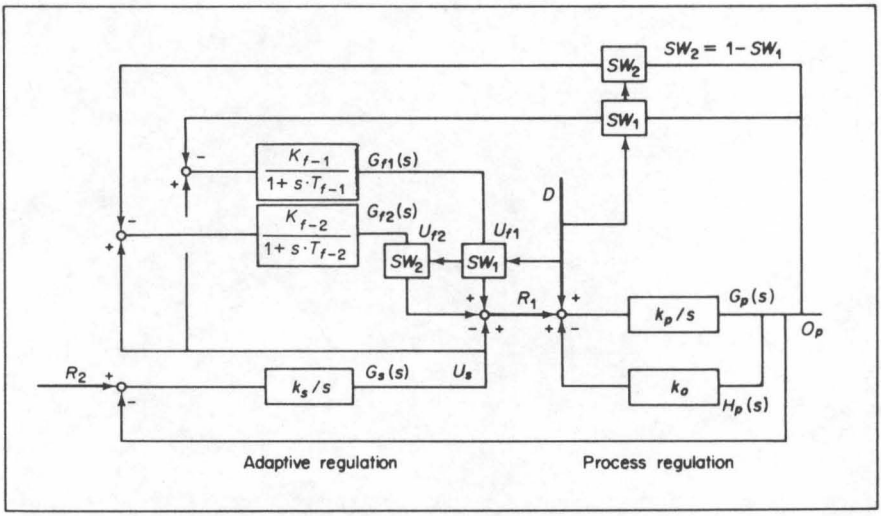

FIG. A1. Block diagram of the model as it is implemented in the computer program. $G_p(s)$ represents the process with a feedback element $H_p(s)$; $G_s(s)$ represents the slow adaptive regulation and $G_{f1}(s)$ and $G_{f2}(s)$ represent the elements of the fast adaptive regulation, for the stimulus on and off respectively. The disturbance D is situated at the sensor input of the process.

path K_o, the transfer function of the primary process obtains the form: $K_p/(s+K_pK_o)$, yielding a high frequency cut-off point of K_pK_o (radians/sec) and an amplification of $1/K_o$. The slow adaptive regulator has been simulated by an integrator of the form K_s/s. Because both the disturbances and the intervals between the disturbances must be regarded as separate stimuli (see section 3), the fast adaptive element is split into two separately switched elements; one active during the stimulus, being switched on at the on-going slope of the stimulus, the other active during the interval, being switched on at the off-going slope of the stimulus.

To express the transfer function of the complete adaptive regulation, the two switched elements are represented by one continuously acting element of the form $K_f/(1+s\,.\,T_f)$, which has a high frequency cut-off point of $1/T_f$ and an amplification K_f. The fast adaptive regulation has the output of the slow regulation as reference. This signal serves as an approximation of the changing reference during the adaptive process. If the time constant of the regulated primary process $1/K_pK_o$ is assumed to be much smaller than the time constants of the adaptive regulation, and if for convenience K_o is taken to equal unity, the transfer function of the primary process can be taken to be 1 for the derivation of the transfer function of the adaptive regulation. The process output O_p is now given by the relation (see Fig. A1)

$$O_p = R_1 + D = U_s + U_f + D \tag{A1}$$

in which U_s and U_f represent the output signal of the slow and the continuously acting fast adaptive element respectively. Because

$$U_s = (R_2 - O_p)\,.\,K_s/s \tag{A2}$$

and

$$U_f = (U_s - O_p)\,.\,K_f/(1+s\,.\,T_f) \tag{A3}$$

the output becomes

$$O_p = (R_2 - O_p)\,.\,K_s/s + (((R_2 - O_p)\,.\,K_s/s) - O_p)\,.\,K_f/(1+s\,.\,T_f) + D. \tag{A4}$$

If the reference value R_2 is assumed to be zero, the transfer function of the stimulus D to the output, $G_{DO}(s)$, is given by

$$G_{DO}(s) = \frac{1}{1 + K_s/s + K_sK_f/(s\,.\,(1+s\,.\,T_f)) + K_f/(1+s\,.\,T_f)} \tag{A5}$$

$$G_{DO}(s) = \frac{s^2 + s/T_f}{s^2 + s\,.\,(K_sT_f + K_f + 1)/T_f + K_s(K_f+1)/T_f}. \tag{A6}$$

Substitution of $C_f = (K_f+1)/T_f$ yields

$$G_{DO}(s) = \frac{s^2 + s/T_f}{s^2 + s\,.\,(K_s + C_f) + K_sC_f} \tag{A7}$$

which equals

$$G_{DO}(s) = \frac{s^2 + s/T_f}{(s+K_s)(s+C_f)} \tag{A8}$$

```
130      FOR N = 1 TO NMAX
250 US = (R2 - O) * KS + US
260 SW1 = Ø : IF D = DMAX THEN SW1 = 1
270 SW2 = 1 - SW1
280 TF1 = TF * COEF : TF2 = TF * (1 - COEF)
290 EXP1 = EXP(-T/TF1) : IF SW1 = Ø THEN EXP1 = EXP(-T/TF1*KA)
300 EXP2 = EXP(-T/TF2) : IF SW2 = Ø THEN EXP2 = EXP(-T/TF2*KA)
310 UF1 = (US - O * SW1) * KF * (1-EXP1) + EXP1 * UF1
320 UF2 = (US - O * SW2) * KF * (1-EXP2) + EXP2 * UF2
330 R1 = US + UF1 * SW1 + UF2 * SW2
340 O = (R1 + D - O * KO) * KP + O
370      NEXT N
```

FIG. A2. The relevant lines from the computer program, written in BASIC (see text). Readers who are interested in the complete program are invited to contact the authors.

which can be represented by the sum of partial fractions (Chestnut & Mayer, 1951; Courant, 1957)

$$G_{DO}(s) = 1 + \frac{C_1}{s+K_s} + \frac{C_2}{s+C_f} \tag{A9}$$

in which $C_1 = (K_s^2 - K_s/T_f)/(C_f - K_s)$ and $C_2 = (C_f^2 - C_f/T_r)/(K_s - C_f)$. The impulse response is now obtained by taking the inverse Laplace transformation (Chesnut & Mayer, 1951; Spiegel, 1965)

$$G_{DO}(t) = C_1 \,.\, \mathrm{e}^{-t.K_s} + C_2 \,.\, e^{-t.C_f}. \tag{A10}$$

Expression (A10) shows time constants of $1/K_s$ and $1/C_f = T_f/(K_f+1)$ for the slow and the fast adaptive elements respectively. To obtain the time constants of the two separately switched elements of the fast adaptive regulation in the computer program, the term $T_f/(K_f+1)$ has to be multiplied with the stimulus-interval coefficient COEF and 1-COEF (see Fig. A2).

For the program, the expressions in s are transformed into expressions in Z (Jury, 1964; Tompkins & Webster, 1981). For an integrator of the form K/s, transformation into the Z-domain yields $K/(1-Z^{-1})$ and a difference equation $Y_{(n)} = K \,.\, X_{(n)} + Y_{(n-1)}$. A high-pass filter of the form $K/(s+a)$ becomes $K/(1-e^{-aT} \,.\, Z^{-1})$ with a difference equation $Y_{(n)} = K(1-e^{-aT}) \,.\, X_{(n)} + e^{-aT} \,.\, Y_{(n-1)}$, in which $(1-e^{-aT})$ is a scaling factor and T the time span between the computed events. In Fig. A2, the relevant lines from the program are shown, written in BASIC for convenience. The calculation of the output signal is executed in a loop of NMAX points. In line 250, the integrative function of the slow adaptive regulator is performed. Line 290 and 300 determine the constants for the two elements of the fast adaptive regulation, which functions are performed in line 310 and 320. During the periods these elements are switched off, their output signal UF1 and UF2 decreases with a time constant which is a factor *KA* larger than the "learning" time constant, to account for the—slow—decrease of adaptation during interruption of drug administration (see line 290 and 300). In line 330, the reference signal for the primary process R1 is formed and in line 340 the output signal of the primary process is computed.