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Compartmental Models of Immunological Tolerance

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An administration of large doses of an antigen brings about immunological tolerance (unresponsiveness) to the next challenge with the same antigen. A hypothesis on the mechanism of tolerance to Human Serum Albumin (HSA) induced in chickens was formulated mathematically using compartmental models. By comparison of the modelled and experimental results, the presence of some additional mechanism was demonstrated.

1. INTRODUCTION

An antigen (molecules which differ in structure from the body's own constituents) elicits an immune response. Under natural conditions, the immune response is accomplished by the cooperation of all the immune mechanisms established during the development, viz., phagocytosis (effected by macrophages), specific cellular response (*T* lymphocytes), and antibody response (*B* lymphocytes)[1]). Thus macrophages and *T* helper cells take part in the initiation of the antibody response and *T* suppressor cells in its regulation. In some cases, however, the antibody response can be elicited by the direct binding of the antigen to the specific receptors on immunocomponent *B* cells. If an optimum dose of antigen is administered, these cells are triggered by the antigen into clonal expansion, antibody production, and formation of memory cells which ensure a more effective secondary response if the repeated encounter with the same antigen occurs (this is the principle of vaccinations).

On the other hand, a very large amount of antigen can induce tolerance, i.e. unresponsiveness to the next challenge, instead of immunity. The mechanisms of

[1]) Lymphocytes as well as other blood cells rise by differentiation of stem cells. *T* lymphocytes pass through the thymus, *B* lymphocytes of birds are "educated" in the bursa of Fabricius (so far it is not known which organ exerts the function of the bursa in mammals).

tolerance are diverse (e.g., inactivation or elimination of immunocompetent cells, terminal differentiation of immunocompetent cells into antibody-forming cells without memory formation, suppression of reactive cells by suppressor *T* cells) and they act at various levels. The tolerance induction is of great importance in preventing the rejection of the transplant by the immune reaction or in the treatment of autoimmune diseases when the immune system fights the tissues of the body itself. (For an introduction to immunology see, e.g., Roitt [18].)

Tolerance to Human Serum Albumin (HSA) induced in chickens early after hatching seems to differ in some aspects from tolerance to heterologous proteins in mammals [13]. In mammals, tolerance in the *T* cell population effects the inhibition of the immune reaction to the tolerated antigen even when the *B* cells of the tolerant animal recover their ability to produce antibodies against that antigen. Thymectomy delays in mammals the escape from tolerance to serum proteins. Thymectomy in chickens tolerant to HSA influenced neither the duration nor the degree of the suppression of the anti-HSA antibody formation [1]. On the other hand, when tolerant chickens were bursectomized after hatching, the inhibition of the anti-HSA antibody production was in these chicknes much deeper and longer lasting than in intact tolerant chickens [8]. The relatively short duration of tolerance to HSA in chickens is similar to the kinetics of *B* cell tolerance to heterologous proteins in mammals. Up to now, we have been unable to detect active suppressor mechanisms operative in chickens tolerant to HSA-see Hraba et al. [8, 9].

These findings together with the finding of other authors that the chicken antibody response to HSA is relatively thymus independent [10], led us to the conclusion that the decisive mechanism in this tolerant state is an inhibition at the *B* cell level. Our earlier findings [7] suggested that the inhibition of the anti-HSA antibody formation induced in adult chickens by a single or repeated administration of large doses of HSA resulted from the interaction of an excess of the antigen with the immune machinery at two levels corresponding possibly to two types of cells. Taking into account the findings of other authors [2, 14, 15] that it is easier to induce tolerance in less mature *B* cells than in more mature ones, we have attempted to explain tolerance to HSA induced in chickens early after hatching simply by postulating two compartments of short-lived *B* cells differing in their tolerance inducibility: immunocompetent (X) cells and their immediate precursors – immature (I) cells.

The maturation both of I cells from stem cells and of X cells from I cells is a spontaneous, antigen independent process. It is assumed that contacts with an excess of the antigen cause the terminal differentiation or inactivation of X cells and the elimination of I cells having receptors specific for the antigen and that both X and I cells do not divide.

Parameters of the model are the following:

S ... rate of appearance of new I cells due to differentiation of stem cells,
T_1 ... maturation time of I cells,
T_2 ... lifetime of X cells,
$a(t)$ ... rate of elimination of X cells due to contacts with an excess of the antigen; it is proportional to the amount of antigen available at time t,
$M\,a(t)$ ... similar function for I cells; $M > 1$ as I cells are more susceptible to elimination than X cells.

The two investigated compartments of I and X cells together with parameters and parameter functions governing the irreversible transitions to and from compartments

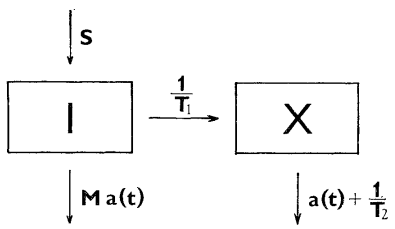

Fig. 1. Compartments of I and X cells with transition rates.

are illustrated in Fig. 1. Like Jílek and Šterzl in [11], we have chosen, in the case of one dose of antigen,

$$a(t) = \alpha e^{-\beta t}, \tag{1}$$

where α is proportional to the amount of antigen injected and β characterizes the rate of its nonimmune elimination.

In accordance with the theory of compartments (see, e.g., Rescigno and Beck [17]) the following system of ordinary differential equations was employed to describe the time course of the I and X compartment sizes:

$$\frac{\mathrm{d}\,I(t)}{\mathrm{d}t} = S - \frac{I(t)}{T_1} - M\,a(t)\,I(t), \tag{2}$$

[1]) This part was originally presented and discussed at the Avian Immunology Section of the 18th International Symposium on Laboratory Animals in Hrubá Skála, 1979 — see Klein et al. [12].

$$\frac{\mathrm{d}X(t)}{\mathrm{d}t} = \frac{I(t)}{T_1} - \frac{X(t)}{T_2} - a(t)\,X(t)\,,$$

with the initial conditions $I(0) = I_0$, $X(0) = X_0$.

The assumed antigen independence of the rate of differentiation of stem cells makes it possible to determine S from the steady state (in the absence of antigen) when a relatively constant number X_E of X cells is maintained [11]. It can be easily derived that $S = X_E/T_2 = I_E/T_1$, where I_E is the number of I cells in the steady state.

In the language of system theory I and X represent the state of the system (2), while a is the input, with the aid of which one can control the system in question. Moreover, the differential equations (2) describe a rather special type of dynamical systems, the so-called bilinear system. Because of this many general results concerning bilinear systems apply to (2). For instance the special form of $a(t)$ used, as given by (1), guarantees the existence and uniqueness of solutions for the system (2) for any finite time interval. This is also true when more doses of antigen are used.

The system of differential equations (2) was solved numerically on the hybrid system EAI PACER 600 using a special simulation language SIMFOR [4]. We fixed X_E at 100 and investigated the sensitivity of the system to changes in parameters T_1, T_2, α, M, X_0, I_0, $\beta = 0.03$ for HSA. The assumption that a high dose of HSA exhausts nearly all X cells affects the choice of the parameter α and brings about insensitivity of the modelled response to the choice of initial values and M in the range of high doses of antigen. For the sake of simplicity, we can thus suppose that chickens have no mature immunocompetent cells at hatching.

From the very scarce data available, we can estimate that the renewal of the full immune responsiveness after the exhaustion of cells by a high dose of HSA in newly hatched chickens occurs in about 12 weeks. As there is no experimental material concerning the time parameters T_1 and T_2, we have used this estimate to find suitable values of these parameters. Then we have tried to simulate the following experimental situation: the chickens were rendered tolerant by four doses of HSA (100 mg each) on days 1, 5, 8, 13 after hatching (Fig. 2). The development of I and X population

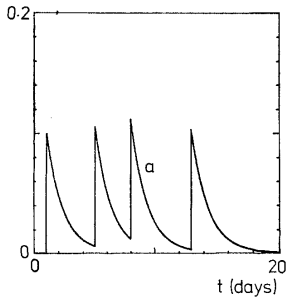

Fig. 2. Clearance of four successive doses of HSA from the circulation: $\alpha_i = 0{\cdot}1$, $i = 1, \ldots, 4$; for HSA with the halftime of decay 24 hrs $\beta = 0{\cdot}03$.

sizes – their exhaustion and subsequent replacement – is shown in Fig. 3. The relation of modelled curves to experimental results is discussed in Section 4.

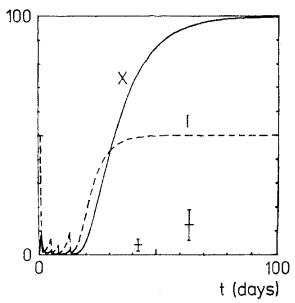

Fig. 3. The deterministically modelled number of I (dashed line) and X (full line) cells together with experimental means and standard errors (from 23 and 6 data, respectively) of percent immune responsiveness (4 ± 3, 14 ± 7). Parameters of the model: $X_0 = 0$, $X_E = 100$, $I_0 = I_E = 50$, $\alpha = 0{\cdot}1$, $M = 5$, $T_1 = 6$ and $T_2 = 12$ days, $\beta = 0{\cdot}03$.

3. STOCHASTIC MODEL

Recently, a stochastic theory of compartments has been developed – see Cobelli and Morato [5] for a survey. Let us now reformulate our model in probabilistic terms and use formulae derived by other authors to find mean value functions and covariance function of our process.

Let $I(t)$ and $X(t)$ be random variables denoting the compartment sizes at time t. Transition rates are deterministic and the same as in the previous model (see Fig. 1). We assume that the cells behave independently of one another.

If $I(t) = m$ and $X(t) = n$, then the probability $P_{ij}(t, t + h)$ that a single cell moves from a compartment i to a compartment j in the time interval $(t, t + h)$ is as follows:

$$P_{OI}(t, t + h) = Sh + o(h),$$

$$P_{IX}(t, t + h) = \frac{m}{T_1} h + o(h),$$

$$P_{IO}(t, t + h) = mM\, a(t)\, h + o(h),$$

$$P_{XO}(t, t + h) = n\left[\frac{1}{T_2} + a(t)\right] h + o(h),$$

where O stands for the exterior of the system. The probability of more than one cell moving from one compartment into another in $(t, t + h)$ is $o(h)$.

Formulae for $\mathrm{E}\, I(t)$, $\mathrm{E}\, X(t)$, $\mathrm{var}\, I(t)$, $\mathrm{var}\, X(t)$, $\mathrm{cov}\,[I(t), X(t)]$ were derived simultaneously by Purdue [16], who employed the queuing theory, and by Cardenas and Matis [3], who used the joint moment generating function of $[I(t), X(t)]$.

It was already mentioned in the preceding section that in the range of high doses of antigen the model is very little sensitive to changes in M. Therefore we can put $M = 1$ in order to avoid computational difficulties.

There is (according to [3]):

$$\begin{aligned}
\mathrm{E}\, I(t) &= I_0\, p_{11}(t) + d_1(t)\,,\\
\mathrm{E}\, X(t) &= X_0\, p_{22}(t) + I_0\, p_{12}(t) + d_2(t)\,,\\
\mathrm{var}\, I(t) &= I_0\, p_{11}(t)\,[1 - p_{11}(t)] + d_1(t)\,,\\
\mathrm{var}\, X(t) &= I_0\, p_{12}(t)\,[1 - p_{12}(t)] + X_0\, p_{22}(t)\,[1 - p_{22}(t)] + d_2(t)\,,\\
\mathrm{cov}\,[I(t), X(t)] &= -I_0\, p_{12}(t)\, p_{11}(t)\,.
\end{aligned}$$

In our case,

$$\begin{aligned}
p_{11}(t) &= \exp\,[-A(t) - ut]\,,\\
p_{12}(t) &= \frac{u}{v-u}\,\{\exp\,[(v-u)\,t] - 1\}\exp\,[-A(t) - vt]\,,\\
p_{22}(t) &= \exp\,[-A(t) - vt]\,,\\
d_1(t) &= S\exp\,[-A(t) - ut]\int_0^t \exp\,[A(\tau) + u\tau]\,\mathrm{d}\tau\,,\\
d_2(t) &= \frac{Su}{v-u}\exp\,[-A(t) - vt]\left\{\exp\,[(v-u)\,t]\int_0^t \exp\,[A(\tau) + u\tau]\,\mathrm{d}\tau - \right.\\
&\left. - \int_0^t \exp\,[A(\tau) + v\tau]\,\mathrm{d}\tau\right\},
\end{aligned}$$

where

$$A(t) = \int_0^t a(\tau)\,\mathrm{d}\tau\,, \quad u = 1/T_1\,, \quad v = 1/T_2\,.$$

Similarly like in the deterministic model and with the same result, S can be determined from the steady state when $\mathrm{E}\, I(t) = I_E$, $\mathrm{E}\, X(t) = X_E$ (see also Getz [6] and Purdue [16]).

The formulae for the experimental scheme described above were again simulated numerically (Fig. 4). Asymptotically, $I(t)$ and $X(t)$ are independent and Poisson distributed [16]. In our case, from day 8 on, with the accuracy 10^{-4}, $\mathrm{E}\, I(t) = \mathrm{var}\, I(t)$,

$E\,X(t) = \text{var}\,X(t)$, $\text{cov}\,[I(t), X(t)] = 0$. It is natural that the mean value functions (Fig. 4) are very similar to their deterministic counterparts (Fig. 3).

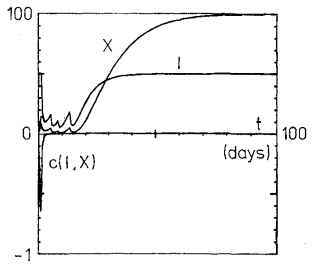

Fig. 4. Simulation of characteristics of $[I(t), X(t)]$ (mean value, variance, and correlation functions) by the stochastic model. For parameters see Legend to Fig. 3. The difference between $E\,I(t)$ and $\text{var}\,I(t)$ vanishes very soon ($E\,I(0) = I_E$, $\text{var}\,I(0) = 0$), that between $E\,X(t)$ and $\text{var}\,X(t)$ can be hardly seen ($E\,X(0) = \text{var}\,X(0) = 0$). The correlation function is denoted $c(I, X)$.

4. COMPARISON WITH EXPERIMENTAL RESULTS AND CONCLUSION

Data for only two time points are available for the comparison of the modelled and the experimental results. The degree of immune responsiveness of chickens recovering from tolerance was determined by the ratio of their antibody titres after challenge in weeks 6 and 9 to the titres of control chickens. As, according to the model, the control chickens would reach the steady state X_E in six weeks, we can compare the experimental data directly to the modelled number of X cells. This number should correspond to antibody formation if we assume that the only mechanism of tolerance is the exhaustion of cells as suggested by our model.

As the disagreement is clear (Fig. 3), we can conclude, in spite of all the simplifications made for the purpose of the modelling, that tolerance to HSA in chickens cannot be accounted for only by the exhaustion of short-lived reactive cells. This can be explained in several ways:

(1) If we had considered two compartments of X cells, short-lived and long-lived, the replacement would have been slower due to the slower turnover of long-lived cells.

(2) Other possible explanation is the regulatory action of other cells on the antibody formation by B cells. Candidates for this function could be macrophages, T cells or even B cells. As a consequence, the curve of replacement of X cells would differ from the course of the escape from tolerance.

(3) Also, the antigen can be, in fact, presented to immunocompetent cells even after its clearance from the circulation and thus cause their elimination for a longer period than our model has assumed.

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