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Role of drug metabolism for breaking tolerance and the localization of drug hypersensitivity

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Abstract

There are three major working hypotheses for the mechanism of drug hypersensitivity reactions: the hapten hypotheses, the danger hypothesis and the PI hypothesis. These hypotheses are difficult to test because of the idiosyncratic nature of hypersensitivity reactions. There is evidence that reactive metabolites are involved in many hypersensitivity reactions, and the reactive metabolite is often formed in the target organ of toxicity, presumably because the half-life of most reactive metabolites is too short to allow them to reach distant sites. In the case of less reactive species that freely circulate the pattern of hypersensitivity usually fits that expected of an extracellular antigen, specifically, an antibody-mediated reaction. We have used two animal models: penicillamine-induced autoimmunity and nevirapine-induced skin rash in Brown Norway rats to test hypotheses. We have found that tolerance is readily induced with a lower dose of the drug, although the nature of tolerance is different in the two models. In the penicillamine model, tolerance is immune-mediated and can be overcome by agents that act as a danger signal. Reactive metabolites may also act as a danger signal. The models can also be used to test the role of reactive species in the mechanism of hypersensitivity reactions.

Keywords: Reactive metabolites; Penicillamine; Nevirapine; Animal models

1. Introduction

Drug hypersensitivity reactions represent a major problem for the patients who sustain such reactions and they also significantly increase the uncertainty of drug development (Lasser et al., 2002). In order to effectively deal with this problem it is essential that we have a much better understanding of the basic mechanisms of such reactions. There are three major working hypotheses that have been used to explain these adverse reactions. The first is the hapten hypothesis (Pohl et al., 1988), which postulates that drugs, or more likely their chemically reactive metabolites, bind to proteins or other macromolecules thus making them "foreign". This, in turn, leads to an immune response, and in some cases, the immune response against the drug-modified protein

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leads to damage and an adverse drug reaction. The second is the danger hypothesis. This concept, taken from a more general hypothesis proposed by Polly Matzinger, postulates that it is not the foreign nature of something that leads to an immune response but rather it is cell damage or other "danger" signal that leads to the initiation of an immune response (Pirmohamed et al., 2002; Seguin and Uetrecht, 2003). In the case of hypersensitivity reactions, the danger signal could be independent of the drug, or the drug or reactive metabolite could cause the cell damage that acts as a danger signal. The PI or pharmaceutical interaction hypothesis is the most recent and is based on the observation that some T cells from patients with a history of drug hypersensitivity reaction proliferate in the presence of drug and in the absence of drug metabolism or covalent binding. This lead Pichler to propose that a drug can interact reversibly with the major histocompatibility (MHC)–T cell receptor (TCR) complex and induce an immune response (Pichler, 2002). However it has not been demonstrated that such a complex can initiate an immune response. These hypotheses are not mutually exclusive. Another way of looking at the problem is to view the induction of an immune response as requiring two signals (Naisbitt et al., 2000; Seguin and Uetrecht, 2003). Signal 1 is the "recognition" by a T cell through the TCR of a processed antigen presented in the cleft of MHC on an antigen presenting cell. Signal 2 is the interaction of the T cell and antigen presenting cell via various costimulatory molecules such as B7 on the antigen presenting cell interacting with CD28 on the T cell. It is believed that signal 1 in the absence of signal 2 leads to tolerance or anergy. The danger signal can upregulate costimulatory molecules thus providing signal 2. Viewed in this way, a drug or its metabolite can generate signal 1 either by acting as a hapten or through a direct interaction with the TCR/MHC complex and signal 2 can arise from either coincidental stimuli, such as an infection, or from the action of drug/reactive metabolite. It is quite possible that different hypersensitivity reactions involve different combinations of these possibilities, but in most cases we simply do not know the mechanism of hypersensitivity reactions. Although little is known with certainty, the following classic examples have helped to shape our view of hypersensitivity reactions.

2. Classic examples of hypersensitivity reactions that provide clues to mechanism

2.1. Penicillin

Penicillin-induced allergic reactions are understood better than any other type of hypersensitivity reaction. Most are clearly immune-mediated and, specifically, they are mediated by IgE antibodies. Penicillin is chemically reactive without metabolism because of the ring strain involved in the β-lactam ring. Penicillin clearly acts as a hapten and binds to various proteins, and most of the IgE antibodies generated recognize penicillin-modified protein (Parker, 1982). It is not clear what provides the danger signal that leads to upregulation of signal 2. There is no clear evidence that covalent binding of penicillin causes cell damage or stress. Some types of penicillin hypersensitivity reactions are markedly potentiated by viral infections; in particular, the incidence of an ampicillin skin rash in patients with mononucleosis is markedly increased (Pullen et al., 1967). However, the mechanism of this rash is uncertain, and it does not appear to be IgE-mediated (Romano, 1998). In general the pattern of penicillin hypersensitivity reactions is what would be expected of an extracellular antigen. Specifically, penicillin can freely circulate and covalently bind to a variety of proteins. Therefore, it is most likely to be processed and presented in the context of MHC-II and leads to an antibody-mediated reaction.

2.2. Halothane

Halothane-induced hepatitis appears to be immune-mediated because it is associated with antibodies against the reactive metabolite of halothane–trifluoroacetyl chloride bond to protein (Vergani et al., 1980). This also strongly suggests that the reactive metabolite acts as a hapten, although there are also antibodies against native protein (Bourdi et al., 1996). In addition, it almost always occurs after multiple exposures to halothane rather than on first exposure, and the earlier exposures often result in a fever (Walton et al., 1976). This suggests that the earlier exposures led to immune-sensitization and that one exposure is too brief to allow a full expansion of immune cells. The reaction is dose-dependent because obesity is a risk factor and halothane is lipophilic thus a larger dose is required to