Pharmacological interaction of drugs with immune receptors: the p-i concept

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Drug-induced hypersensitivity reactions have been explained by the hapten concept, according to which a small chemical compound is too small to be recognized by the immune system. Only after covalently binding to an endogenous protein the immune system reacts to this so called hapten-carrier complex, as the larger molecule (protein) is modified, and thus immunogenic for B and T cells. Consequently, a B and T cell immune response might develop to the drug with very heterogeneous clinical manifestations. In recent years, however, evidence has become stronger that not all drugs need to bind covalently to the MHC-peptide complex in order to trigger an immune response. Rather, some drugs may bind directly and reversibly to immune receptors like the major histocompatibility complex (MHC) or the T cell receptor (TCR), thereby stimulating the cells similar to a pharmacological activation of other receptors. This concept has been termed pharmacological interaction with immune receptors the (p-i) concept. While the exact mechanism is still a matter of debate, non-covalent drug presentation clearly leads to the activation of drug-specific T cells as documented for various drugs (lidocaine, sulfamethoxazole (SMX), lamotrigine, carbamazepine, p-phenylenediamine, etc.). In some patients with drug hypersensitivity, such a response may occur within hours even upon the first exposure to the drug. Thus, the reaction to the drug may not be due to a classical, primary response, but rather be mediated by stimulating existing, pre-activated, peptide-specific T cells that are cross specific for the drug. In this way, certain drugs may circumvent the checkpoints for immune activation imposed by the classical antigen processing and presentation mechanisms, which may help to explain the peculiar nature of many drug hypersensitivity reactions.

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