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COMMENTARY

ANTIBODIES AS PHARMACOLOGICAL AGENTS

SYDNEY SPECTOR

Roche Institute of Molecular Biology, Nutley, N.J. 07110, U.S.A.

One aspect of pharmacology that makes it such a dynamic discipline is that the pharmacologist, in an attempt to resolve some of the problems that confront him, has to exploit many of the techniques and thinking of other disciplines. As a consequence, we find either hybrid words or hyphenated terms being generated to describe these subdivisions of pharmacology, i.e. biochemical pharmacology and neuropharmacology. The field of immunopharmacology is also developing into such a sub-specialty of pharmacology.

Vertebrate animals have a unique and potent surveillance mechanism, the immune process. This system has as its principal function the repulsion and destruction of foreign organisms or substances. Although the immune system is divisible into two parts, this discussion will consider only the humoral division in which immunoglobulins are produced. These antibodies are synthesized in response to a provoking substance called an antigen. One of the qualities that a substance must possess to elicit antibody formation is a sufficiently high molecular weight. Drugs usually have a molecular weight well below the critical size required to stimulate antibody production, but they are capable of serving as a partial antigen when bound to another substance, which is denoted as the carrier molecule, and the carrier molecule should be of high molecular weight. The parent drug is then referred to as a hapten. The hapten–carrier complex can provoke an immune response, and the antibodies stimulated by the complex are capable of reacting with the hapten. Landsteiner in his book, *The Specificity of Serological Reactions* published in 1945 [1], points out the extraordinary degree of specificity of the antibodies and the ability of antibodies to discriminate between small differences in the shape of the hapten. This capacity of specific antibodies to interact with haptens has been exploited to develop quantitative methods for various drugs; however, in this commentary, I should like to discuss the utilization of this high degree of specificity inherent in the antibody molecule as the basis of their use as therapeutically efficacious agents, this being of prime concern to the pharmacologist.

One of the earliest attempts to modify the physiological actions of a haptenic substance (drug) was to neutralize the biological effects of exogenously administered steroids [2–6]. What such investigations have shown is that steroid hormones can be made antigenic by covalently conjugating them to protein carriers and that the antisera evoked by these antigens when passively administered inhibited not only the biological effects of exogenously administered estrone, testosterone, cortisol or aldosterone, but also neutralized effects produced by endogenously formed steroids. An important question which can be raised by these studies as well as subsequent studies in which antibodies neutralized the effects of haptens, or any antigen for that matter, pertains to the quantitative aspects of the inhibition. How much antibody is necessary to block the effects of a particular hapten? As one reads the literature, one finds papers reporting an inhibition with a molar ratio of antibody to hapten of 10 or greater. On the other hand, one also finds situations in which the molar ratio of antibody to hapten is 1/50. An explanation for the differences in these examples may lie in the nature of the binding between the hapten and its antibody. In the first situation, where one requires an excess of antiserum to neutralize biological or pharmacological activity, the affinity constant of the hapten–antibody complex may be relatively weak as compared to the binding of the haptenic molecule to its specific target organ protein. On the other hand, it is difficult to explain the low molar ratio in which the antibody is so efficient in neutralizing the hapten unless one speculates that the antibody does not bind all the circulating hapten but is concentrated near the target organ and has a very high affinity constant so that a small amount of antibody can sequester the drug from the target organ. If a high affinity antibody can remove a drug from a target tissue, it then can be used as an effective antidote for drugs. It would be particularly useful for those drugs which lack an effective antidote. A drug which is extensively used in therapy, and for which there is no effective antidote, is the cardiac glycoside, digoxin; one of the dangers of digoxin use is the hazard of over-digitalizing the patient.

The digoxin antibodies have been used as pharmacological agents to reverse the toxic actions of the cardiac glycoside [7–14]. These specific antibodies are not only used as antagonists to reverse the toxic manifestations of digoxin but have also been important in focusing down on how and where digoxin acts. Using rabbits and dogs, it has been reported that the toxicity can readily be reversed by the judicious addition of the antibodies. The studies were done using the immunoglobulin G which contains four polypeptide chains and some associated carbohydrate. As Butler justifiably points out, there are dangers that have to be considered if one administers an antibody, one being the possibility of hypersensitivity reactions resulting from the administration of a foreign protein such as an antibody. Another, which we have observed in our studies using morphine antibodies to reverse the pharmacological effects of morphine,

is that the antibody-bound drug can act as a depot for the drug and that with time there can occur a release of the drug from the binding sites of the antibody as the antibody is being metabolized or degraded by the body. However, only a small portion of the immunoglobulin molecule is necessary to neutralize the drug, that portion referred to as the Fab fragment. The advantage of using the Fab fragment rather than the entire immunoglobulin is that it is cleared through the kidney in hours in contrast to the days it takes to rid the body of the intact antibody. Also, the possibility of evoking a hypersensitivity reaction is markedly reduced.

One can cite other examples in which antibodies have been used to diminish the effects of drugs as a consequence of the sequestration of the drug from circulation by binding to the antibody. Boyd and Peart [14] demonstrated that immune plasma containing gamma globulin directed against the polypeptide angiotensin could neutralize the biological activity of angiotensin II. We have shown [15, 16] that active immunity with a morphine immunogen can alter the distribution and metabolism of morphine and consequently modify the analgesic action of morphine. Bonese *et al.* [17] have also reported that the self-administration of heroin was decreased in rhesus monkies immunized against morphine. The question that immediately comes to mind when one reads of modifying heroin effects with antibodies is whether it might not have therapeutic applicability for addicts. The problem here is that there are a limited number of antibody binding sites, so that by increasing the dose of the opiate, the addict can then saturate those sites on the antibody and reverse the neutralizing action of the antibodies. This also raises the very important question concerning drug tolerance. It is known that many drugs bind to serum albumin; one could speculate that the serum albumin–drug complex, although not of covalent binding, might act as an immunogen and thereby stimulate antibody production. Thus, as the antibody sequesters the drug from circulation, more of the drug is required. Ryan *et al.* [18] have reported on the binding of morphine by a gamma globulin fraction in the serum of some heroin addicts. However, Webster *et al.* [19] were unable to implicate an immune response to heroin as being a factor in opiate tolerance, addiction or complications following opiate administration. An interesting twist to this immunopharmacologic approach to block morphine action was introduced by Gunne *et al.* [20] who generated a circulating pool of antibodies against nalorphine. They then bound nalorphine to the antibodies. Now when animals were challenged with morphine, it displaced the bound nalorphine which could then antagonize the morphine. Using antibody bound nalorphine, they had created a circulating depot of the antagonist which could be displaced by morphine.

There is another side of the immunopharmacologic "coin" that should be considered, and that is, rather than inactivating a drug by sequestering it with an antibody, the question can be raised as to whether drug effects can be potentiated when a drug is bound to the antibody. There are a number of mechanisms the body has to inactivate a substance, e.g. drug-metabolizing enzymes of the liver microsomes, excretion and, with biogenic amines, an uptake process. If a drug or an endogenous substance is bound to the antibody, and that portion of the molecule which interacts with the tissue receptor is still accessible to interact with the tissue receptor, it is possible there might be a potentiation of effects, as the inactivating processes could be impaired. It offers many interesting possibilities. I feel these immunological approaches open the way for exciting research for the pharmacologist.

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