Reports

Possible Mechanism of Tolerance to Narcotic Drugs

Although many hypotheses have been offered to explain the development of tolerance to narcotic drugs (*1*), adequate experimental data have not been presented to elucidate this phenomenon. In recent studies at this laboratory, we have observed several striking similarities between the receptors for narcotic drugs and the enzymes that N-demethylate these drugs. The enzymes and receptors have been found to be alike with respect to substrates with which they interact, stereospecificity, and antagonism by N-allylnormorphine (*2*). Since the enzymes that N-demethylate narcotic drugs were similar in several ways to narcotic drug receptors, it appeared likely that these enzymes might serve as a model for the receptors. Thus, any changes occurring in enzyme activity during the development of tolerance might reflect changes taking place on the drug receptor. With this in mind, an examination of the effect of repeated administration of morphine to rats on the enzymic N-demethylation of morphine and other narcotic drugs was undertaken. The effect of the administration of morphine, together with its antagonist, N-allylnormorphine, on enzymic N-demethylation was also investigated, since it has been shown that this combination reduces the development of tolerance (*3*).

Twelve rats were made tolerant to morphine by a daily intraperitoneal injection of morphine sulfate. The animals were given an initial dose of 20 mg/kg of morphine sulfate, and the amount of drug administered was then progressively increased during a period of 35 days until daily injection of 150 mg/kg was reached (group M). Another group of eight rats was given N-allylnormorphine and morphine in a ratio of 1/4 for 35 days (group NM). A group of 12 rats was given the same dosage regimen of morphine as described in group M for 35 days, following which the drug was abruptly withdrawn for 12 days (group W). Fourteen rats receiving a daily injection of isotonic saline served as controls (group C). Fisher-strain male rats that were 120 to 130 days old when the study was begun were used throughout the study. The average gain in weight in all groups of rats was approximately the same.

Twenty-four hours after the test period the animals were sacrificed, and the livers were examined for their ability to N-demethylate morphine, dilaudid, meperidine (Demerol), and cocaine. The livers were prepared for enzyme assay by a procedure described previously (*2*), and the degree of enzymic N-demethylation was determined by estimating the amount of formaldehyde liberated (*4*).

The changes in the enzymic N-demethylation in the various groups of rats are shown in Fig. 1. In the case of morphine-treated animals (group M), a profound reduction in the ability to N-demethylate morphine occurred. In addition, the enzymic N-demethylation of dilaudid, a compound that shows cross-tolerance to morphine (*5*), was reduced to about the same degree as that of morphine, while the demethylation of meperidine, a drug that exhibits limited cross-tolerance to morphine (*6*), was only partially reduced. Enzymic N-demethylation of cocaine, for which no cross-tolerance to morphine occurs (*5*), was unaffected by chronic morphine administration. In the group of animals that was treated with both N-allylnormorphine and morphine (group NM), the reduction in the enzymic demethylation of narcotic drugs was significantly less than in those that received morphine only. The enzyme activity with respect to all substrates had returned to the control level or above in withdrawn animals (group W).

Other pathways in the *in vitro* metabolism of narcotic drugs, such as O-demethylation of codeine (*7*), hydrolysis of diacetyl morphine (*8*), and conjugation of morphine (*9*), were also examined. No differences in the enzymic O-demethylation, hydrolysis, and conjugation of narcotic drugs in the control- and morphine-treated rats were found.

From the results described here, a striking parallelism between the enzymic N-demethylation of narcotic drugs and the development of tolerance to these drugs was found. The repeated administration of morphine reduced both enzymic demethylation and pharmacological response. In addition, there was a correlation between demethylation of substrates and cross-tolerance to morphine. Furthermore, N-allylnormorphine, which blocks development of tolerance to morphine, also blocks reduction of enzyme activity. It appears that N-allylnormorphine not only antagonizes the pharmacological action and the enzymic demethylation of narcotic drugs but also protects the enzyme and perhaps the receptor sites. Animals that are withdrawn from narcotic drugs recover their pharmacological responses to these drugs; similarly, the demethylating-enzyme activity in rats withdrawn from morphine returns to normal.

The changes in enzyme activity in morphine-treated rats suggest a mechanism for the development of tolerance, if one assumes that enzymes which N-demethylate narcotic drugs and the receptors for these drugs are probably closely related. The continuous interaction of narcotic drugs with the demethylating enzymes inactivates the enzymes. Likewise, the

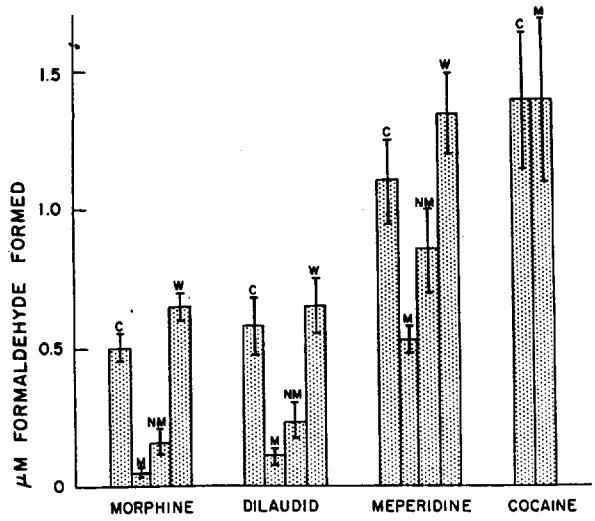

Fig. 1. Effect of morphine treatment, N-allylnormorphine, and withdrawal on the enzymic N-demethylation of narcotic drugs. Vertical bracketed lines on bars are standard deviation of the mean. (group M) morphine-treated rats; (group NM) morphine- and N-allylnormorphine-treated rats; (group W) rats treated with morphine and then withdrawn; (group C) normal rats.

continuous interaction of narcotic drugs with their receptors may inactivate the receptors. Thus, a decreased response to the narcotic drugs may develop as a result of unavailability of receptor sites (*10*).

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References and Note

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