TEST METHODS FOR PREDICTING TARDIVE TOXICITY OF THERAPEUTIC DRUGS USING LABORATORY ANIMALS

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Introduction

Tardive toxicity of a drug is characterized by delayed onset of the toxic manifestation of the drug, or toxicity that appears only after repeated administration of the drug. Tardive dyskinesia is one typical example. This dyskinesia is characterized as a syndrome involving involuntary hyperkinetic abnormal movements occurring in susceptible individuals during, or following the cessation of, long-term neuroleptic drug treatment (Casey, 1987). Although prediction of delayed toxicity of therapeutic drugs is very important, methods for predicting such toxicity using laboratory animals have not yet been wholly established.

In the present paper, examples of late-emerging drug toxicities found in monkeys and rats are described. These are tardive dyskinesia caused by repeated haloperidol administration in Cebus apella monkeys and delayed disorder of discrimination learning caused by repeated methamphetamine administration in rats. The mechanisms underlying these phenomena may be mainly understood as sensitivity changes of the brain dopamine receptors caused by repeated administration of a dopamine receptor antagonist (haloperidol) or an indirect dopamine receptor agonist (methamphetamine).

1. Tardive dyskinesia by neuroleptics in Cebus apella monkeys

Tardive dyskinesia is characterized by involuntary, repetitive, purposeless hyperkinetic movements. The original descriptions emphasized orofacial signs: chewing, tongue protrusion, lip smacking, etc. Cebus apella monkeys that received repeated administration of haloperidol for more than 3 months showed a stable low degree of persistent symptoms of tardive dyskinesia (Gunne and Barany, 1979). Single administration of neuroleptics such as haloperidol, chlorpromazine, and clozapine attenuated the dyskinesia temporarily. On the other hand, the haloperidol-induced dyskinesia disappeared after about 3 months of withdrawal from haloperidol. Single administration of haloperidol or of chlorpromazine, thioridazine, or fluphenazine elicited dyskinesia again, while single administration of clozapine did not. Clozapine, which has been removed from the market due to hematological toxicity, seemed to represent a new class of neuroleptics with very low risk of extrapyramidal side-effects (Baldessarini, 1990). As it is clinically well-known that butyrophenones (e.g. haloperidol etc.) and phenothiazines (e.g. chlorpromazine etc.) induce dyskinesia while clozapine does not, the test method using monkeys described above was considered to be useful and valid for predicting tardive dyskinesia in humans. Since no cure for irreversible tardive dyskinesia is presently known, it is crucial to screen new neuroleptics for their potential risk to cause
neurological side-effects such as tardive dyskinesia.

To understand the mechanism of tardive dyskinesia, it is important to realize that the striatum is the site responsible for extrapyramidal side-effects, and dopamine receptor antagonists such as haloperidol and chlorpromazine can occupy the receptors for long period of time. Thus, tardive dyskinesia may be thought to be attributable to the denervation supersensitivity of dopamine receptors at the striatum. Since clozapine primarily acts on serotonin receptors, the lack of tardive dyskinesia with clozapine may be attributable to this difference of action.

2. Delayed disorder of learning caused by repeated methamphetamine administration in rats

Amphetamines are used for the treatment of narcolepsy and minimum-brain-damage syndrome, which is a hyperactive behavioral disorder in children. One of the maladaptive behavioral changes caused by amphetamines is impaired judgment (DSM-III-R). Disorders in cognitive function, learning, and thinking were also reported after repeated administration of amphetamines in abusers. Thus, it is worthwhile to study disorder of animal learning behavior caused by amphetamines in the framework of delayed toxicity.

A delayed toxicity was observed regarding light-dark discrimination in rats by repeated administration of methamphetamine (Yanagita et al., 1995). Rats were trained to press the illuminated lever in a choice of 2 levers for food reinforcement in an operant chamber. After establishment of the light-dark discrimination, methamphetamine was subcutaneously administered at 0.5 mg/kg in one group of rats (low-dose group) and at 2 mg/kg in another group of rats (high-dose group). Both groups received drug administration daily. Light-dark discrimination was tested every 2 or 3 days. The percent of correct responses did not decrease in the low dose group as the discrimination tests proceeded, but did decrease in the high dose group (Fig. 1). Thus, delayed disorder of light-dark discrimination was clearly detected in the high dose group after repeated administration of methamphetamine. The mechanism of the delayed disorder is not clear but it is an interesting phenomenon, and it may be important to examine the involvement of the mesolimbic and mesocortical dopamine

![Fig. 1. Effects of repeated administration of methamphetamine on light-dark discrimination in rats. Mean percent of correct choices is shown with standard error. Methamphetamine at 0.5 mg/kg and the same drug at 2 mg/kg were administered subcutaneously once daily to the low dose group and to the high dose group, respectively. Light-dark discrimination tests were performed every 2 or 3 days during repeated methamphetamine administration period. *: P<0.05 and **: P<0.01, each against saline control (indicated by "SAL").]
systems in this regard.

3. The relationship between delayed toxicity and the dopamine system

In the present paper, examples of delayed toxicity with haloperidol and methamphetamine have been described. Both of these drugs are known to act on the brain dopamine receptors. Haloperidol and other neuroleptics block the post synaptic dopamine receptors, while amphetamines release dopamine from the presynaptic terminals and inhibit reuptake of dopamine into the presynaptic terminals. Repeated administration of these drugs may change the sensitivity of the receptor and the signal transduction system as manners of neuroadaptation. The mode of sensitivity changes and site of actions may differ depending on the drug. These differences in the modes of action of these drugs cause the different types of delayed toxicity. In order to establish useful and valid methods using laboratory animals for predicting delayed toxicity in humans, it is important to understand the mechanism underlying the delayed toxicity.

References


