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PASSIVE GLYPINE TOLERANCE IN MONKEYS

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Habituation to therapeutic preparations has been observed for a long time [1], including to drugs with central cholinolytic properties [2, 3]. It is also known that a state of passive tolerance can be created, to morphine for example, by injecting blood serum [4] or brain homogenate [5] obtained from animals actively tolerant to this drug, into intact animals.

The object of this investigation was to attempt to create passive tolerance to the cholinolytic glypine by injecting blood plasma from a tolerant animal into an intact recipient.

EXPERIMENTAL METHOD

Six male baboons *(Papio hamadryas)* were used. The mean age of the baboons was about 7 years and their mean weight about 20 kg. Before the experiments the animals were kept in a group.

Tolerance was produced in two monkeys by daily intramuscular injection of glypine in a dose of 0.05 mg/kg. The experimental scheme is shown in Fig. 1.

The possibility of creation of passive tolerance was studied in two intact monkeys after injection of plasma from tolerant animals into them. Blood was taken from tolerant monkeys 24 h after the last injection of glypine by total exsanguination of the animal under hexobarbital anesthesia. The blood cells were removed by centrifugation. The plasma was injected without further treatment on the same day, intravenously into intact monkeys in a dose of 10 ml/kg body weight. Glypine in a dose of 0.05 mg/kg was injected into the animals 30 min later and the magnitude of the effect of this cholinolytic, if present, was determined. Parallel experiments on two intact monkeys served as the control for the action of glypine. Observations on the animals' behavior continued for 6 h.

Because of the extremely small number of monkeys available, experiments could not be carried out with preliminary injection of intact plasma into control animals. However, similar experiments performed previously on dogs showed that preliminary injection of intact plasma into the animals does not alter their response to subsequent injection of the cholinolytic.

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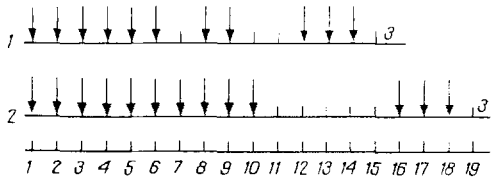

Fig. 1. Scheme of experiments to produce tolerance to glypine in monkeys. Arrows indicate injections of glypine (0.05 mg/kg); 1) scheme of administration of glypine to first monkey; 2) to second monkey; 3) taking blood. Abscissa, days of injection.

The experiments were performed at the Institute of Experimental Pathology and Therapy, Academy of Medical Sciences of the USSR, Sukhumi.

EXPERIMENTAL RESULTS

Observations were made on the monkeys for 2 days before injection of the cholinolytic. The animals were active, with good coordination, and they took and ate food rapidly. They also quickly took objects thrown into the cage. The monkeys watched closely the movements of people and objects outside the cage and reacted quickly to threats.

The animals developed noticeable signs of the action of the cholinolytic 30 min after the first injection of glypine and these gradually increased. The animals first became apathetic and tended to remain for a short time in a particular posture, after which they refused to eat, became indifferent to movement of people and other monkeys, and even failed to respond to touch. The strongest manifestations of the action of glypine were observed 2 h after injection of the cholinolytic. After 4 h the monkeys' behavior was similar to its initial pattern, i.e., almost indistinguishable from the behavior of the intact control baboons. After the second injection of glypine the intensity of the effect of the cholinolytic in the first experimental monkey was appreciably reduced, and the animal was basically in a state of inhibition (apathy). After subsequent injections of glypine no abnormality of the animal's behaviorwas observed. After 6 days, injections of glypine were suspended for 1 day. General apathy was observed 1-1.5 h after the next injection. The monkey responded very lazily to movement of objects and took food and ate it apathetically. Injection of the cholinolytic next day led to no marked changes in behavior. A gap of 2 days in administration of the drug was then made, after which the injections of glypine were resumed. The manifestations of the action of glypine characteristic of the first injection were thereupon observed practically fully. However, injections of glypine on the next 2 days caused no changes in the baboon's behavior.

The development of habituation of glypine by the second baboon differed considerably from its course in the first. Signs of the action of glypine in the second monkey did not disappear until the fifth daily injection of the cholinolytic. After 10 days, injections of glypine were interrupted for 5 days. The next injection of glypine was followed by lethargy and by slight disturbance of movement coordination, and apathy during eating. The duration of these manifestations of the action of glypine was about the same as on the first day of its administration. During subsequent daily injections of glypine the effect of tolerance to the cholinolytic was fully restored after 2 days. After the effect of tolerance to glypine in both monkeys had been fuly restored, total exsanguination was carried out 24 h after the last injection of the cholinolytic. The plasma obtained from the blood was injected into two intact monkeys, and 30-60 min later these animals were given an injection of glypine in a dose of 0.05 mg/kg. No manifestations of the action of the cholinolytic appeared in these animals. A slightly increased response to threats was observed in one of the monkeys. Slight apathy was observed in the second monkey 2 h after injection of glypine. The animals' behavior in the group was unchanged, they were communicative, they obeyed the leader, and carried out active searching for food and eating it.

In parallel experiments on intact animals glypine led to the appearance of the usual features of its action.

These experiments showed that during daily injections of glypine monkeys quickly develop tolerance to the cholinolytic. Injection of blood plasma obtained from monkeys tolerant to

glypine into intact animals creates a state of passive tolerance to this cholinolytic in the recipients. The mechanism of these phenomena is not yet explained. Meanwhile the fact that a state of passive tolerance to glypine can be created in intact animals with the aid of tolerant plasma suggests the appearance of a certain factor in the blood of tolerant animals, which evidently is responsible for the development of tolerance in the recipient.

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