Antiaggressive and Motor Effects of Haloperidol Show Different Temporal Patterns in the Development of Tolerance

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Navarro, J. F., J. Miñarro and V. M. Simón. Antiaggressive and motor effects of haloperidol show different temporal patterns in the development of tolerance. PHYSIOL BEHAV 53(6) 1055-1059, 1993.—The study of the temporal course of tolerance development was used as a means to separate different aspects of the action of haloperidol on social behavior. Agonistic behavior was studied in isolated male mice that confronted standard opponents (anosmic and grouped conspecifics) in a neutral area. The aggressive and motor behaviors of the experimental animals were evaluated 30 min or 24 h either after a single injection of haloperidol (0.4 mg/kg) or following the last of a series of 15 or 30 injections. When animals were evaluated 30 min after the haloperidol injection, no tolerance to the antiaggressive effects was evident. The action on immobility, on the contrary, showed a clear tolerance development with repeated drug administration, both with 15 and 30 injections. When evaluated 24 h after the last injection, tolerance to the antiaggressive effects developed with repeated injections. Increased immobility was never found in the tests carried out after 24 h, not even in the single injection group. The clear divergence found in the temporal courses of tolerance to haloperidol in its antiaggressive and motor effects suggests that these actions are mediated through different neurophysiological mechanisms. A parallel with extrapyramidal and therapeutic effects is discussed.

Haloperidol Tolerance Aggression Agonistic behavior Motility Mice

Existing published data suggest that different actions of a given drug may be mediated through different neural loci (27). Thus, it has been proposed that motor effects of neuroleptic drugs are mediated mainly through the nigrostriatal system, whereas its antiaggressive effects may be mediated mainly through the mesolimbic system (28,29), or perhaps via serotonergic mechanisms. Accordingly, drugs that have diverse effects on these structures will affect motor and aggressive behaviors differently. The main evidence supporting this hypothesis is that while all neuroleptics investigated disrupt aggression in a similar manner, not all of them affect motor behavior in the same way. In this sense, typical neuroleptics (like haloperidol) are very potent inhibitors of motor behaviors, whereas atypical ones (like sulpiride or clozapine) only have a weak action on motility (10,14,26). Such disparity is also supported by different neurochemical profiles of the actions of typical and atypical neuroleptics on nigrostriatal and mesolimbic neurons (7).

If antiaggressive and motor effects of neuroleptics have separate neurochemical underlying mechanisms, one would expect them to undergo different temporal changes in response to repeated administration of these compounds. Tolerance is a term currently used to describe the progressive decrement of a given response to the repeated administration of a drug, but it does not imply that a particular mechanism is responsible for the phenomenon. The mechanisms involved can be very different; environmental, metabolic, neural, and subcellular processes may play a role with possible interrelationships among them (16).

It is generally accepted that prolonged administration of classic neuroleptic drugs results in the development of tolerance to their motor actions, especially catalepsy (1,5,11,18). Thus, Asper et al. (1) found that upon daily administration of haloperidol (HAL) (1.5 mg/kg) for 21 consecutive days, rats developed a very marked and fairly long-lasting tolerance towards the motor effects of the drug. Using a longer period of treatment, Campbell and Baldessarini (5) administered HAL (3 mg/kg) daily for 5 months, evaluating the tolerance to catalepsy and palpebral ptosis responses. Their results showed “that both responses reached half of their initial values by approximately 5 and 10 weeks, respectively.” More recently, Lappalainen et al. (18) found a marked tolerance to the cataleptic effect of HAL (1 mg/kg) during repeated administration, which was already evident 6 days after the beginning of treatment. From a clinical point of view, it is

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also accepted that extrapyramidal side effects of HAL develop a certain degree of tolerance to the drug in the course of long periods of treatment (2).

On the other hand, aggression is a complex set of behaviors reliably disrupted by dopaminergic antagonists (15). Haloperidol, like other neuroleptic agents, decreases aggressive behavior in a range of species (13,21–23,35), including humans (6,24,31). Evidence concerning the development of tolerance to the antiagressive effects after repeated administration of HAL or other neuroleptic drugs is inconsistent. Hegstrand and Eichelmann (17), using shock-elicited aggression, found no tolerance to the effects of 1 mg/kg of HAL administered for 14 days. Yoshimura and Ogawa (32), using a maternal aggression paradigm, found that after 20 days of treatment with 0.2 mg/kg of HAL, females showed no decrease in the number of bites, whereas a single administration of 0.2 mg/kg did reduce them, suggesting tolerance to the antiagressive effects of the drug. There is no evidence of tolerance using an isolation-induced aggression paradigm.

On the whole, the evidence for a development of tolerance to the antiagressive effects of HAL is missing or at least inconclusive, which clearly contrasts with the almost unanimous finding of tolerance development to its motor effects. This study represents a further attempt to investigate if motor and aggressive behaviors respond in a similar or in a different manner to the repeated administration of HAL (0.4 mg/kg, IP), using an isolation-induced aggression model. Different temporal courses in the development of tolerance to antiagressive and motor effects of HAL would represent additional evidence that diverse actions of the neuroleptic drugs may be mediated through different neural systems.

METHOD

Subjects

Three hundred and six OF-1 strain albino male mice, aged 42 days (Servicio de Animales de Laboratorio, Granada, Spain) were housed under standard laboratory conditions: constant temperature (21°C), a reversed light schedule (white lights on: 0100–1300 h), with food and water available ad lib, except during behavioral testing. Half were individually housed in transparent plastic cages (24 × 13.5 × 13 cm) and were employed as experimental animals. The remainder were housed in groups of six to be used as standard opponents and were made temporarily anosmic by intranasal lavage with 4% zinc sulphate solution on both 1 and 3 days before testing (30). Such animals do not initiate attack but provoke aggressive behavior in the isolated aggressive mice (3). All animals underwent an adaptation period of 30 days before experimental treatments were applied.

Procedure

Drug treatment. Animals were injected IP with 0.4 mg/kg (in a volume of 0.01 ml/g) of HAL (Haloperidol®, Latino Laboratories, Spain) or physiological saline (control group), for 1, 15, or 30 days. Behaviors were evaluated 30 min or 24 h after the last injection (see Experimental Design). This HAL dose has been used by numerous researchers in behavioral experiments with mice (10,22,25,32). In a pilot experiment in which a broad range of HAL doses was examined, 0.4 mg/kg was found to be appropriate, since its effect on aggressive behavior is evident while its depressing action on motor activity is moderate.

Social encounters. After treatments, an experimental animal and a standard opponent confronted each other in a neutral cage for 10 min. The animals were allowed 1 min of adaptation to the neutral cage, whilst separated by means of a plastic barrier.

RESULTS

Behavior Evaluated 30 min After the Last Injection

Table 1 illustrates the medians of the accumulated times allocated to the three categories of behavior described above, when animals were tested 30 min after the last injection of HAL.

In the three conditions studied (1, 15, and 30 days of administration), HAL decreased attack significantly in comparison with the saline groups, but no differences were found among the three conditions. Haloperidol also decreased threat behavior with respect to saline groups in the three conditions, but this effect was significant (p < 0.02) only in the single-injection group.

Immobility increased significantly (p < 0.002) in all groups receiving HAL when compared with their saline controls. In the single-injection group, immobility was also significantly greater than in the groups treated for 15 (p < 0.02) or 30 days (p < 0.05) with the drug.
Behavior Evaluated 24 h After the Last Injection

Table 2 illustrates medians of accumulated times allocated to the three categories of behavior described above, when animals were tested 24 h after the last injection of HAL.

Animals acutely treated with HAL decreased significantly the time spent in attack (p < 0.05) or threat (p < 0.02) behaviors when compared with their saline controls. Animals treated with the drug during 15 or 30 days did not show any significant differences when compared with their saline controls, either in threat or attack behaviors. The single-injection group showed significantly less offensive behaviors (threat or attack) when compared with the 15- or 30-day treatment groups (p < 0.02).

Haloperidol produced no immobility when animals were tested at this time after injection.

Comparison Between Both Evaluations (30 min vs. 24 h)

In the animals treated for 15 or 30 days with HAL, there was more attack behavior in the groups evaluated 24 h after the injection than in those evaluated 30 min after it (p < 0.05 in the 15-day group and p < 0.02 for the 30-day group). In the group that received only one injection, no significant differences were found between both evaluations. Threat behavior presents a similar profile, with the exception of the 30-day group in which the difference between both evaluations did not reach significance.

Immobility was significantly greater in the animals tested 30 min after the injection than in those tested 24 h afterwards (p < 0.02). But this difference reached significance only in the single-injection group, not in the groups treated for 15 or 30 days with the drug.

Since the baseline levels of certain behaviors of the different groups showed an apparently high variability, they were also compared among themselves, but no significant difference was found in any comparison.

DISCUSSION

The temporal course of tolerance development may be different for diverse actions of a given drug. In the present study, we have found that the antiaggressive and motor effects of HAL (0.4 mg/kg daily for 15 or 30 days) showed different temporal patterns in the development of tolerance depending on the interval since the last drug administration. As shown in Tables 1 and 2, animals evaluated 24 h after the last injection of HAL showed tolerance to the antiaggressive effects of the drug, but when tested 30 min after the injection no tolerance was evident in attack behavior, although some tolerance was observed in threat behavior. The results described here are apparently
first for a model of isolation-induced aggression. Yoshimura and Ogawa (32) also found tolerance to the antiaggressive effects of HAL (0.2 mg/kg), but in a maternal aggression model.

In contrast to the antiaggressive action of the drug, its motor effects showed a different pattern in the development of tolerance. When animals were evaluated 30 min after the last injection, tolerance to the motor effects of HAL was found (using immobility as a measure of motor behavior). This action was evident in the animals that received a daily injection of the drug for 15 as well as for 30 days. In the animals evaluated 24 h after the last HAL injection, no statement about the presence or absence of tolerance can be made, since no immobility was evident.

In summary, the temporal courses of the antiaggressive and motor effects of HAL are clearly divergent. Whereas immobility largely disappears with repeated administration of the drug (from 65 s after the first administration, to 3 s after 15 days, and to 2 s after 30 days), attack behavior remains depressed, even after 30 days of treatment (0 s in comparison with 59 s in the control group). This finding suggests that the antiaggressive properties of HAL in animal models are not dependent on its motor effects and that the neurophysiological processes underlying aggression and immobility are different.

The distinction between the antiaggressive and motor effects found in these experiments may be compared to the disparity that has been described in the clinical action of neuroleptic drugs. Antipsychotic activity does not show any apparent decline (8,12), whereas adverse extrapyramidal side effects decrease with the passage of time. It seems plausible, therefore, to think of the antiaggressive properties shown by HAL in experimental animals as a possible behavioral model of its antipsychotic effects on humans. The evaluation of the antiaggressive effects (unexplained by parallel motor impairments) shown by the new compounds in animal models might have a potential value as a screening procedure predicting antipsychotic efficacy in humans.

Another time-related finding of this study was the apparent dissociation in the waning of the antiaggressive and the motor effects of HAL after a single injection. Thirty minutes after the injection, a significant decrement in attack behavior was found, accompanied by a concomitant increase in immobility. This combination of effects (decreased aggression and increased immobility) makes possible a nonspecific explanation of the antiaggressive action of the compound (22,23). But when tested 24 h after the HAL administration, the reduction of aggressive behavior is still evident, whereas no increase in immobility could be detected. These results emphasize the relevance of the time period that had elapsed between the drug administration and the test occasion. On the other hand, they suggest that the reduction of aggressive behavior cannot be explained only in terms of an unspecific effect of the drug on all types of motor behavior. Otherwise, aggression and motility should run in parallel. The persistence of some of the HAL effects after 24 h may be due to the continued presence of the drug in brain tissues or to long-lasting (and unknown) physiological changes produced by the previous exposure to the compound. Thus, some longer-term studies suggest that neuroleptics may remain in tissues at substantial concentrations long after administration has stopped (9).

A divergence in the development of tolerance in two or more behavioral tasks proves to shed some light on the neurophysiological basis of these behaviors. In this sense, the present investigation represents an effort to sort out, by means of the study of tolerance phenomena, different behavioral elements that are apparently related but that must be, in reality, assigned to different neurophysiological mechanisms.

REFERENCES


