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Tripelennamine Effects on Body and Organ Weights, Water Intake, and Several Behaviors of Rats[1]

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NANRY, K. P., R. G. SEWELL, JR., J. A. GALLUS, S. A. VANECEK AND A. POLING. *Tripelennamine effects on body and organ weights, water intake, and several behaviors of rats.* PHARMACOL BIOCHEM BEHAV **19**(5) 821–825, 1983.—The effects of 14 daily injections of tripelennamine on several dependent measures were determined in groups of rats that received 0.0 (vehicle only), 2.0, 4.0, 8.0, or 16.0 mg/kg of the drug. Tripelennamine did not affect body weights, organ weights (heart, liver, adrenals, kidneys), or blood glucose levels. Daily water intake was, however, directly and significantly related to tripelennamine dose. The drug failed to influence performance in a grasping response assay, or locomotion as measured in running wheels when rats received footshocks immediately before assessment of locomotion. Tripelennamine did significantly reduce locomotion when rats were not shocked before testing. Nociception, as measured via a hot-plate assay, also was altered by the drug. Here, rats exposed to 16 mg/kg evinced paw-lick latencies far greater than those that received lower doses. These results indicate that tripelennamine produces observable behavioral effects at doses which are not obviously toxic.

Tripelennamine Body weights Water intake Organ weights Nociception Grasping response Locomotion Blood glucose Rats

ANTIHISTAMINIC drugs which block H_1 receptors were first recognized 45 years ago [2], and have been used therapeutically for over three decades [5]. Many such compounds are available, and have been studied to the extent that their pharmacological properties can be specified with considerable precision [5,16]. One antihistaminic, tripelennamine, has recently generated considerable research interest, in large part because the drug is sometimes combined with pentazocine and the mixture substituted for heroin by street users [13,21].

The lethality of tripelennamine and pentazocine has been examined in nonhumans [14,23], as have the discriminative stimulus properties of the mixture [20], and its analgesic actions [4]. Fully understanding the actions of the two drugs together presupposes knowledge of their individual actions and, as noted above, the pharmacological actions of tripelennamine are rather well understood. The same is true of pentazocine, whose behavioral effects have also been studied in considerable detail (e.g., [6, 8, 9]).

Surprisingly little is known concerning the behavioral effects of tripelennamine. In humans, the drug typically produces behavioral sedation, although excitation is occasionally observed, most frequently in children or in adults who have ingested relatively low doses [5]. The behavioral effects of tripelennamine in nonhumans have not been systematically explored, although the drug occasionally has been tested in various assays (e.g., [1,11]).

The present study used a battery of tests previously employed to assess the effects of prednisolone [19] to examine the effects of tripelennamine on several behavioral and physiological dependent measures, the latter intended primarily to detect gross toxicity. Further analysis of tripelennamine's actions may be of interest since the drug is being abused with increasing frequency, and is also chronically administered medicinally to deal with pollinosis, urticaria, and other allergies [5]. In addition, data implicating histamine as a neurotransmitter are amassing [7, 17, 22], which may render information regarding the actions of antihistaminics significant to neuropharmacologists, as well as to behavioral pharmacologists.

METHOD

Subjects

Thirty adult female Sprague-Dawley rats (mean body weight=246 g), born and reared in our colony, served as

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subjects. They were individually housed (in steel cages 32 cm long, 24 cm wide, and 20 cm high) with unlimited access to water and Purina Rodent Chow (Ralston-Purina, St. Louis) in a constantly-illuminated colony area maintained at 23°C.

Apparatus

The apparatus used is described in detail elsewhere [19]. In brief, water intake was measured via inverted graduated cylinders equipped with drinking spouts, body weights were determined with a top-leading scale, and excised organs were weighed with an analytical balance. Locomotor activity was determined through the use of running wheels (35 cm diameter, 11 cm width) equipped with microswitches which allowed full revolutions in either direction to be determined. Electric shocks of specified intensity and duration were delivered to the rats' feet via a modified shuttlebox. Nociception was measured via a hot-plate (63 cm long, 16 cm wide) assay with the plate maintained at 59°C, and the grasping response was measured by suspending rats from a wire (0.013 cm diameter) located 43 cm above the floor. Blood glucose levels were determined through the use of a commercially prepared glucose-analysis reagent (Glucostat, Ortho Diagnostic, Raritan, NJ).

Procedure

The present study examined the effects of daily intraperitoneal (IP) injections of 0.0 (vehicle only), 2.0, 4.0, 8.0, and 16.0 mg/kg tripelennamine hydrochloride (Sigma, St. Louis). These doses were selected on the basis of earlier reports [1,15], and the drug was dissolved in isotonic saline solution injected at a 1.0 ml/kg volume. A group design was employed, wherein an individual drug dose was given to members of one randomly-selected group of six rats for 14 consecutive days, at the same time each day. During the first 12 days, water intake was determined and subjects weighed at 24-hr intervals. These measures were taken at the time of drug injection.

Thirty minutes after injection on the thirteenth day of the study, subjects were individually placed in running wheels for a 30-min locomotion assessment session, then returned to home cages. On the fourteenth day of the investigation, subjects were injected, then placed within 2 min in the modified shuttlebox, where they received 120 footshocks (1.0 mA, 0.5 sec) in 30 min. Shocks were delivered under a fixed-time 15-sec schedule. After exposure to shock, subjects were placed in running wheels and a second 30-min locomotion assessment session conducted.

Immediately after this session, grasping response tests were conducted. In this assay, the rat was held in a vertical position, head up, and moved slowly downward toward the wire to be grasped, which was located immediately in front of the subject. When the rat grasped the wire, it was released, suspended by the forepaws. An observer recorded the latency from the time the subject was released until it fell from the wire. If the animal had not dropped at the end of 3 min, it was removed from the wire and a latency of 3 min recorded. Five grasping response trials, separated by 1-min intervals, were arranged for each rat.

Following assessment of the grasping response, subjects were studied in a hot-plate analgesia test [24]. Each rat received five sequential exposures to the hot plate, with individual trials separated by 2 min. In each trial, the subject was placed on the hot plate and a running time meter started; when the subject was observed to lick either of its hindpaws, the meter was switched off and the response latency recorded. To minimize tissue damage, rats were removed from the plate after 30 sec, regardless of their performance. A latency of 30 sec was recorded if a subject failed to lick during a trial.

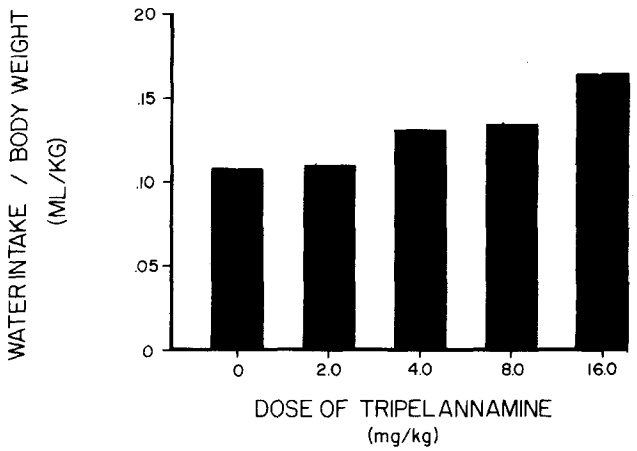

FIG. 1. Water consumed (ml/kg body weight) per rat per day by each experimental group during the first 12 days of the study. Tripelennamine at the indicated dose was injected once per day during this period. Standard errors are too small to appear in this figure.

On the fifteenth and final day, no injections were given. Subjects were deeply anesthetized with ether and 0.9 ml of blood removed from each rat via heart puncture. Blood samples were centrifuged for 20 min at 1,500 rpm's, the derived plasma frozen, and blood glucose levels determined at a later date. After blood was withdrawn, the heart, liver, adrenals, and kidneys of each rat were removed and weighed.

Data Analysis

Repeated measures analyses of variance [10] were used to evaluate group differences in daily body weight and water intake, and performance in the running wheel (pre- and post-shock), grasping response, and hot-plate (nociception) assays. Planned comparisons tests (t_{LSD} [10]) were used to compare performance across doses in the nociception (hot-plate) assay. One-way analyses of variance [10] were used to evaluate group differences in organ weights (absolute and relative) and blood glucose levels. All data are reported as group means (N=6/group) ±1 standard error.

RESULTS

Figure 1 shows that average daily water intake (ml water/kg body weight) was generally dose-related; this effect was statistically significant ($F=17.5$, $p<0.05$). Over all experimental groups, subjects gained a significant amount of weight across the course of the study ($F=24.12$, $p<0.01$). However, weights at the end of the study (Table 1) and the rapidity of weight gain did not significantly differ as a function of drug dose (F for dose=0.02, $p>0.05$; F for dose by days=0.94, $p>0.05$). Absolute and relative organ weights for hearts, livers, adrenal pairs, and kidney pairs, and plasma glucose levels also were not significantly related to dose ($p>0.05$ for each measure). These data are shown in Table 1.

TABLE 1

EFFECTS OF CHRONIC TRIPELENNAMINE ADMINISTRATION ON BODY WEIGHT, ORGAN WEIGHTS, AND BLOOD GLUCOSE

Dependent Measure	Tripelennamine Dose (mg/kg) 0.0	2.0	4.0	8.0	16.0	Statistical Outcome
Body weight*	262.330	250.830	250.830	249.500	262.500	F=0.86
	10.280	8.460	2.420	5.460	6.740	$p>0.05$
Heart weight:	0.793	0.724	0.731	0.729	0.765	F=2.00
absolute*	0.026	0.018	0.017	0.027	0.015	$p>0.05$
Heart weight:	3.040	2.900	2.910	2.920	2.910	F=0.38
relative†	0.014	0.121	0.056	0.082	0.020	$p>0.05$
Liver weight:	9.710	9.010	9.260	9.180	10.100	F=1.41
absolute*	0.336	0.251	0.634	0.206	0.344	$p>0.05$
Liver weight:	3.700	3.610	3.690	3.670	3.990	F=0.95
relative†	0.077	0.130	0.243	0.140	0.110	$p>0.05$
Adrenals weight:	0.074	0.075	0.078	0.070	0.073	F=0.45
absolute*	0.005	0.003	0.004	0.005	0.002	$p>0.05$
Adrenals weight:	2.840	3.020	3.110	2.820	2.800	F=0.59
relative†	0.187	0.159	0.130	0.263	0.072	$p>0.05$
Kidneys weight:	1.880	1.770	1.850	1.590	1.880	F=1.51
absolute*	0.071	0.049	0.162	0.093	0.083	$p>0.05$
Kidneys weight:	7.360	7.110	7.350	6.610	7.480	F=1.11
relative†	0.154	0.322	0.577	0.220	0.189	$p>0.05$
Blood glucose‡	99.830	86.330	79.500	79.160	80.830	F=1.42
	6.120	9.670	5.170	7.010	7.680	$p>0.05$

*All weights are expressed as grams; the upper figure for each dependent measure represents the mean, the lower figure one standard error. Mean body weights (±1 standard error) one day prior to the study were 242.2 (±1.2), 247.3 (±10.7), 240.7 (±1.8), 238.3 (±8.7), and 239.6 (±4.9) grams for the 0.0, 2.0, 4.0, 8.0, and 16.0 mg/kg dose groups respectively. Differences between these body weights were not statistically significant ($F=0.43$, $p>0.05$).

†Relative weights were calculated by dividing organ weights by body weights and mutliplying by a factor of 100 for livers, 1,000 for hearts and kidneys, and 10,000 for adenals.

‡Blood glucose levels are expressed in terms of mg/dl; the upper figure represents the mean, the lower figure one standard error.

Figure 2 shows the mean number of wheel revolutions made by animals in each experimental group during 30-min no-shock and post-shock sessions. When shocks did not precede the session (i.e., in no-shock sessions), the average number of revolutions varied directly with dose; this effect was statistically significant ($F=5.23$, $p<0.01$). Data were more equivocal for sessions preceded by electric shocks (i.e., post-shock sessions). Here, number of wheel revolutions was not significantly related to tripelennamine dose ($F=0.46$, $p>0.05$).

Figure 3 presents data for the grasping response and hot-plate assays. In the hot plate (nociception) assay, mean paw-lick latencies were significantly ($F=4.73$, $p<0.01$) related to tripelennamine dose. In this assay, the mean latency was significantly greater (t_{LSD}, $p<0.05$) for the 16 mg/kg group than for any other group. However, animals exposed to 16 mg/kg were not simply non-responsive; they hopped, vocalized and ran when placed on the plate, although they did not readily lick their hind paws.

DISCUSSION

An earlier study [19] used the procedures employed in the present experiment to evaluate the effects of prednisolone, a synthetic glucocorticoid. In that study, evidence of systemic toxicity as indicated by dose-related decreases in body and organ weights were apparent. Significant behavioral actions of prednisolone were also observed. No evidence of systemic tripelennamine toxicity was apparent in the present study, although the drug clearly affected certain behaviors, namely drinking, wheel-running in sessions not preceded by shock, and paw-licking in the hot-plate assay of nociception. Other behaviors (i.e., the grasping response, post-shock wheel-running) were not significantly affected by the drug.

Few previous studies have examined the behavioral effects of tripelennamine in nonhumans. The finding that tripelennamine reduced locomotion (wheel-running) in sessions not preceded by shock is consistent with an earlier report concerning the effects of acute tripelennamine admin-

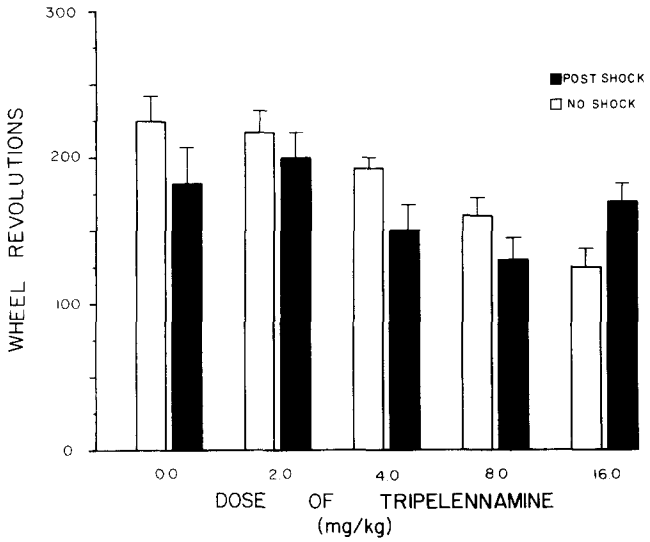

FIG. 2. Effects of tripelennamine on wheel-running when assessment was (closed bars) and was not (open bars) immediately preceded by footshocks. Bars represent mean number of complete wheel revolutions per animal during 30-min sessions; vertical lines indicate 1 standard error.

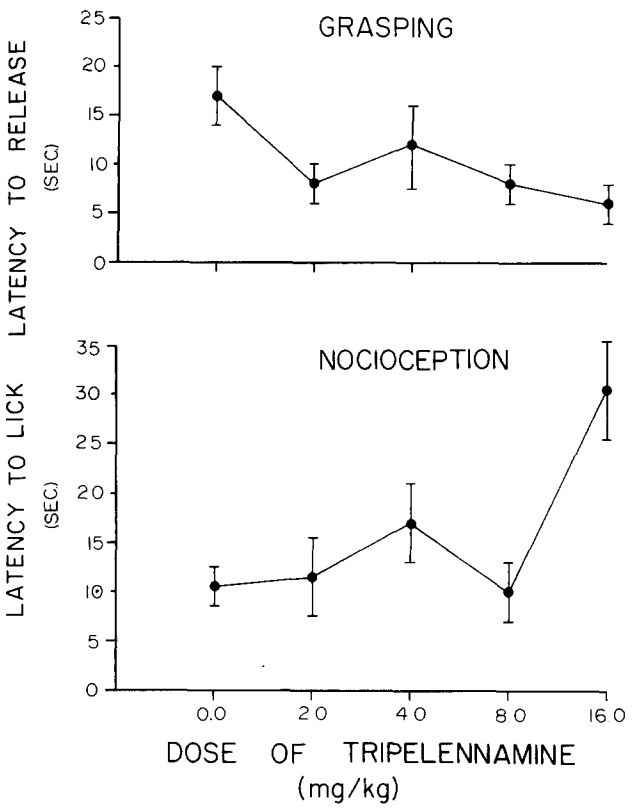

FIG. 3. Tripelennamine effects on the grasping response and nociception. Grasping response data indicate mean seconds elapsed (±1 standard error) from the initiation to the release of wire-grasps. Nociception data represent the mean latency (in seconds, ±1 standard error) from the time rats were placed on the hot plate (59°C) until they licked a hind-paw. For both the grasping and nociception measures, five trials were conducted in succession for each subject, and data for all trials were averaged.

istrations on the open-field performance of mice [4]. That report also indicated that paw-lick latencies in a hot-plate assay were slightly, but not significantly, elevated by tripelennamine at doses of 10 mg/kg and less. Paw-lick latencies in the present study were most affected by the 16.0 mg/kg dose; as in the prior investigation, relatively low doses only slightly elevated latencies relative to control values. No previous studies have examined the effects of tripelennamine on drinking, post-shock performance, or the grasping response. However, it has been found that tripelennamine at nontoxic doses does not affect rats' open-field performance when it is assessed in sessions preceded by exposure to intense white noise [11]. Electric shock and loud white noise may well be stressors with similar actions; in any case, tripelennamine's effects on locomotion following exposure to each appears similar.

The present findings demonstrate that tripelennamine at doses below those associated with systemic toxicity produces behavioral effects readily detected via simple assays. The mechanism responsible for these effects is speculative.

Data from several sources implicate histamine as a neurotransmitter [7, 12, 17, 22]. Specific histamine binding sites in brain tissue have been reported [3], and it appears that activation of H_1 receptors is associated with behavioral arousal, whereas activation of H_2 receptors produces behavioral depression and somnolence [3,12]. The finding that tripelennamine, an H_1 blocker, when active in the present study produced what may be considered as depressant effects is consistent with this model. However, it is misleading to suggest that tripelennamine-treated rats were obviously inactive. They were not: As noted earlier, in the hot-plate assay rats which received 16 mg/kg tripelennamine were quite active—they ran, vocalized, and reared against the walls of the apparatus despite evidencing elevated paw-lick latencies. Thus, the mechanism responsible for the apparent analgesia (i.e., the increased paw-lick latency) does not appear to be motor incapacitation, or other obvious behavioral depression. In addition, tripelennamine increased water intake in the present study. This action cannot be related to what have to date been posited as histamine's actions as a neurotransmitter. While it certainly is possible that the increased drinking associated with tripelennamine is centrally mediated, it may also reflect the drug's peripheral anticholinergic properties. The atropine-like actions of tripelennamine, described elsewhere [5], include drying of the mouth. It is tenable that this effect contributed to the increased water intake produced by tripelennamine.

That tripelennamine's effects were selective, and not manifested in all behavioral tests, is not surprising. It is a fundamental tenet of behavioral pharmacology that the response measured, as well as the environmental circumstances under which it is assessed, can crucially determine whether or not a drug is behaviorally active and, if so, whether its action is excitatory or inhibitory (for examples see [18]). That tripelennamine produced selective effects that differed from those of prednisolone in the battery of tests used in the present study does indicate that this battery may be of value for screening behaviorally active drugs, although further study will be required to determine its utility and cost-effectiveness.

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