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Oral Intake of Morphine in Selectively Bred Rats[1]

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SATINDER, K. P. *Oral intake of morphine in selectively bred rats.* PHARMAC. BIOCHEM. BEHAV. 7(1) 43–49, 1977. – Oral intake of morphine was investigated in selectively bred strains of rats. It was possible to induce all the five genetic lines to consume morphine in distilled water. Withdrawal of morphine resulted in significant decrease in the body weights of all the genetic lines in both the experiments. Significant drug-preference behavior was found only in three genetic lines with a common characteristic of relatively high emotional reactivity as compared to the two lines not showing such a behavior.

Oral intake of morphine Strain differences in morphine intake Morphine withdrawal effects

ORAL INTAKE of morphine in rats without premedication has been produced by forcing thirsty animals to drink morphine in water [16]. Development of morphine preference in rats has also been induced by presenting morphine in various concentrations of sucrose [4,5] and morphine-adulterated food [5]. However, it was not possible to induce morphine preference by presenting morphine in water or in saline [6]. In the present investigation an attempt has been made to induce preference for morphine in water in comparison with water alone.

In spite of the desirability of investigating the genetic bases of morphine intake, research with morphine involving such a method has been minimal. The only studies known to the author are the ones in which selective breeding was used to produce two strains of rats that differed in their susceptibility to morphine intake [8], and the oral ingestion of morphine hydrochloride and morphine sulfate water solutions in Wistar and hooded rats [7]. It seems to be of significant interest to study the role of genetically selected behaviors in morphine intake, especially when behaviors involved are considered to be of theoretical importance in drug intake. Hence, the main purpose of this investigation was to study the morphine intake in lines selectively bred for emotional reactivity and avoidance conditionability. These lines of rats have shown differential effects of intraperitoneal administration of d-amphetamine [10,12] and morphine [15] as well as oral intake of alcohol [11,13] on various indices of behavior.

EXPERIMENT 1

The purpose of this experiment was to investigate the oral intake of morphine, followed by withdrawal of morphine and subsequent choice selection of morphine.

Method

Animals. Forty naive male rats, 8 each from MNR/Har/Lu, MR/Har/Lu, RCA/Lu, RHA/Lu, and RLA/Lu strains were used. The MNR/Lu and MR/Har/Lu strains have been subject to genetic selection for low and high open-field emotional reactivity, respectively. The RHA/Lu and RLA/Lu lines have been genetically selected for high and low rates of avoidance learning, respectively, and the RCA/Lu represents a nonselected control line. Further details regarding the history of these strains have been reported earlier [10,11]. The animals were bred and reared in the laboratory, weaned at 28 days, and were 100 days of age at the start of the experiment. Before experimentation the animals were housed in the same-sex pairs and strains on separate cage racks. During experimentation the animals were coded and housed individually to ensure that the experimenter did not know the strain of the animals. The laboratory temperature was thermostatically controlled at 22 ± 1° C., and the humidity level was maintained at 40%. Fluorescent lights were on a 12 hr light-darkness cycle.

Procedure. The cage setting described in an earlier study [11] was used. In both experiments the strategy of self-selected drinking was used. All the solutions were

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made up in distilled water. The animals were given a choice trial between 0.1 mg/ml morphine sulfate in 5% sucrose solution and 5% sucrose solution for one day. For the next two days, the animals were given only 0.1 mg/ml morphine in 5% sucrose, for the next two days the sucrose content was reduced to 2.5% but the morphine concentration remained the same. For the next two days 0.2 mg/ml morphine sulfate was given in 2.5% sucrose and then for two days sucrose was reduced to 1.25% but the morphine concentration remained at 0.2 mg/ml. After this morphine was given in water only and animals were progressively exposed to increasing concentrations of 0.2, 0.3, 0.4, 0.5, 0.7, 0.9, and 1.2 mg/ml morphine for five days each with no choice; on the 2 days following each five-day period of forced morphine a choice trial between water and morphine solution was given. Before the choice trial for 1.2 mg/ml morphine was given, the animals were withdrawn from morphine for 48 hr, but food and water were available continuously. The rationale behind this schedule of mixed vehicle presentation and of increasing morphine concentration was, first to induce animals to start drinking morphine and then to provide enough morphine by increasing concentration, to produce dependence on the drug. The animals were disturbed at 24 hr-intervals to record body weight and fluid intake, to replenish food, and to empty, clean, and refill the drinking bottles. The position of bottles was changed every day in a systematic rotation.

Results and Discussion

The following measures were obtained from each animal for every morphine concentration based on the number of days referred to in the procedure. (1) Intake of morphine solution expresses as a percentage of the total fluid intake during choice trials. (2) The amount of morphine expressed in mg/kg/24 hr both during choice and forced trials. (3) The fluid (ml/kg/24 hr) intake during both choice and forced trials. The results were evaluated by analysis of variance.

The mean percentages of morphine solution consumed during choice days under each concentration are presented for all the five strains in Fig. 1. There were significant differences among the strains, $F(4,35) = 28.2$, $p < 0.001$, and among various (0.2 – 1.2 mg/ml) concentrations, $F(6,210) = 11.5$, $p < 0.001$. There was a significant interaction between strains and concentrations, $F(24,210) = 2.6$, $p < 0.01$, indicating that strains showed differential percentage intake of morphine. In the MNR and RLA lines there were no significant changes in the consumption of various concentrations. In the MR, $F(6,42) = 9.1$, $p < 0.001$, RCA ($p < 0.025$) and RHA ($p < 0.001$) lines changes in the percentage consumption of various concentrations were significant.

Comparison of the mean percentages of morphine intake (refer to Fig. 1) between the MR and MNR strains showed that the MR strain had significantly ($p < 0.001$) higher proportional morphine intake than the MNR strain. Furthermore, a significant strains × concentrations interaction showed that these two strains had different proportional morphine intake under various concentrations except under 0.2 and 1.2 mg/ml conditions. The corresponding analysis between the RHA and RLA lines indicated that although the RHA line had higher levels of proportional morphine intake than the RLA line, none of the differences were statistically significant, except during 1.2 mg/ml choice, when RHA increased its consumption and RLA showed decrease in consumption.

Considering significant intake of morphine over 50% as an active, drug-preference behavior, it is clear from Fig. 1 that only the RHA, RLA, and MR strains showed an obvious preference for morphine. However, in the MNR and RCA strains, the development of preference for morphine was absent.

Means of morphine (mg/kg/24 hr) consumed during choice trials are presented in Table 1. There were significant differences among the strains, $F(4,35) = 37.2$, $p < 0.001$, and among various concentrations (0.2 – 1.2 mg/ml), $F(6,210) = 67.4$, $p < 0.001$, in the consumption of morphine. In the MNR line there were no significant changes among concentrations. In the MR line there were significant differences in the morphine consumed under various concentrations, $F(6,42) = 7.8$, $p < 0.001$, the same was true in the RCA, RHA and RLA strains, ($p < 0.01$) during choice trials.

Comparison between the MR and MNR lines showed that the MR line consumed significantly larger amounts of morphine than the MNR line, $F(1,14) = 7.1$, $p < 0.025$. Strains × concentrations interaction, $F(6,84) = 2.4$, $p < 0.05$, showed that these two lines of rats took different amounts of morphine under various concentrations, predominantly between 0.3 0.9 mg/ml concentrations. The similar comparison between the RHA and RLA lines showed that the RHA line consumed significantly ($p < 0.01$) larger amount of morphine than the RLA line. There was also a significant interaction between strains and concentrations ($p < 0.005$).

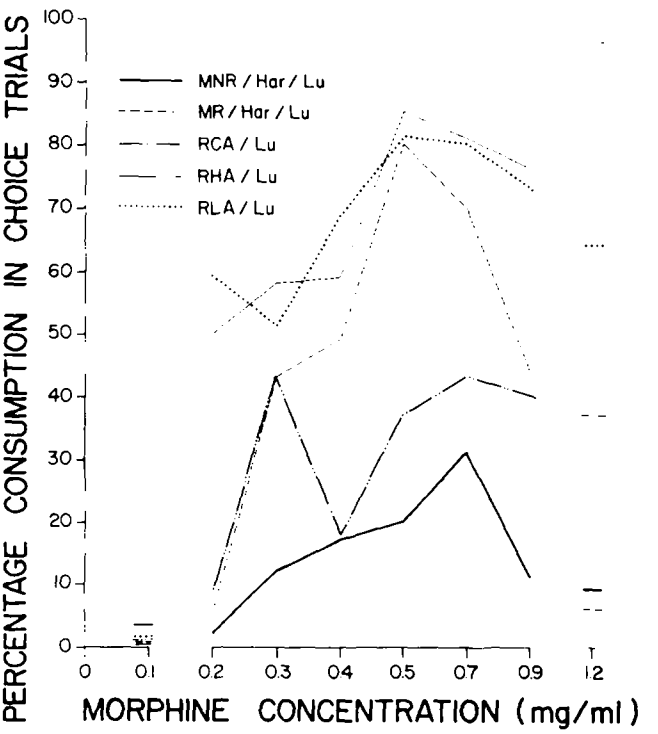

FIG. 1. Percentage consumption of morphine by five genetic lines in choice trials between morphine solutions and water.

TABLE 1

MEANS OF MORPHINE INTAKE (mg/kg/24 hr) IN CHOICE TRIALS.

Genetic Lines	Morphine Concentrations (mg/ml) 0.1 in 5% sucrose	0.2	0.3	0.4	0.5	0.7	0.9	1.2
MNR/Har/Lu	1.1	0.7	2.4	5.6	8.6	17.0	8.2	9.3
MR/Har/Lu	0.0	0.9	7.4	11.7	26.1	28.9	23.8	4.4
RCA/Lu	0.0	1.5	6.5	3.9	10.5	16.4	19.4	34.1
RHA/Lu	0.0	8.7	13.7	16.8	30.1	42.9	50.0	99.1
RLA/Lu	0.1	8.2	9.3	17.5	25.7	38.7	42.5	58.5

TABLE 2

MEANS OF MORPHINE (mg/kg/24 hr) INTAKE IN FORCED TRIALS.

Genetic Lines	Morphine Concentrations (mg/ml) 0.1 in 5%	0.1 in 2.5% sucrose	0.2 in 2.5%	0.2 in 1.25%	0.2	0.3	0.4	0.5 in distilled water	0.7	0.9	1.2
MNR/Har/Lu	10.6	10.0	14.3	13.8	15.1	20.8	25.9	35.9	48.3	62.0	81.0
MR/Har/Lu	10.6	11.8	22.6	12.8	12.6	18.4	26.4	34.4	45.4	60.5	67.1
RCA/Lu	5.7	5.7	7.2	10.0	11.9	16.6	22.5	29.4	39.4	52.5	66.3
RHA/Lu	15.8	8.2	18.5	11.9	15.2	21.4	28.4	35.6	45.7	59.6	83.3
RLA/Lu	10.5	7.0	12.1	12.4	13.1	18.3	24.6	30.6	43.1	54.3	69.5
p	< 0.005	< 0.01			<0.005	<0.005		<0.025			<0.005

TABLE 3

MEANS OF BODY WEIGHTS AND FOOD INTAKE DURING 48 HR. OF PREWITHDRAWAL, WITHDRAWAL, AND POSTWITHDRAWAL OF FORCED 1.2 mg/ml MORPHINE INTAKE.

Genetic Lines	Body weights (g) At the start of morphine withdrawal	48 hr after morphine withdrawal	48 hr after resumption of morphine	Food Intake (g) During 48 hr before morphine withdrawal	During 48 hr of morphine withdrawal	During 48 hr after resumption of morphine
MNR/Har/Lu	268	248	260	37	33	42
MR/Har/Lu	326	310	320	33	38	40
RCA/Lu	395	357	383	48	42	47
RHA/Lu	352	320	340	46	40	36
RLA/Lu	363	324	350	44	31	39

Table 2 shows the mean amount of morphine consumed by the strains during the forced intake. There were significant differences among the strains under various concentrations as indicated in Table 2. In general, the RHA strain showed the highest morphine intake followed, in order, by the MNR, MR, RLA and RCA lines leading to overall significant differences among the strains ($p<0.01$). However, comparisons between the pairs of the bidirectionally selected strains showed that during forced intake of morphine the MR and RHA line did not differ significantly from the MNR and RLA lines, respectively. Mean fluid intake during forced trials was relatively constant in all the genetic lines under increasing morphine concentrations.

Changes in body weight and food intake during 48 hr withdrawal of 1.2 mg/ml morphine were evaluated by analysis of variance. The means are presented in Table 3. There was a significant decrease ($p<0.01$) in the body weights of all the strains after 48 hr of morphine withdrawal. All the strains showed significant increases ($p<0.01$) in body weights during the 48 hr postwithdrawal period in which choice between 1.2 mg/ml morphine and water was provided. There was no differential effects among the strains in the relative changes in body weights among the schedules presented in Table 3.

Food intake (see Table 3) was lower in all the strains except the MR strain during 48 hr morphine withdrawal compared to the corresponding prewithdrawal period, however, this reduced intake was significant only in the RHA strain $F(1,7) = 20.8$, $p<0.005$, and RLA strain ($p<0.001$). Food intake was also lower during 48 hr of drug

withdrawal as compared to corresponding postwithdrawal period in all the strains except the RHA strain. Overall reduction in food intake during morphine withdrawal is in the line with previous findings [2].

EXPERIMENT 2

Although the results of Experiment 1 clearly demonstrated the strain differences in oral intake of morphine, interpretation of these findings cannot be unequivocal for the following reasons. First, the pattern of the increasing amounts of morphine consumption during forced trials could be due to the possibility of an increasing desensitization to bitter taste of morphine or else because the animals maintained a constant fluid intake on forced trials as noted in Experiment 1. Second, the increasing proportional intake of morphine during choice trials could not be interpreted as need for morphine because preference for morphine could not be demonstrated justifiably in the absence of a control group which was not exposed to the forced intake of morphine. Hence, the purpose of this experiment was to investigate further the oral intake of morphine by providing appropriate controls for the questions raised above.

Method

Animals. One hundred and twenty experimentally naive rats equally represented by the five strains and both the sexes were used. The animals were 100 days old. Other conditions were exactly the same as in Experiment 1.

Experimental design. To account for the taste desensitization to the bitter solution of morphine, a control group was included which was exposed to equiaversive solution of a pharmacologically inert substance, i.e., quinine. To eliminate the confounding produced by the increasing concentration of morphine, a single concentration of 0.5 mg/ml morphine sulfate was used [4,16]. To investigate the development of preference for morphine, another control group was included, which was not exposed to the forced intake of morphine but was given choice trials for morphine along with the group given both forced and choice trials of morphine. This control group also eliminated the requirement for the consumption of at least 50% of morphine solution in choice trials to demonstrate preference for morphine, as done in Experiment 1 and considered essential by other investigators [17]. In a pilot investigation it was found that 0.25 mg/ml of quinine sulfate was equiavarsive to 0.5 mg/ml of morphine sulfate.

Procedure. The cage setting was the same as in Experiment 1. All the animals were given distilled water for two days, and on the basis of water consumption the animals were matched and divided into three groups, thus forming 15 equal groups to represent five strains and three experimental conditions. On a random basis these groups were designated as forced and choice morphine groups (MM), forced and choice quinine groups (QQ), and forced water and choice morphine groups (WM). To establish base line consumption of the drugs, the MM and WM groups were given a choice between 0.5 mg/ml morphine and water, and the QQ group was given choice between 0.25 mg/ml quinine and water for the next two days. Then for five days, the MM group was given forced morphine (0.5 mg/ml), and the WM group was given water only, and the QQ group was given forced quinine (0.25 mg/ml). After this forced intake for five days, all the groups were given choice trials as described above. This forced-choice schedule was repeated six times. After the last (seventh) forced trial and before the choice trial, all the animals were deprived of both food and water for 48 hr and then were given the last respective choice trial along with food. Food and water deprivation for 48 hr was intended to disassociate body weight loss during withdrawal [18] due to changes in food and water intake. The rest of the procedure was exactly the same as in Experiment 1.

Results and Discussion

Based on the number of days referred to in the procedure, the following measures were obtained from each

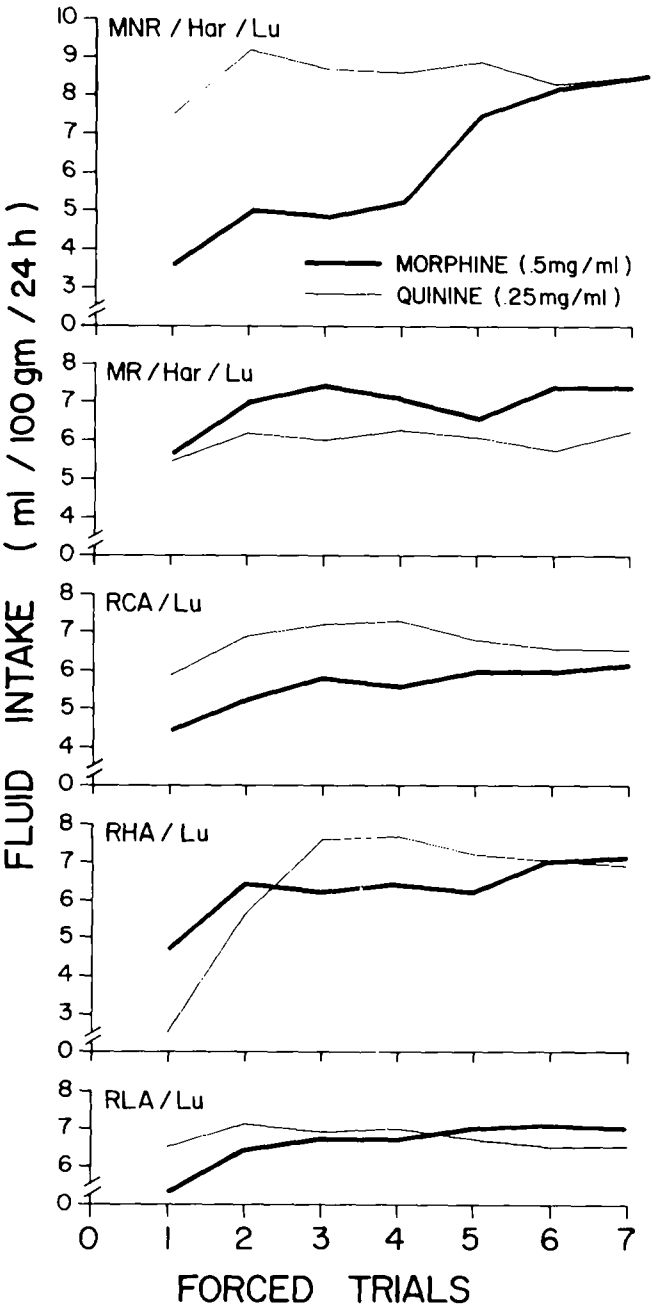

FIG. 2. Consumption of morphine and quinine solutions by each of the five genetic lines during forced trials.

of the animals. (1) Intake of morphine and quinine solutions expressed as a percentage of the total fluid-intake during choice trials. (2) The amounts of morphine and quinine expressed in mg/kg/24 hr both during forced and choice trials. (3) The fluid (ml/kg/24 hr) intake both during forced and choice trials. The results were evaluated by analysis of variance.

The fluid intakes during the forced intake trials are presented for the MM and QQ groups in Fig. 2. There were no significant differences between the groups among all the genetic lines except MNR, $F(1,12) = 21.2$, $p < 0.01$, which also disappeared during the last two trials. This finding clearly indicates that the 0.5 mg/ml morphine and 0.25 mg/ml quinine were equiaversive for all the strains, except the MNR line to start with. This significant difference between MM and QQ groups in the MNR line was due to the fact that females in the MM group had a very low consumption during the first four trials as compared to the males, whereas no such drastic differences were found in the QQ group between the sexes. There were no significant differences among strains in the forced intake fluids in MM and QQ groups. However, there was a significant interaction between the strains and groups, $F(4,60) = 3.8$, $p < 0.008$, as evident from Fig. 2. The animals of the WM group had significantly higher fluid intake than either MM, $F(1,60) = 119.0$, $p < 0.001$, or QQ ($p < 0.001$) group. This was true in all the strains during the forced intake trials.

The means of the percentages of morphine and quinine solutions consumed during each of the choice trials are presented in Fig. 3 for MM, WM, QQ groups and genetic lines.

There were significant differences among the genetic lines in the MM, $F(4,30) = 6.3$, $p < 0.001$, group but not in the WW and QQ groups. There were also significant increases in the percentages of the drug consumed in successive choice trials in the MM, $F(7,210) = 28.1$, $p < 0.001$, group and not in the WM and QQ groups. Comparisons between the MM and WM groups of the respective genetic lines showed that the differences between the groups were significant in the MR, $F(1,12) = 35.7$, $p < 0.001$, RHA ($p < 0.006$) and RLA ($p < 0.002$) and not in the MNR and RCA lines. This finding clearly indicates that a morphine preference had developed in the MR, RHA, and RLA lines only. These findings are in support of the findings reported in Experiment 1. In general, there were significant differences between the MM and WM groups, $F(1,60) = 48.7$ $p < 0.001$, and the MM and QQ groups ($p < 0.001$) and not between the WM and QQ groups in the percentages of the respective drugs consumed. It is to be noted (Fig. 3) that there was a significant interaction between strains and successive choice trials in the MM groups, $F(28,210) = 4.0$, $p < 0.001$, and not in the WM and QQ groups. Furthermore the comparisons between the percentage consumption of morphine during choice trials indicated that the differences between the MM and WM groups and among genetic lines were not significant during first three choice trials. However, from the fourth to the eighth trial the difference between the MM and WM groups and among lines in the MM group became significant. There were no significant differences between the sexes in the percentages of the drugs consumed during the choice trials in any of the groups.

Means of the respective drugs consumed during choice trials by the experimental groups and genetic lines are presented in Table 4.

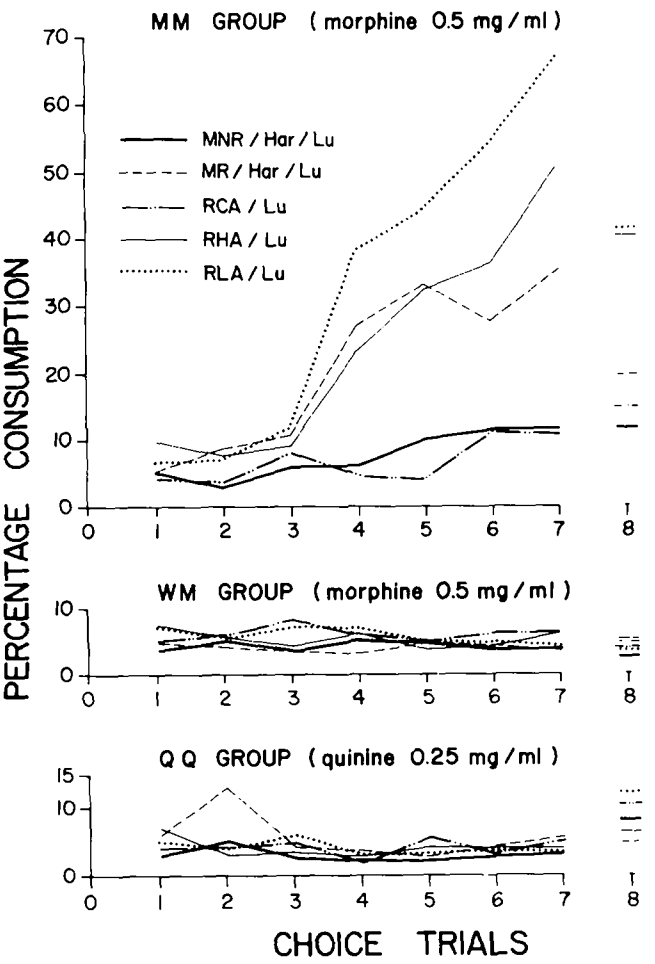

FIG. 3. Percentage consumption of morphine and quinine in choice trials between the respective drug and distilled water of five genetic lines in MM, WM, and QQ groups.

There were significant differences among the genetic lines in the MM group, $F(1,30) = 2.5$, $p < 0.001$), and not in the WM and QQ groups. This indicated that only in the MM group the genetic lines consumed differing amounts of drug as the choice trials progressed. Comparisons between the MM and WM groups of the respective genetic lines showed that the difference between the groups were significant in the MR ($p < 0.006$), RHA ($p < 0.006$) and RLA ($p < 0.002$) and not in the MNR and RCA lines.

The MR animals had both higher proportional as well as amounts of morphine intake during choice trials than the MNR animals, however the differences were significant only in the proportional intake, $F(1,12) = 12.4$, $p < 0.005$, and not in the amount of morphine. The findings are in general agreement with the findings of Experiment 1. The RLA animals had higher intake in both the aspects as compared to the RHA animals and differences were not significant in either.

The means of body weights of the experimental groups and genetic lines at various stages of the experiment are presented in Table 5.

There was no significant difference among the experimental groups in the body weight at the start of the experiment. However, there were significant differences among genetic lines ($p < 0.001$) and between sexes

TABLE 4

MEANS OF DRUGS (mg/kg/24 hr) CONSUMED DURING CHOICE TRIALS.

Experimental Groups	Genetic Lines	Choice Trials 1	2	3	4	5	6	7	8	Average amount of drug consumed in each choice trial
	MNR/Har:Lu	4.0	2.6	4.8	4.2	7.4	7.5	6.9	9.0	5.8
	MR/Har:Lu	2.4	3.8	3.9	11.4	13.3	8.7	11.6	13.2	8.5
MM	RCA:Lu	1.8	2.3	3.2	2.3	2.3	5.6	5.1	8.8	3.9
	RHA:Lu	4.9	4.4	3.9	9.1	13.3	14.0	19.2	23.9	11.6
	RLA:Lu	3.8	3.3	5.2	16.2	17.4	20.5	23.7	23.2	14.2
	MNR/Har:Lu	2.8	3.8	2.6	3.5	3.3	2.5	2.6	1.8	2.9
	MR/Har:Lu	2.3	2.1	1.9	1.6	2.6	2.2	1.7	2.7	2.1
WM	RCA:Lu	2.5	2.8	3.2	2.7	2.4	2.4	2.9	2.6	2.7
	RHA:Lu	3.7	2.8	2.2	3.1	1.9	2.1	3.0	3.4	2.8
	RLA:Lu	4.7	3.3	4.3	3.9	2.6	2.4	2.3	2.5	3.3
	MNR/Har:Lu	1.2	2.8	1.3	0.9	0.8	1.1	1.3	4.0	1.7
	MR/Har:Lu	1.5	1.2	1.1	1.1	0.8	1.2	1.7	1.5	1.3
QQ	RCA:Lu	1.0	1.3	1.5	0.5	1.3	1.0	1.5	3.3	1.4
	RHA:Lu	1.9	1.3	1.5	1.3	1.3	1.3	1.2	2.5	1.5
	RLA:Lu	1.4	1.4	1.6	1.0	0.9	1.1	1.2	3.8	1.6

TABLE 5

MEANS OF BODY WEIGHTS (g) AT VARIOUS STAGES OF THE EXPERIMENT

Columns		1	2	3	4
Genetic Lines	Experimental Groups	At the start of the experiment	At the start of food & drug withdrawal	48 h after food and drug withdrawal	Percentage change between columns 1 and 3
	MM	218	218	180	17
MNR/Har:Lu	QQ	215	232	201	7
	WM	212	234	201	5
	MM	249	256	215	14
MR/Har:Lu	QQ	249	263	232	7
	WM	241	269	236	2
	MM	314	294	254	−19
RCA:Lu	QQ	319	338	300	− 6
	WM	322	343	299	7
	MM	281	294	252	− 10
RHA:Lu	QQ	290	308	273	6
	WM	264	300	261	1
	MM	271	280	240	−11
RLA:Lu	QQ	280	306	271	− 3
	WM	276	306	267	− 3

($p < 0.001$), which remained significant throughout the experiment. There were significant differences among the experimental groups in body weight at the start of the food and drug withdrawal, $F(2,90) = 6.6$, $p < 0.003$, as well as after 48 hr of withdrawal of food and drug ($p < 0.001$). However, these were clearly due to the differences between the MM and either of the other two groups and not between QQ and WM groups. It is evident from the percentage changes between the body weights at the start of the experiment and after 48 hr of food and drug withdrawal (Table 5, Column 4). On the average, decrease in the body weights of the MM groups was 14% as compared to 6% in the QQ groups and 4% in the WM groups. It is to be noted that it was only in the MM groups

of all the genetic lines that significant differences emerged between the body weights at the start of the experiment and 48 hr after the food and drug withdrawal.

GENERAL DISCUSSION

The oral intake of morphine, an active, drug-seeking behavior, which reflects the development of need for morphine or dependence on it, is related to genetic background of the animals, as indicated by the findings of Experiments 1 and 2. It may be recalled that it was only the RHA, RLA, and MR genetic lines that showed significantly increasing consumption of morphine during choice trials, whereas no such behavior was found in the RCA and MNR lines. On the other hand, significant decrease in body weight were found in all five strains on withdrawal of morphine (Tables 3 and 5), which shows the development of drug dependence, as body weight loss is a reliable index of withdrawal [1, 9, 16], although observation of other withdrawal signs, as noted with these strains previously [15] could have provided more reliable information. It is to be noted that the Roman (RCA, RHA, and RLA) strains did not differ significantly from each other in relation to the percentage change in body weight during morphine withdrawal whereas the Maudsley (MNR and MR) strains differed from each other as well as from the Roman strains with regard to the body weight changes. Both active, drug-seeking behavior and withdrawal syndrome are considered as valid criteria for the demonstration of the development of drug dependence, but there is a need for caution if both the criteria are to be used interchangably to demonstrate the phenomenon, because body weight loss was found in all the strains and active morphine-seeking was present only in three of the strains.

Why was an active morphine-seeking behavior shown by the RHA, RLA, and MR lines and not by the RCA and MNR lines? One of the common characteristics of these genetic lines showing the active morphine-seeking behavior is their relatively higher level of open-field emotional reactivity [14] as compared to the RCA and MNR lines. Emotional reactivity may be considered as an index of the sensitivity of the organism to environmental changes, which implies an increased susceptibility to stress situations. This interpretation of emotional reactivity in relation to morphine consumption may indicate that the organisms highly susceptible to stress tend to show higher rates of choice selection of morphine. In other words, the animals more responsive to stress may select morphine solution as a learned adaptive response [11].

No significant differences between the consumption of 0.5 mg/ml morphine and 0.25 mg/ml quinine in Experiment 2 indicated equiaversiveness of both the solutions, hence provided a control for desensitization to the aversive taste of morphine. However, possibility still remains that the preference for morphine displayed by some of the strains could be due to an interaction between acclimatization to morphine's taste and the reinforcing pharmacological effects of morphine. To account for this possibility it would have been preferable to offer some rats in the quinine (QQ) group a choice between morphine and water during choice trials. If acclimation to aversive tastes had played a primary role in morphine preference, these rats would presumably have shown preference similar to that of the rats given forced morphine before the choice trials.

The present findings in relation to the oral intake of morphine show some similarity to those found in alcohol intake of these selected strains [11,13]. This possible genetic correlation between morphine and alcohol intake in these strains is in line with the previous findings [8] in which strains selected for differential susceptibility to morphine intake were also found to differ in alcohol intake. It is to be emphasized, however, that the observed phenotypic correlation between morphine and alcohol cannot be considered genetically based until these phenotypic correlations are also found in the crossbred generations of these strains.

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