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Alcohol Intake in High Alcohol Drinking (HAD) Rats is Suppressed by FG5865, a Novel 5-HT_{1A} Agonist/5-HT_2 Antagonist

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LONG, T. A., G. W. KALMUS, A. BJÖRK AND R. D. MYERS. *Alcohol intake in high alcohol drinking (HAD) rats is suppressed by FG5865, a novel 5-HT_{1A} agonist/5-HT_2 antagonist.* PHARMACOL BIOCHEM BEHAV **53**(1) 33-40, 1996. — Both the 5-HT_2 antagonist, FG5606 (amperozide), and the mixed 5-HT_1 agonist/5-HT_2 antagonist, FG5893, attenuate significantly the volitional intake of alcohol in the cyanamide treated rat. The purpose of the present study was to investigate the effect on alcohol drinking in the selectively bred, high alcohol drinking (HAD) rat of a new and novel 5-HT_{1A} agonist/5-HT_2 antagonist, FG5865 (2-[4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl]-3-pyridinecarboxylic acid methyl ester), which shares pharmacological properties with FG5893. Initially, a standard three bottle preference test for water vs. 3% to 30% alcohol solutions was given over 11 days to determine the maximally preferred concentration for each animal. Then water and this solution, which ranged between 9% and 20% with an overall mean absolute intake of 6.3 ± 0.5 g/kg per day, was offered over three consecutive 4-day test sequences: (1) predrug control; (2) SC injections b.i.d. of either 1.0 mg/kg or 2.5 mg/kg FG5865 or saline control vehicle; and (3) postdrug. Whereas saline failed to alter alcohol consumption of the HAD rats, FG5865 caused a significant dose dependent reduction by as much as 75% in the intakes of alcohol during its administration in terms of both g/kg ($p < 0.01$) and proportion of alcohol to total fluid intake ($p < 0.01$). During the administration of 2.5 mg/kg FG5865, alcohol drinking declined from 6.5 ± 0.3 g/kg to as low as 2.3 ± 0.2 g/kg per day. Neither the body weight of the HAD animals nor their intake of food was affected by either dose of FG5865. These results uphold the concept that the 5-HT_{1A} and 5-HT_2 receptor subtypes in the brain play a part in the aberrant drinking of alcohol of the HAD rat. Because FG5865 influences the activity of serotonergic neurons in the mesolimbic system of the rat, it is envisaged that the drug suppresses alcohol drinking by way of its action on these neurons.

FG5865 (2-[4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl]-3-pyridinecarboxamide) Alcohol drinking
Serotonin receptors Ethanol alcohol preference 5-Hydroxytryptamine Alcoholism
Aberrant drinking HAD rats

PHARMACOLOGICAL studies historically have shown that an elevation in the levels of serotonin (5-HT) in the brain as well as the inhibition of 5-HT reuptake can attenuate the preference for alcohol in the rat and other species (5,7,8,10, 11,29,31,38). Alternatively, the global or localized depletion of neuronal stores of 5-HT in the brain by a serotonergic neurotoxin can act to augment the preference for alcohol (22,30). More recently, it has become clear that receptor subtypes for 5-HT apparently are involved in the self-selection of alcohol in the experimental animal. Certain drugs with differential affinities for 5-HT_1, 5-HT_2 and 5-HT_3 receptors can reduce the voluntary drinking of alcohol to varying degrees (3,6,15,21,35,37) but also produce confounding side effects such as the impairment of caloric intake (8,25,30). However, FG5606 (amperozide), a 5-HT_2 receptor antagonist (1), attenuates significantly the intake of alcohol in rats without modifying the intake of food or other function (32), a critical consideration in view of the caloric value of alcohol (8,30). Amperozide suppresses alcohol consumption in rats induced to drink by pretreatment with cyanamide (32) as well as in alcohol preferring (P) rats, which consume up to 11 g/kg per day of 25% alcohol (17,34). When given continuously by mini-pump over 7 days, amperozide irreversibly suppresses alcohol drinking (33). Taken together, these findings indicate a potential clinical utility for this drug (26).

A novel 5-HT_1 receptor agonist/5-HT_2 antagonist, FG5893

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(2-[4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl]-3-pyridinecarboxylic acid methyl ester), also exhibits properties similar to those of amperozide in that it diminishes alcohol consumption in the cyanamide treated rat for a prolonged period, again with no notable side effects on body weight or on fluid and food intakes (40). Recently, FG5865 (2-[4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl]-3-pyridinecarboxamide) has been found to have a pharmacological profile similar to that of FG5893 in that both compounds possess high binding affinities for both 5-HT_2 and 5-HT_{1A} receptors, are structurally related to amperozide and have antidepressant and antiaggressive properties in the rat (2,12,36).

In view of the actions of amperozide and FG5893 in suppressing alcohol preference, the present study was undertaken to determine whether FG5865 would alter the pattern of drinking of the selectively bred, high alcohol drinking (HAD) rat. Previously it was shown that the HAD rat prefers 10% alcohol over water (18) and exhibits preference for much higher concentrations with a maximum intake of 10.6 g/kg per day at the 20% concentration (16). In comparison to the alcohol nonpreferring low alcohol drinking (LAD) rat, the HAD rat has 10%–20% lower levels of 5-HT, dopamine, and their respective metabolites in discrete regions of the brain including the nucleus accumbens, corpus striatum, and the cerebral cortex (9,44). The subtypes of 5-HT receptors as well as GABAergic nerve terminals in different cerebral structures also differ in their densities between the HAD and LAD rats (13,20). Finally, alcohol has been shown to enhance the extracellular level of both 5-HT and dopamine in the HAD animal (43).

METHODS

Male HAD rats of the F_{21} generation ($N = 7$), weighing from 310 to 403 g and naive to alcohol, were obtained from the Alcohol Research Center of Indiana University Medical Center (Indianapolis, IN). Each rat was housed individually in a wire mesh cage in a temperature controlled room at 22–24°C and maintained on a 12 h light cycle with lights on at 0600 h. Agway NIH-07 formulation rat chow and tap water were provided to the rats throughout the experiment. At 0830 h, measures of food and fluid intakes as well as body weight were recorded daily.

Determination of Alcohol Preference

The preference for alcohol vs. water was determined for each rat individually by means of a standard three bottle, two choice procedure carried out over 11 days (4,17). Three 100 ml Kimax drinking tubes were affixed equidistantly to the front of each cage: one tube contained tap water, a second contained a solution of alcohol in tap water, and the third tube was empty; the tubes were rotated daily to deter the development of a position habit (27). A 3% v/v concentration of alcohol was offered to each animal on the first day and then the concentration was increased on each successive day over the next 10 days as follows: 4%, 5%, 7%, 9%, 11%, 13%, 15%, 20%, 25%, and 30%. At the end of this preference test, the maximally preferred solution of alcohol was determined individually for each rat which represented the highest concentration consumed during the 3%–30% screen prior to a downward shift below the 0.50 level in the proportion of alcohol to the total fluid ingested (17,32). The preferred concentrations of the animals were as follows: 9% ($N = 1$); 13% ($N = 3$); 15% ($N = 2$); and 20% ($N = 1$).

Treatment with FG5865

After the initial 11 day preference test, water and the preferred concentration of alcohol were offered to each HAD rat for 12 consecutive days. The first interval of 4 days constituted a predrug control test period; then the rats were divided randomly into three groups, and over a second 4-day period, either a dose of 1.0 mg/kg or 2.5 mg/kg of FG5865 or the saline control vehicle was injected subcutaneously. Each solution of FG5865 was prepared freshly in the vehicle and administered at 1600 and 2200 h. The two doses were selected on the basis of previous findings on the efficacy of FG5893 and amperozide (32,40). Testing of the rats for their preferred concentration of alcohol was continued for an additional interval of 4 days. Following a counterbalanced design, the groups were rotated in both the second and third series of 12-day preference tests, so that all rats in each group received the opposite dose of the drug or saline.

Statistical Analysis

All data were analyzed using the InStat software program (GraphPad San Diego, CA). Analyses of variance followed by Bonferroni tests were used to determine the differences between alcohol, food, and water intakes as well as body weight during the 4-day injection period and the 4-day pre- and postinjection periods. In addition, the mean percent decline in the g/kg and proportional values of alcohol consumed was correlated against the constant concentration of alcohol offered to each rat. A p value of < 0.05 was considered statistically significant.

RESULTS

The absolute grams/kilograms and the proportional intakes of alcohol per day of the HAD rats recorded during the initial 3% to 30% alcohol preference screen corresponded to the data on their pattern of drinking reported previously (16). As shown in Fig. 1 (top), the proportional value rose to a peak of 0.90 ± 0.05 at the 5% concentration and remained at elevated levels until declining through the 15% to 30% solutions. However, as the percent concentration was increased during the 3% to 30% preference test, the drinking of the absolute amount of alcohol of the HAD rats climbed significantly (Fig 1., bottom) to reach a peak consumption of 9.4 ± 1.5 g/kg per day at the 25% concentration.

Dose Response To FG5865

A composite analysis of the mean effects of the two doses of FG5865 administered subcutaneously is presented in Fig. 2. An analysis of the drinking responses to the two doses of FG5865 and the saline control vehicle revealed a significant difference between groups [$F(2, 83) = 22.5$, $p < 0.01$]. The overall mean proportional intakes of alcohol (Fig. 2, top) declined significantly from 0.81 ± 0.02 predrug (PRE) to 0.58 ± 0.05 during the injection (INJECT) of 1.0 mg/kg FG5865 [$F(1, 55) = 18.2$, $p < 0.01$] and from 0.75 ± 0.03 to 0.36 ± 0.03 during treatment with the higher dose of 2.5 mg/kg [$F(1, 55) = 84.5$, $p < 0.01$]. However, there were no significant differences in the proportional intakes of alcohol between the pre- and postdrug interval (Fig. 2, top). As illustrated in Fig. 2 (bottom), the mean absolute intake of alcohol in g/kg per day also was suppressed significantly by FG5865 from 6.9 ± 0.3 to 3.5 ± 0.27 during the injection of the 1.0 mg/kg dose [$F(1, 55) = 71.8$, $p < 0.01$], and from 6.4 ± 0.3 to 2.2 ± 0.3 during the administration of the 2.5 mg/kg dose [$F(1,$

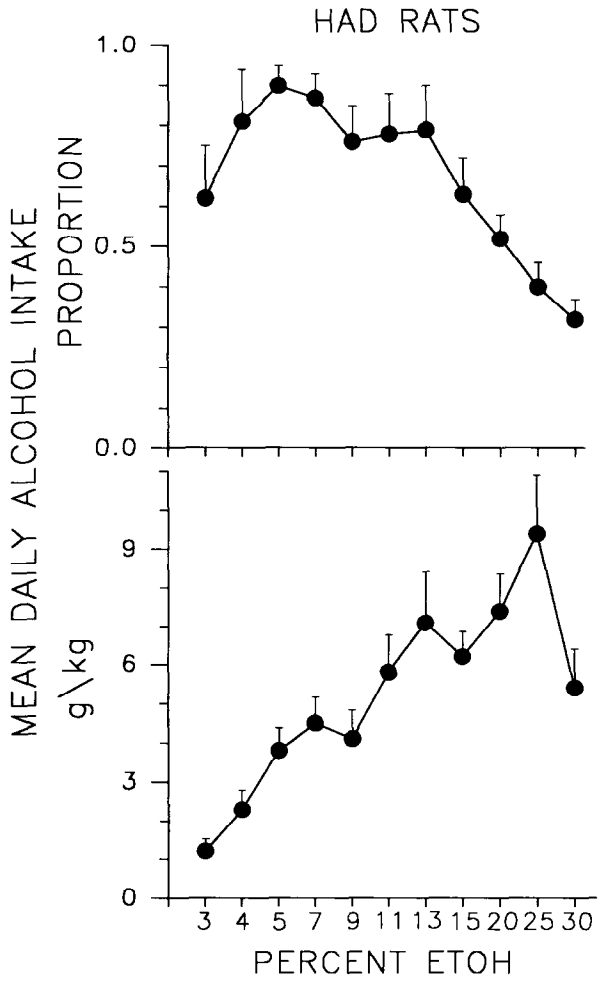

FIG. 1. Mean ± SE daily intakes of alcohol of high alcohol drinking (HAD) rats in terms of proportion of alcohol to total fluid (top) and absolute g/kg (bottom) during preference test in which water and an alcohol concentration was increased on successive days from 3% to 30% over an 11-day period.

55) = 97.9, $p < 0.01$]. The differences in the g/kg intake of alcohol between the 1.0 and 2.5 mg/kg doses and the saline controls during the injections were dose dependent [$F(2, 83) = 17.4, p < 0.01$].

An analysis of the daily pattern of alcohol drinking during and after the administration of FG5865 is presented in Fig. 3 in terms of the daily proportion of alcohol to total fluid and the g/kg consumed on each day. FG5865 caused a dose dependent decline in drinking after the first set of injections in both the proportional value (Fig. 3, top) and absolute grams/kilograms intake (Fig. 3, bottom), which continued throughout its treatment. The higher dose suppressed the intake immediately to below 2.0 g/kg within 24 h (1.9 ± 0.4 g/kg); however, the maximal decline in the proportional intake did not occur until the fourth day of injections of the 2.5 dose of FG5865 (0.31 ± 0.06). On cessation of treatment, the daily pattern of drinking resumed fully to basal levels by either the second or third day.

Table 1 presents a composite analysis of the overall mean ± SEM changes in the intakes of food, water, and alcohol as well as the level of body weight during each of the test conditions. Only minimal changes in both the intakes of food and body weight were produced by FG5865 during and after the administration of either dose of the drug. The 1.0 mg/kg dose of FG5865 caused a significant decline in the consumption of alcohol expressed in ml per day [$F(2, 83) = 11.8, p < 0.01$] but a significant rise in the intake of water [$F(2, 83) = 4.6, p < 0.01$]. The higher dose of FG5865 also significantly increased the intake of water [$F(2, 83) = 7.1, p < 0.01$] in the HAD rats while simultaneously attenuating alcohol drinking [$F(2, 83) = 35.2, p < 0.01$] without altering body weight. The control injections of the saline vehicle were without effect.

To determine if the percent alcohol preferred by individual rats determined the magnitude of the suppressant effects of FG5865 on drinking, the mean percent declines in intake of alcohol, in both g/kg and proportional values, were correlated against the constant concentration of alcohol offered to each rat. The interaction between the strength of alcohol and the

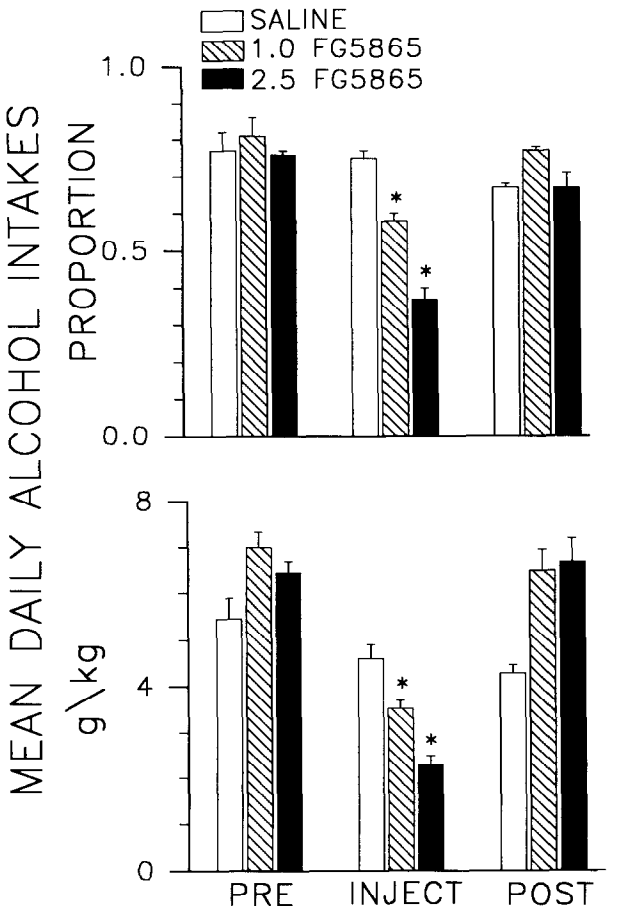

FIG. 2. Mean ± SE composite daily intakes of alcohol of high alcohol drinking (HAD) rats in terms of proportion of alcohol to total fluid (top) and absolute g/kg (bottom) during 4 days before (PRE), 4 days during injection (INJECT) b.i.d. of the saline control vehicle or FG5865 (FG) in a dose of 1.0 mg/kg or 2.5 mg/kg and 4 days (POST) after the injections. $N = 7$ rats per group. *$p < 0.01$ significant from PRE injection values.

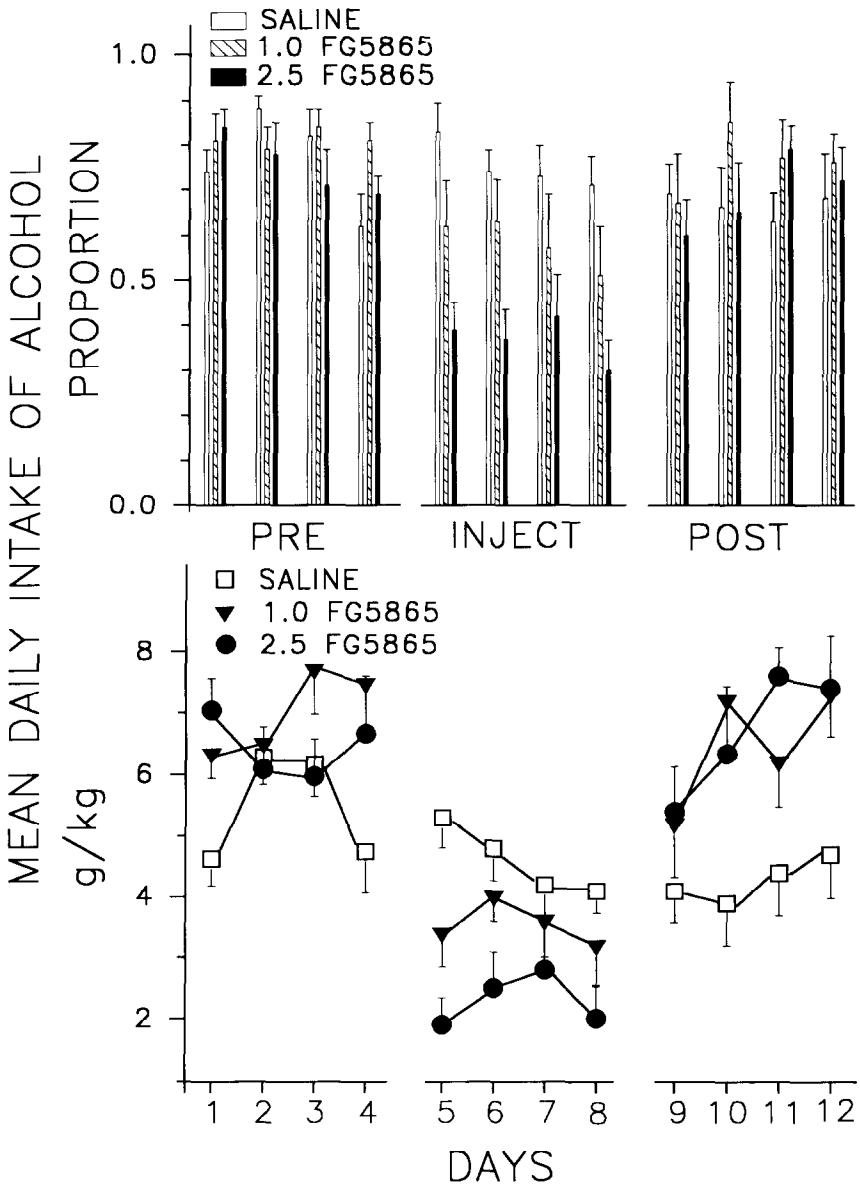

FIG. 3. Mean ± SE intakes of alcohol in high alcohol drinking (HAD) rats in terms of the proportion of alcohol to total fluid (top) and absolute g/kg per day (bottom). Intakes of individually determined, maximally preferred concentrations of alcohol were recorded for 4 days before (PRE), 4 days during administration of FG5865 (INJECT), and 4 days after (POST) FG5865 injections of saline control vehicle or 1.0 mg/kg or 2.5 mg/kg of FG5865 given b.i.d. N = 7 rats per group.

decline in drinking was not significantly correlated (r = 0.41 for g/kg and r = 0.51 for proportional values).

Individual Responses to FG5865

An analysis of the effects of FG5865 on the intake of alcohol in individual HAD rats was undertaken in terms of the mean percent change from the 4-day baseline (PRE) interval. As shown in Fig. 4 (left top), the mean percent g/kg alcohol intake declined in all seven animals during injection of the lower dose of FG5865 and was suppressed in three animals after drug treatment. The 2.5 mg/kg dose of FG5865 reduced the mean percent g/kg intake of alcohol below the 50% level in six of seven rats (Fig. 4, left bottom), and drinking continued to be suppressed in three rats. Similarly, the proportional intakes decreased during injections of the 1.0 mg/kg dose of FG5865 (Fig. 4, right top) in six of seven animals and persisted after treatment in three rats. The mean percent daily proportional consumption of alcohol also declined precipitously in all seven animals while the 2.5 mg/kg dose was given (Fig. 4, right bottom) and was maintained in four rats.

Each of the HAD rats exhibited individual differences in

TABLE 1

MEAN ± SE INTAKES OF FOOD, WATER, AND ALCOHOL AS WELL AS THE BODY WEIGHTS OF HAD RATS INJECTED SUBCUTANEOUSLY WITH EITHER 1.0 mg/kg OR 2.5 mg/kg FG5865 OR THE SALINE CONTROL VEHICLE TWICE DAILY

	Food (g)	Water (ml)	Alcohol (ml)	Weight (g)
1.0 mg/kg dose (N = 7)				
PRE	20 ± 1	6 ± 0.8	29 ± 2	424 ± 10
1.0 mg/kg	19 ± 0.5	11 ± 1*	15 ± 2*	421 ± 10
POST	20 ± 0.6	7 ± 1	28 ± 3	421 ± 10
2.5 mg/kg dose (N = 7)				
PRE	20 ± 0.8	8 ± 1	24 ± 1	416 ± 10
2.5 mg/kg	17 ± 0.9	15 ± 1*	9 ± 1*	402 ± 9
POST	20 ± 0.7	11 ± 1	26 ± 2	403 ± 9
Saline control (N = 7)				
PRE	21 ± 0.8	7 ± 0.9	23 ± 1	447 ± 9
SALINE	19 ± 0.7	7 ± 1	21 ± 1	450 ± 9
POST	20 ± 0.7	10 ± 1	20 ± 2	451 ± 9

Preinjection period, injection period, and postinjection periods were 4 days. HAD = high alcohol drinking; N = number of rats; *p = <0.01.

their daily drinking responses during and after the administration of FG5865. As illustrated in Fig. 5, the 1.0 mg/kg dose of FG5865 given to two representative HAD rats, Rat A and Rat B, was less efficacious in attenuating the ingestion of alcohol than that of 2.5 mg/kg. This dose suppressed the consumption of alcohol almost entirely in this rat by the third day of treatment; further, its recovery of drinking to the previously high basal levels, both proportional and g/kg values, was delayed after the drug was discontinued. Although the decline in drinking of Rat B was not as intense as that of Rat A, and showed less dose dependency, the effect persisted throughout the drug injections. In contrast, Rat B resumed high levels of alcohol drinking as soon as the drug treatment ended, particularly following the injection of the 2.5 mg/kg dose of FG5865.

DISCUSSION

The present results show that FG5865 attenuates alcohol consumption in a dose-dependent manner in the selectively bred HAD rat predisposed to drink alcohol. FG5865 produced no untoward side effects on the intakes of food and water nor on the body weight of the rat either during or following its administration. The latter finding is in contrast to the anorexic effects of an opiate antagonist such as naltrexone or of 5-HT reuptake inhibitors such as fluoxetine, zimelidine, and sertraline, which can suppress both food intake and drinking of alcohol concomitantly (4,8,10,26,27,30). Thus, the attenuation of alcohol drinking caused by FG5865 was not due to a secondary side effect of the drug to impair those pathways responsible for the central regulation of caloric intake or ingestion of fluids.

Although the central mechanism of action of FG5865 currently is unknown, its pharmacological characteristics correspond to the concept that 5-HT plays a role in the magnitude of alcohol drinking. FG5865 acts to block the reuptake of 5-HT in synaptosomes in the frontal cortex and corpus striatum of the rat (Björk, unpublished data). FG5865 shares the properties of another mixed 5-HT_1 agonist/5-HT_2 antagonist, FG5893, in blocking the reuptake of 5-HT into serotonergic synapses (12) and in attenuating, for a prolonged period, the preference for alcohol of rats induced to drink by cyanamide (40). In addition, both FG5865 and fenfluramine enhance the basal release of [^{3}H]5-HT from tissue of frontal cortex of the rat (12). In accord with these findings, an excess in the extracellular levels of 5-HT in the brain has been implicated previously in the aberrant drinking of alcohol (24,26). Experiments using in vitro binding show also that FG5865 possesses a high, nearly equal affinity for both 5-HT_{1A} and 5-HT_2 receptors (12), with the selectivity of these receptors being similar to that of 5893, that is, FG5865 K_i values of 2.8 nM for 5-HT_{1A} receptors and 3.1 nM for 5-HT_2 receptors, and FG5893 K_i values of 0.7 nM for 5-HT_{1A} receptors and 4.2 nM for 5-HT_2 receptors, respectively (12). Since buspirone, 8-OH-DPAT and other 5-HT_{1A} agonists also diminish the preference for alcohol under different experimental conditions (33,37,41), whereas 5-HT_{1A} antagonists do not enhance drinking (15,19), it is likely, therefore, that FG5865 is acting collectively on both 5-HT_{1A} and 5-HT_2 receptors centrally in the HAD rat to significantly modify the serotonergic component underlying the drinking of alcohol.

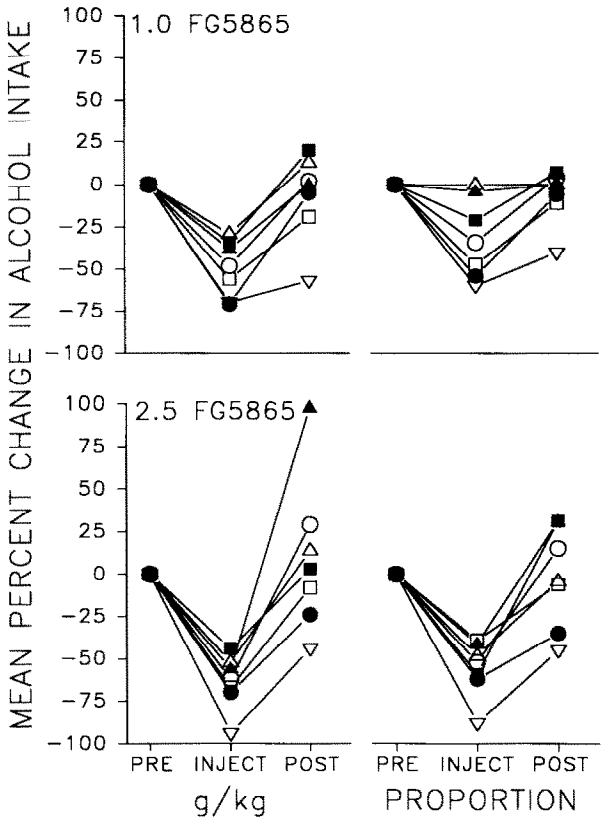

FIG. 4. Mean percent change from baseline intakes of alcohol (PRE) in individual rats in terms of g/kg (left) and proportion of alcohol to total fluid (right). Injections were given b.i.d. of 1.0 mg/kg (top) or of 2.5 mg/kg (bottom) FG5865 (INJECT). Each value represents the individual mean of 4 days during treatment and 4 days after the injection sequence (POST). N = 7 per group.

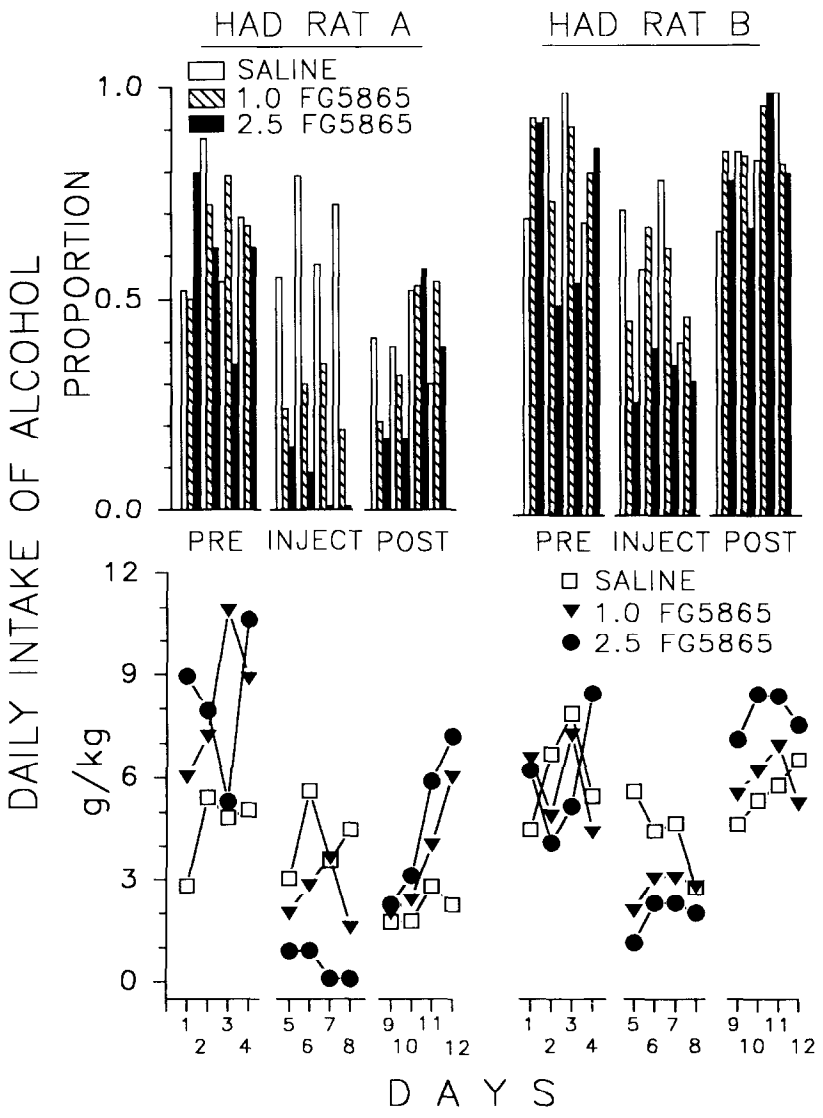

FIG. 5. Daily intakes of alcohol of two representative high alcohol drinking (HAD) animals, Rat A (left) and Rat B (right), in terms of proportion of alcohol to total fluid (top) and absolute g/kg (bottom) for animals over the 12-day test interval: 4 control days before (PRE), 4 days during injections of FG5865 (INJECT), and 4 days after (POST) administration b.i.d. of control saline vehicle or FG5865 in a dose of 1.0 mg/kg or 2.5 mg/kg.

That the selectively bred HAD rat possesses a lower level of 5-HT and its metabolites in the brain than the low alcohol drinking LAD rat (9) would suggest an equal involvement of central serotonergic synapses in the genetically linked preference for alcohol (16). Because FG5865 augments the release of 5-HT in the cerebral cortex (12), the subsequent elevation in serotonergic activity in the limbic system would be expected to diminish alcohol drinking. This explanation corresponds to the inhibitory effect on alcohol drinking of other drugs that enhance the presynaptic release of 5-HT or augment its extracellular level in the synapses of serotonergic neurons (36).

Another possible mechanism of action of FG5865 centers on the fact that this drug selectively augments the release of dopamine in the mesolimbic system in a manner similar to that of amperozide (14). Inasmuch as FG5865 acts also to inhibit the synaptic reuptake of dopamine (Björk, personal communication), an elevated level of dopamine could simultaneously diminish the rewarding effect of alcohol in the HAD rat (26). In this connection, lower cerebral levels of dopamine and its metabolites have been found in the HAD rat, in comparison to the LAD rat, particularly in the mesolimbic system (9). Further, a circuit of dopaminergic neurons extending from the ventral tegmental area to the nucleus accumbens and other forebrain structures, earlier implicated in the rewarding

property of alcohol (24), has been identified which underlies the intense preference for alcohol induced by tetrahydropapaveroline (27). Thus, a modification by FG5865 in the function of the synapses within this system could also contribute to the suppression of alcohol drinking in the HAD rat. The combination of properties of FG5865 as a 5-HT_2 antagonist/5-HT_{1A} agonist, coupled with its potential action on mesolimbic dopamine pathways, apparently would account for the effects in ameliorating alcohol drinking.

In conclusion, FG5865 causes a decline in alcohol consumption in a dose-dependent manner in the selectively bred HAD rat without producing a reduction in caloric intake or other side effects. That this drug could be used clinically is a possibility in view of the fact that the 5-HT_2 antagonist ritanserin has been reported to reduce the compulsion to consume alcohol (23). However, in several experimental studies, ritanserin given in appropriately low doses was without significant effects on alcohol drinking rats (28,42). Nevertheless, further research on FG5865 and related drugs, particularly on the prolonged effects of the compound, would seem to be warranted to elucidate further the role of different 5-HT receptor subtypes in the aberrant drinking of alcohol.

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