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Alcohol Drinking Attenuated by Sertraline in Rats With 6-OHDA or 5,7-DHT Lesions of N. Accumbens: A Caloric Response?

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MYERS, R. D. AND S. D. QUARFORDT. *Alcohol drinking attenuated by sertraline in rats with 6-OHDA or 5,7-DHT lesions of N. accumbens: A caloric response?* PHARMACOL BIOCHEM BEHAV **40**(4) 923–928, 1991.—The purpose of this study was to elucidate further the role of serotonin (5-HT) in the preference for ethyl alcohol induced in the Sprague-Dawley rat by lesions of the N. accumbens. Following a standard preference test for 3–30% alcohol, dopaminergic or serotonergic neurons in the N. accumbens of the rat were lesioned bilaterally by 6-hydroxydopamine (6-OHDA) or 5,7-dihydroxytryptamine (5,7-DHT), respectively. After recovery postoperatively, each rat was offered water and its maximally preferred concentration of alcohol, which ranged from 7% to 11%. Following a 4-day pretest, either the saline control vehicle or the 5-HT reuptake inhibitor, sertraline, was injected subcutaneously in a dose of either 3.0 or 10 mg/kg b.i.d. at 0800 and 2000 h over the next 3 days. Alcohol preference during the injection sequence and for 4 days thereafter was significantly reduced by sertraline in terms of both absolute g/kg and proportion of alcohol to water intakes. Saline was without effect on alcohol drinking. Comparisons of the drinking profiles of serotonergic versus dopaminergic lesioned rats revealed a dose dependent response to sertraline only in the 5,7-DHT lesioned animals. Although sertraline did not alter water drinking, the consumption of food declined significantly during and after its administration with a decline in body weight also observed at the higher dose. These results suggest that in addition to dopaminergic neurons in the N. accumbens, the synaptic activity of 5-HT in this structure contributes to the aberrant drinking of alcohol. However, this interpretation is tempered by the fact that caloric intake was suppressed concomitantly by the drug. Thus the presumed central action of sertraline may not be functionally specific to the reinforcing or other behavioral properties of alcohol.

Alcohol drinking Sertraline Serotonin reuptake Ethanol Alcohol preference Dopamine
6-Hydroxydopamine Nucleus accumbens Lesioning Neurotoxins Mesolimbic reward system Drinking

IN the late 1960s, the indoleamine neurotransmitter, serotonin (5-HT), was first implicated in the addictive liability of ethyl alcohol (29). Initial experiments in the rat with p-chlorophenylalanine led to the hypothesis that the level of 5-HT in the brain underlies the mechanism of preference for alcohol (25,31). When 5-HT or 5-hydroxytryptophan (5-HTP) is given by the intracerebroventricular (ICV) route alcohol drinking is reduced (32), whereas lesions of circumventricular structures by 5,7-dihydroxytryptamine (5,7-DHT) augments the intake of alcohol (17,28). Thus it was proposed that excess cerebral 5-HT assuages the preference for alcohol, but a deficiency in the amine augments alcohol intake (27,29).

Pharmacological studies with other compounds which alter the function of central 5-HT generally have affirmed its involvement in alcohol drinking (15). For example, when the endogenous level of 5-HT is elevated by the inhibition of its synaptic reuptake by drugs such as zimelidine, fluoxamine and fluoxetine, the consumption of alcohol typically is reduced (1, 7, 10, 20). In the human problem drinker, alcohol drinking similarly is attenuated by the 5-HT reuptake inhibitor, citalopram (34). Another 5-HT reuptake blocker, sertraline, which is more selective for 5-HT reuptake than for NE (12), also ameliorates alcohol intake in the rat (8), but the ingestion of food is suppressed concurrently at the doses given (9).

In view of the questions surrounding the utility of employing a 5-HT reuptake inhibitor in the treatment strategy for alcoholism, this study was undertaken to further elucidate the potential palliative role of this class of drug. In these experiments, rats of a nondrinking strain (17) were surgically prepared with neurotoxin lesions of N. accumbens because: (a) this structure is highly reactive to the aldehyde adduct, tetrahydropapaveroline (THP) in terms of its evocation of alcohol preference (30); (b) buspirone, a 5-HT_{1A} pre- and postsynaptic receptor agonist (16), inhibits alcohol drinking induced in the rat by THP microinjected repeatedly in the N. accumbens (37); and (c) bilateral lesions of the N. accumbens by the catecholamine neurotoxin, 6-hydroxydopamine (6-OHDA), or the serotonergic neurotoxin, 5,7-DHT, enhances markedly the self-administration of alcohol or opiate agonists (38–40, 43). In these experiments, sertraline was administered in doses lower than those used previously to rats offered their maximally preferred concentration of alcohol. In addition, measures of the intakes of food and water as well as body weight of each animal were simultaneously monitored before, during and after the administration of sertraline.

METHOD

Male rats (n = 11) of the Sprague-Dawley strain, obtained from Charles River and weighing 260–310 g, were housed individually in wire-meshed cages. Throughout the experiment, the animals were maintained at an ambient temperature of 21–23°C and on a 12-h light cycle with lights on from 0700–1900 h. Purina rat chow, water and a solution of alcohol were always available ad lib. Records of body weight and intakes of food and fluids of each rat were taken daily at 0830–0900 h.

Determination of Alcohol Preference

The pattern of self-selection of alcohol was determined for each rat over 10 days by a standard three bottle, two-choice random rotation method used to prevent the development of a position habit (22). Three graduated 100-ml drinking tubes mounted equidistantly on the front of each cage were: filled with a solution of alcohol and tap water; with only tap water; or remained empty. On each day of the 10-day test, the solution of alcohol was increased stepwise by one concentration as follows: 3, 4, 5, 7, 9, 11 13, 15, 20, and 30%. Individual measures of alcohol intake were recorded in terms of the daily absolute g/kg body weight and the proportion of alcohol to total fluid.

Surgical Procedures

Each rat was anesthetized with 35–40 mg/kg sodium pentobarbital injected intraperitoneally. After the head was placed in a stereotaxic instrument, a dose of 5.0 mg/kg of either desipramine HCl or amfonelic acid was administered intraperitoneally prior to a 6-OHDA or 5,7-DHT micro-injection to protect noradrenergic and dopaminergic neurons from neurotoxicity, respectively. Craniotomy holes then were drilled bilaterally in the calvarium above the intended site of the lesion following aseptic procedures described previously (21). A solution of 6-OHDA or 5,7-DHT was prepared in a concentration of 2.0 μg/μl in an artificial CSF vehicle containing 0.1 mg/ml ascorbic acid (17). Each solution of neurotoxin was passed through a 22 μM filter and loaded into the injection system which consisted of a sterilized 24-ga thin-walled stainless steel injector needle connected by PE tubing to a 50 μl Hamilton syringe mounted on a Sage Instruments pump.

The needle containing the solution of 6-OHDA or 5,7-DHT was lowered through the craniotomy holes to a predetermined depth below the dura according to the following stereotaxic coordinates: AP 1.0–1.5; LAT 1.0–1.5; and HOR 8.0–9.0 mm (36). The infusion was given bilaterally at a rate of 1.0 μl/min over an interval of 2.0 min to deliver 4.0 μg of the respective neurotoxin. Then the needle was kept in place for an additional 3.0 min to prevent reflux of the solution (21).

Administration Of Sertraline

Upon postoperative recovery, a series of three 10-day preference tests for alcohol and water drinking again were undertaken (39) at weekly or biweekly intervals. At the end of the third test, each rat was offered water together with its maximally preferred concentration of alcohol as based on the final 3–30% preference test, i.e., 7%, 9% or 11% concentration (mean ± S.D. = 8.1 ± 1.48). An experimental design was used (18,19) in which the single concentration of alcohol was offered over: a predrug interval of 4 days; a 3-day interval when one of two doses of sertraline (Pfizer, Groton, CT) or the saline control vehicle was administered; and a final 4-day postinjection preference test. During the 3-day period of injections, the saline vehicle or sertraline (salt) was administered subcutaneously to the rats in a randomized counterbalanced design, twice daily at 0700 and 1900 h. The 3.0 mg and 10 mg/kg doses of sertraline were selected on the basis of previous reports (8) and randomized with the control saline vehicle administered isovolumetrically by the same route. Between each of the 11-day preinjection, treatment, and posttreatment intervals, one week elapsed without exposure of the animals to alcohol before the next 11-day sequence commenced.

Statistical Analyses

The data on the absolute g/kg intakes of alcohol, proportion of alcohol to total fluid ingested, intakes of water and food as well as changes in body weight of each rat were analyzed statistically by computer using the Stat-Mate computer software program. Standard analyses of variance were performed for comparisons between the pretreatment period, 3-day interval of sertraline treatment and the posttreatment period of alcohol preference testing (18,19). Further analyses using Newman-Keuls post hoc and Student's *t*-tests were conducted for comparisons between individual groups and mean values. A p value of <0.05 was considered to be statistically significant.

RESULTS

Both doses of sertraline reduced the drinking of alcohol during the 3 days of its administration in those rats bearing lesions of the N. accumbens produced by either 6-OHDA or 5,7-DHT. A composite analysis of data from both lesion groups combined, as shown in Fig. 1, revealed that sertraline was efficacious at both the lower, $F(2,118) = 18.78$, $p<0.01$, and higher doses, $F(2,118) = 38.4$, $p<0.01$. In the 4-day period following systemically administered sertraline, the absolute g/kg intake of the rats was still suppressed by the lower ($p<0.01$) and higher doses ($p<0.01$) of the drug, but then rose toward the pretreatment levels. Similarly, the overall proportional values of alcohol to total fluid consumed by the rats also were significantly different during the period of injections with sertraline (Fig. 1) in rats given both the lower, $F(2,118) = 12.17$, $p<0.01$, and higher doses, $F(2,118) = 19.21$, $p<0.01$. In both cases, this decline persisted during the 4-day posttest interval ($p<0.01$). The alcohol drinking responses of the rats during the administration of the saline control vehicle in terms of g/kg and proportional values were not significantly altered.

6-OHDA-Lesioned Rats

In the six rats bearing 6-OHDA lesions of N. accumbens, the changes in alcohol drinking induced by sertraline are illustrated in Fig. 2 (bottom). The intake of alcohol in terms of g/kg was reduced significantly, $F(2,63) = 8.74$, $p<0.01$, in these animals by the higher dose of sertraline during ($p<0.01$) and after ($p<0.05$) the injections of sertraline. Similarly, the administration of the lower dose of the 5-HT reuptake inhibitor likewise was effective in lowering the g/kg intakes, $F(2,63) = 7.34$, $p<0.01$, of the rats (Fig. 2, bottom) both during ($p<0.05$) and after their treatment ($p<0.05$). However, the proportional intakes of alcohol (Fig. 2, top) which declined during and after injections of the two doses, were not significantly different from the pretest values. Further, no differences in the drinking pattern of rats were produced by the control solution in respect to either g/kg or proportion of alcohol to total fluid consumed (Fig. 2).

5,7-DHT-Lesioned Rats

As illustrated in Fig. 3, sertraline was more efficacious in reducing alcohol drinking in rats having 5,7-DHT lesions of N.

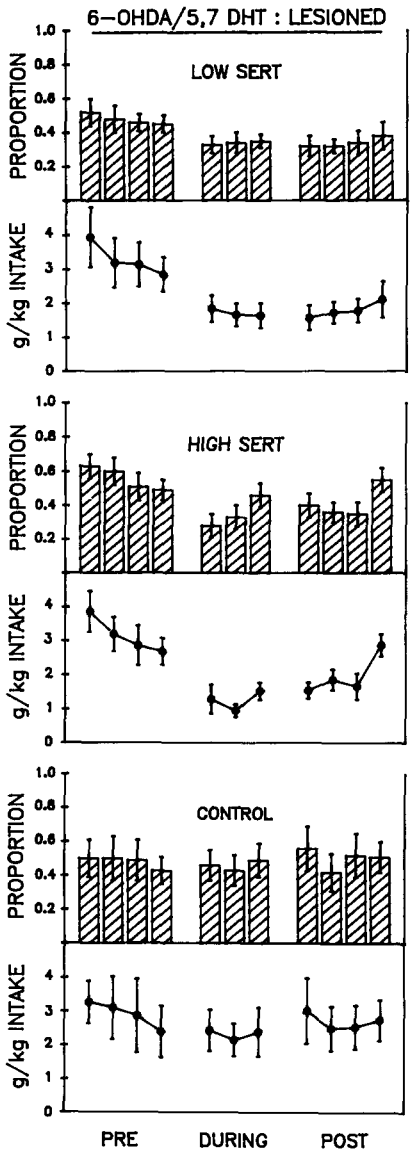

FIG. 1. Composite mean ± S.E. intakes of alcohol of combined groups of rats (n = 11) having bilateral lesions of N. accumbens produced by 6-OHDA or 5,7-DHT. Ordinates show proportion of alcohol to total fluid (top) and absolute g/kg intake (bottom). Three preference tests were done at 4 days before (PRETEST), 3 days during (SERT), and 4 days after (POSTTEST) administration of the 3.0 mg/kg dose (LOW SERT) and 10 mg/kg dose (HIGH SERT) of sertraline or saline control vehicle.

accumbens when compared to those with 6-OHDA lesions of this structure. During and after sertraline injections, the g/kg intakes of alcohol were suppressed overall by the higher, $F(2,52) = 9.89$, $p<0.01$, and lower doses, $F(2,52) = 5.44$, $p<0.01$, with the posttest differences (Fig. 3, bottom) also significantly different in both cases from the pretest ($p<0.01$). A dose response also was evident between the 3.0 and 10 mg doses which was significant for the g/kg intakes, $t(28) = 2.048$, $p<0.05$. The overall mean proportional intakes were significantly different across the three test intervals at both the higher, $F(2,52) = 9.31$, $p<0.01$, and lower doses of the drug, $F(2,52) = 6.17$, $p<0.01$.

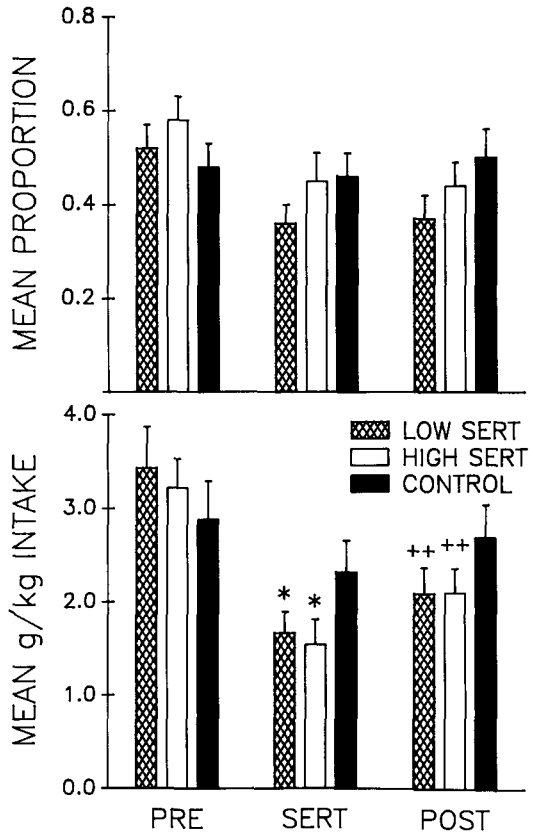

FIG. 2. Mean ± S.E. intakes of alcohol of rats (n = 6) with bilateral 6-OHDA lesions of N. accumbens in terms of proportion of alcohol to total fluid (top) and absolute g/kg intake (bottom) in three preference tests: 4 days before (PRETEST), 3 days during (SERT), and 4 days after (POSTTEST) administration of the 3.0 and 10 mg/kg doses of sertraline or saline control vehicle. *Pretest significant from sertraline; + Posttest significant from sertraline; + + Pretest significant from posttest.

The proportional intakes during the sequence of injections of the high dose of sertraline were significantly lower than that of the pretest values ($p<0.01$). No differences were found in the g/kg or proportional intakes of alcohol in response to the saline control vehicle.

Food And Water Intakes; Body Weight

As portrayed in Table 1, the 10 mg/kg dose of sertraline caused an overall decline in mean body weights of the rats which was significant across the test sequence, $F(2,118) = 5.11$, $p<0.01$. In comparison to the increases in the body weights of the control rats, the decline in weight persisted after the 3-day period of injections of the drug ($p<0.01$). The lower dose of sertraline also caused a significant increase in the daily intake of water of the rats, $F(2,118) = 6.75$, $p<0.01$, above the pretest level during ($p<0.01$) and after ($p<0.01$) the administration of the drug; however, the higher dose did not alter the amount of water ingested (Table 1). In contrast, the daily consumption of food by the rats was markedly diminished overall by the injections of sertraline given at both the lower, $F(2,118) = 56.45$, $p<0.01$, and higher, $F(2,118) = 119.69$, $p<0.01$, doses. This reduction in the intake of food persisted also over the 4-day posttest interval

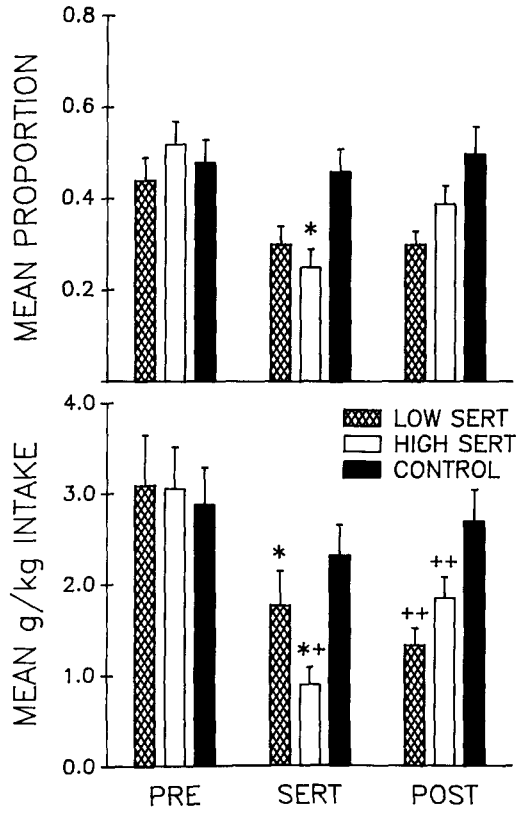

FIG. 3. Mean ± S.E. intakes of alcohol of rats with bilateral 5,7-DHT lesions of N. accumbens in terms of proportion of alcohol to total fluid (top) and absolute g/kg intake (bottom) in three preference tests: 4 days before (PRETEST), 3 days during (SERT), and 4 days after (POST-TEST) administration of the 3.0 and 10 mg/kg doses of sertraline or saline control vehicle. *Pretest significant from sertraline; +Posttest significant from sertraline; + +Pretest significant from posttest.

in both cases ($p<0.01$). Again, injections of the saline control vehicle were without significant effects on food and water intakes as well as body weights of the animals.

DISCUSSION

The present results demonstrate that in the rat bearing a neurotoxic lesion of the N. accumbens, successive injections of the 5-HT reuptake inhibitor, sertraline, induce a significant reduction in the preference for alcohol. Thus the viewpoint is supported that a serotonergic mechanism is, in part, involved in the volitional drinking of alcohol. A comparison of the responses of the two lesioned groups showed that those rats with 5,7-DHT lesions of the N. accumbens were more reactive to sertraline administered in the higher dose than the 6-OHDA lesioned animals. The decline in drinking was greater in terms of absolute g/kg intake of alcohol, the reduction in proportional intakes was significant; and a dose response was evident only in the 5,7-DHT lesioned animals. The reason for the differences in the efficacy of sertraline could lie in the magnitude of denervation supersensitivity of the neurons within the region of the 5,7-DHT lesion. That is, the functionally remaining serotonergic synapses in the N. accumbens, containing residual quanta of 5-HT, apparently are more reactive to the process of reuptake inhibition.

Based on previous experiments over the last two decades, the serotonergic mechanism, whereby alcohol consumption is modified, presumably would operate centrally within specific 5-HT pathways in the limbic system (15,29). Initially, it was proposed that an insufficient level of 5-HT within the brain leads to drinking of alcohol due to an increase in craving and/or a greater reinforcing effect of the fluid (28, 29, 32). In accord with this view, a surfeit of synaptic 5-HT in the same synapses would act conversely to diminish craving for alcohol and/or nullify its reinforcing quality (15, 17, 29). Thus, when the reuptake of 5-HT in central serotonergic neurons is retarded by a drug such as sertraline, the unique pharmacological effect of alcohol would be reduced and its intake thereby attenuated.

One clue to the decrement in drinking accompanying excess cerebral 5-HT lies in the early results with p-chlorophenylalanine (pCPA), an inhibitor of tryptophan hydroxylase, which assuaged alcohol preference during and following its administration (31). An explanation of this effect had centered on a compensatory rebound increase in the cerebral synthesis and/or release of 5-HT in serotonergic neurons (29) or a protracted supersensitivity of postsynaptic receptors on serotonergic neurons within the mesolimbic system (13) to released 5-HT. These alternatives are constrained, however, by the fact that 5-HT_1 or 5-HT_2 receptor antagonists fail to alter the reduced drinking of alcohol-preferring rats pretreated with a 5-HT reuptake inhibitor (20). To answer this question, the direct effect of a receptor antagonist as well as the localized pharmacological inhibition of 5-HT reuptake within circumscribed structures in the brain will be required.

Equally implicated in the mechanism underlying alcohol drinking are dopaminergic and noradrenergic pathways in the brain (23). Early studies showed that 6-OHDA given by the ICV route diminishes alcohol consumption, whereas 5,6-DHT or 5,7-DHT enhance the preference for the fluid (17, 28, 38). However, when the catecholaminergic neurotoxin or 5,7-DHT is delivered directly to the N. accumbens, alcohol intake is augmented (11, 38, 39). Thus, it is conceivable that due to the ICV route of administration of these lesioning agents, the morphological specificity of their penetration into circumventricular structures of the limbic system is problematic. In fact, these neurotoxins may not act selectively on the neuronal pathways responsible for the reinforcing or other action of alcohol.

TABLE 1

MEAN ± S. E. MEASURES OF INTAKES OF FOOD AND WATER AS WELL AS BODY WEIGHT BEFORE (4 DAYS PRETEST), DURING (3 DAYS) AND AFTER (4 DAYS POSTTEST) INJECTIONS OF BOTH DOSES OF SERTRALINE AND THE SALINE CONTROL VEHICLE IN RATS WITH 5,7-DHT AND 6-OHDA LESIONS OF N. ACCUMBENS (N = 11 PER GROUP)

	Pretest	Sertraline	Posttest
		Mean Body Weight (g)	
High Dose	615.3 ± 9.9	599.9 ± 11.8	‡595.4 ± 8.6
Low Dose	604.6 ± 5.2	607.1 ± 6.2	612.2 ± 4.9
Control	648.0 ± 5.9	655.1 ± 7.6	‡662.3 ± 6.9
		Mean Daily Water Intake (ml)	
High Dose	21.8 ± 3.0	19.2 ± 3.6	23.1 ± 2.4
Low Dose	24.1 ± 2.1	†26.8 ± 2.6	‡31.2 ± 2.5
Control	25.9 ± 2.7	25.9 ± 3.2	25.4 ± 3.4
		Mean Daily Food Intake (g)	
High Dose	*34.7 ± 0.9	†21.7 ± 1.7	‡27.3 ± 1.1
Low Dose	*35.4 ± 1.1	†27.4 ± 1.3	‡32.5 ± 0.9
Control	34.1 ± 0.8	34.2 ± 1.0	34.3 ± 0.8

*Pretest significant from sertraline; †Posttest significant from sertraline; ‡Pretest significant from posttest.

Taken together with previous findings, our results suggest that a balance in the presynaptic activity between 5-HT and dopamine and/or norepinephrine within specific pathways of the brain is a pivotal factor underlying the predilection for or aversion to alcohol (23, 27, 32). Based on anatomical studies, dopaminergic systems in the brain-stem which project from the mesencephalon to regions encompassing both ventral and rostral forebrain seem clearly to be involved in the onset and maintenance of alcohol drinking (24). For example, the precursor to morphine, THP, injected into the ventral tegmental area, N. accumbens and other dopaminergic structures activates the preference for alcohol and then enhances its consumption (5,30). In view of the similarity in alcohol drinking produced by a neurotoxic lesion of either dopaminergic or 5-HT neurons in the N. accumbens (38,39), sertraline could offset this deficit by augmenting the synaptic level of 5-HT in these mesolimbic structures.

In addition to the dopaminergic system, Li and others have described a serotonergic pathway which projects from the mesencephalon to N. accumbens (13,44). It is notable that the concentration of 5-HT and its metabolite, 5-HIAA, is much lower in the N. accumbens of the alcohol preferring rat when compared to the nonpreferring animal (15). Further, immunocytochemically stained 5-HT fibers within the medial and posterior parts of the N. accumbens of the P rat are fewer in number or even undetectable in comparison to those of the NP animal (45). In this connection, 5-HT containing neurons in the N. accumbens are thought also to mediate the analgesia induced by an opiate drug, seemingly through the release of 5-HT onto contiguous enkephalinergic neurons within this structure (44). In parallel with this viewpoint, the loss of either 5-HT- or dopamine-containing neurons within the N. accumbens has the same net effect on preference for alcohol (38,39), which suggests that these monoaminergic neurotransmitters function on two sides of the same coin. That is, neurons within the mesolimbic system apparently comprise at least one of the structural components underlying the mechanism responsible for drinking: reinforcing property of alcohol, characteristic craving and neuronal tolerance to the fluid.

Specificity of Drugs Acting on 5-HT?

When the mechanism for feeding is impaired by a centrally acting drug, the specificity of its pharmacological action can be questioned (1,9). For example, if the intake of food and/or water of the animal is inhibited by a drug, it is likely that the central mechanism regulating the ingestion of a nutrient and/or fluid is compromised. Consequently, when the intake of calories or water drinking is inhibited, the effect of the drug on alcohol drinking could be secondary to its action on the mechanisms for caloric regulation and water-electrolyte balance. Therefore, a caveat in the interpretation of the present results is necessitated by the fact that sertraline reduces the ingestion of food concomitantly with alcohol. Previous studies have, in fact, documented the hypophagic or anorectic effects of several 5-HT reuptake inhibitors (2, 3, 35, 41, 42) alone or in the presence of alcohol during a self-selection test (1,6). A dose of 10 mg or higher of sertraline inhibits the consumption of food typically within the first h after its injection (14). In either the human volunteer or problem drinker, the consumption of alcohol is reduced similarly by one of several 5-HT reuptake inhibitors (33,34). Thus, the effect of the 10 mg/kg dose of sertraline parallels that of other 5-HT acting drugs, such as pCPA, in reducing food intake and body weight (29,31). Drugs such as naloxone, morphine and naltrexone which diminish food intake also suppress the preference for alcohol (4,26).

In summary, the level of 5-HT in serotonergic synapses may not be the essential determinant of the preference for alcohol once the pharmacological properties of this fluid are experienced. As suggested earlier (9), a shift in the intake of alcohol during sertraline treatment may be due to a secondary effect of the drug. Clearly, a nonspecific perturbation of serotonergic synapses would affect all of the telencephalic mechanisms involved in feeding behavior, olfactory and gustatory functions, water-electrolyte balance, sleep-waking cycles, thermoregulation and other vital processes. Since an overabundance of 5-HT in the brain could lead to a nonspecific reduction in caloric requirement or a shift in the taste threshold for alcohol (22,32), a decline in the subsequent drinking of alcohol would not be unexpected.

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