COMBINATION PHARMACOTHERAPY: A MIXTURE OF SMALL DOSES OF NALTREXONE, FLUOXETINE, AND A THYROTROPIN-RELEASING HORMONE ANALOGUE REDUCES ALCOHOL INTAKE IN THREE STRAINS OF ALCOHOL-PREFERRING RATS

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Abstract — It is common to treat some diseases with more than one medication simultaneously. Since more than one neurotransmitter system is involved in alcohol-seeking behaviour, then a therapeutic approach that targets more than one system should be more effective in reducing alcohol intake than one addressing a single system. To test this hypothesis, we compared the efficacy of low doses of individual drugs reported to reduce voluntary alcohol drinking to the efficacy of a mixture of these agents at the same low doses in reducing alcohol intake in three strains of alcohol-preferring rats (P, HAD, and Fawn-Hooded). After establishment of a stable baseline for alcohol intake in a continuous access paradigm, each rat received separate single i.p. injections of relatively low doses of either naltrexone (2.0 mg/kg), fluoxetine (1.0 mg/kg), the thyrotropin-releasing hormone analogue TA-0910 (0.2 mg/kg), a mixture of all three drugs, or the vehicle at 09:30. Each rat received all treatments, with an inter-injection washout period of at least 3 days. Alcohol and water intakes were measured at 6 and 24 h, and food intake was measured at 24 h, after the injection. Our results show that individual drugs did not significantly affect food, water, or alcohol intake. However, the mixture significantly reduced alcohol intake in all three strains, but had no effect on food intake. Similar results were obtained when the HAD rats received an oral dose of the individual drugs or the mixture. When P rats were given an i.p. injection of the mixture for 10 consecutive days, there was a continued suppressing effect. These findings show that a combination treatment designed to target simultaneously serotoninergic, dopaminergic, and opioidergic systems can reduce alcohol intake, even though the doses of the individual drugs in the mixture are relatively low and ineffective when given singly.

INTRODUCTION

Alcoholism is a major health problem. In spite of large and intense efforts devoted to the treatment of this devastating disease, remediation of alcohol dependence remains a great challenge. In addition to disulfiram (antabuse) which is not an effective therapy for most alcoholics, several pharmacological agents including the opioid receptor antagonists naloxone and naltrexone (Froehlich et al., 1990; O’Malley et al., 1992; Volpicelli et al., 1992), calcium channel blockers (Rezvani and Janowsky, 1990; Rezvani et al., 1991a; Pucilowski et al., 1992), dopaminergic agents (McBride et al., 1990; Hodge et al., 1993a), serotonin antagonists (Hodge et al., 1993b), serotonin uptake inhibitors (Rezvani et al., 1986, 1990, 1991b; McBride et al., 1990), and GABA-altering drugs (McBride et al., 1990) have been shown to reduce alcohol intake significantly or to diminish relapse in rodent models of alcoholism and in alcoholics. However, many of these compounds, in addition to reducing alcohol intake, may suppress appetite or have other undesirable effects. Thus, the development of suitable medications with greater selectivity toward excessive alcohol intake remains a major goal of alcohol researchers.

It is common to treat some medical diseases with more than one medication simultaneously. This strategy is currently employed in the treatment of several major diseases and medical conditions including hypertension (Chalmers, 1993; Menard, 1993; Bakris and Williams, 1995; Levine et al., 1995; Prisant et al., 1995), depression (Tiller et al., 1992; Birkenhager et al., 1995), autoimmune diseases (Schum-Draeger, 1993), cancer (Nakagawa et al., 1996), diabetes (Rosenthal, 1992), and nicotine addiction (Rose and Levin, 1992). There is considerable evidence that alcoholism is a multi-factorial disease that may involve impairment of central serotonergic (McBride et al., 1990; Rezvani et al., 1990; Rezvani and Grady, 1994; Grant, 1995), dopaminergic (McBride et al., 1990; Koob et al., 1994), opioidergic (Froehlich et al., 1990; Reid et al., 1991), and GABAergic systems (McBride et al., 1990). If deficits in more than one of these systems additively or synergistically contribute to alcohol-seeking behaviour, theoretically, a therapeutic approach that targets more than one system should be more effective than one addressing a single system.

To test this hypothesis, we examined the effect on alcohol intake of administering simultaneously low doses of three pharmacological agents, which, at higher doses, have been shown to reduce alcohol intake in several strains of alcohol-preferring rats. For this initial study, we compared the effects of naltrexone, an opioid receptor antagonist; fluoxetine, a serotonin reuptake inhibitor; and TA-0910, a thyrotropin-releasing hormone (TRH) analogue with dopaminergic properties (Mason et al., 1994, 1996) to those of a mixture of these drugs on the intakes of alcohol, water, and food in three different strains of alcohol-preferring rats. The strains of rats used were: alcohol preferring (P, generation 40) rat and the high alcohol-drinking (HAD, generation 25) rat, which were developed at Indiana University by T. K. Li and colleagues (Li and McBride, 1995), and the inbred alcohol-preferring Fawn-Hooded (FH) strain which was developed by A. H. Rezvani at the University of North Carolina at Chapel Hill (Rezvani et al., 1990). These rats have been used extensively for studying
compounds which reduce alcohol intake (Murphy et al., 1988; McBride et al., 1990; Rezvani et al., 1990, 1991a, 1992; Rezvani and Grady, 1994; Mason et al., 1997). We hypothesized that the combination treatment would be more potent than the individual compounds in suppressing alcohol intake, because more than one neurotransmitter system in the brain is involved in alcohol-seeking behaviour. Our findings do indeed support the hypothesis.

MATERIALS AND METHODS

Animals

The three strains of alcohol-prefering rats were housed individually in stainless-steel wire mesh cages (26 x 34 x 20 cm) under constant temperature of 21 ± 1°C and reversed 12 h light–12 h dark cycle (10:00–22:00 dark). These rats consume significantly more alcohol than their respective control strains: the selectively-bred alcohol non-prefering (NP), the low alcohol-drinking (LAD) rat, and the Wistar rat. The FH and P rats were derived from the Wistar rat. Water and food (Agway Prolab Rat/Mouse/Hamster 3000 formula, Agway, Syracuse, USA) were provided ad lib.

Establishment of baseline

Following the standard method (Murphy et al., 1988; Rezvani and Grady, 1994; Rezvani et al., 1995), rats were given 1 day access to water in a Richter tube followed by 3 days of free access to a solution of 10% (v/v) ethanol given as the only source of fluid. Thereafter, the rats were given a choice between alcohol and water for the remainder of the study. All experiments involved 24-h free access to food, water, and alcohol in a two-bottle choice paradigm.

Preparation of drugs

Naltrexone HCl (RBI, Natick, MA, USA), fluoxetine HCl (Eli Lilly and Co., Indianapolis, IN, USA), and TA-0910 (Tanabi, Seiyaku, Co. Ltd., Osaka, Japan) were dissolved in saline freshly each day. The concentrations of naltrexone, fluoxetine, and TA-0910 in the mixture or in separate treatments were 2.0, 1.0, and 0.2 mg/ml, respectively. The doses chosen for these experiments are relatively small and although they may reduce alcohol intake in a 1–2 h scheduled access paradigm (Froehlich et al., 1990; McBride et al., 1990; Froehlich and Li, 1993), they exert no significant effect on alcohol intake in alcohol-prefering rats in the 24-h access protocol. The volume of systemic injections was always 1 ml/kg and that for oral administration was 4 ml/kg. Based on our experience comparing the potencies of compounds given systemically and orally, an oral dose three times that given i.p. will exert a similar effect (Overstreet et al., 1996). Alcohol solutions (10%, v/v) were prepared every 2 days from distilled water and a stock solution of 95% reagent grade ethanol.

Experimental protocols

Experiment 1: acute systemic administration. After establishment of a stable baseline for alcohol and water intakes, animals were maintained on a continuous access to alcohol and water via a two-bottle choice paradigm for about 2 months. Then, rats (n = 8 for P and HAD rats and n = 15 for FH rats) received a single i.p. injection of the saline vehicle, naltrexone (2.0 mg/kg), fluoxetine (1.0 mg/kg), TA-0910 (0.2 mg/kg), or a mixture of the three drugs at 09:30. Alcohol and water intakes were measured at 6 and 24 h after the injection. Food intake was measured 24 h after the injection. Each rat received all five treatments, separated by washout periods of at least 3 days.

Experiment 2: acute oral administration. Any compound, which might be used in human subjects, should be orally active. To investigate the effect of the oral administration of the mixture on alcohol intake, the same HAD rats used in experiment 1 received a single oral administration of either the saline vehicle, naltrexone (6.0 mg/kg), fluoxetine (3.0 mg/kg), TA-0910 (0.6 mg/kg), or the mixture of the three drugs at 09:30. All solutions were delivered by gastric intubation into the stomach through a special ball-tipped 16-gauge stainless-steel gavage needle (Beckton Dickinson) (Rezvani et al., 1986). Alcohol and water intakes were measured at 6 and 24 h after drug administration, whereas food intake was measured 24 h after the treatment. Each rat received all five treatments separated by washout periods of at least 3 days.

Experiment 3: chronic systemic administration. It has been shown that tolerance develops to the suppressing effects of naltrexone, fluoxetine, and TA-0910 and some other drugs on alcohol intake in rats (Rezvani et al., 1993; Mason et al., 1994; Cowen et al., 1999). To test this phenomenon with the mixture, a chronic experiment was conducted with nine adult male P rats. After establishment of stable baselines for alcohol and water intakes, and following a cross-over design, the mixture or vehicle was given i.p. once a day for 10 consecutive days. Alcohol and water intakes were measured at 6 and 24 h after the treatment, whereas food intake was measured 24 h after the treatment. Each rat received both treatments, and a washout period of 3 days was imposed between treatments.

Statistical analysis

The results were expressed as means ± standard error of means (SEM). Alcohol intake (g/kg) was calculated by multiplying the volume of alcohol consumed by 10% and 0.7893 (ethanol density)/animal body weight in kg. Alcohol preference, expressed as a percentage, was calculated as follows: (volume of alcohol consumed in ml/total fluid intake in ml) × 100 (Rezvani et al., 1990; Rezvani and Grady, 1994). Statistical differences between different groups were determined using analysis of variance followed by Newman–Keuls protected t-test.

RESULTS

Experiment 1: acute systemic administration

Baseline consumption levels of alcohol were 8.47 ± 0.73, 6.9 ± 0.8, and 6.1 ± 0.56 g/kg/day for P, HAD, and FH rats, respectively (means ± SEM). Compared to the vehicle, a single injection of the mixture significantly suppressed alcohol intake (Fig. 1A) and alcohol preference (Fig. 1B) in P rats. Separately administered naltrexone or TA-0910 did not induce a significant effect on 6-h alcohol intake and alcohol preference, and the effect of fluoxetine was significantly less than that of the mixture of drugs (Fig. 1A). The mixture of drugs, but not the individual drugs, significantly increased water intake at 6 h (Fig. 1C). Neither the mixture of drugs nor the individual drugs changed food intake (Fig. 1D).
In both HAD and FH rats, systemic administration of the mixture, but not its individual constituents, also significantly reduced alcohol intake (Fig. 2). However, contrary to P rats, water intake was not significantly affected in these two strains (Table 1). Food intake was also unaffected by the mixture or by individual drugs in FH or HAD rats (Table 1).

**Experiment 2: acute oral administration**

Compared with the vehicle, oral administration of the mixture, and fluoxetine alone, significantly reduced alcohol intake in HAD rats at 6 h (Fig. 3). However, fluoxetine administration was significantly \((P < 0.01)\) less effective than the mixture (Fig. 3) and also significantly \((P < 0.01)\) reduced water intake in HAD rats (Table 2). Neither the mixture nor its constituents reduced the 24-h food intake (Table 2). Oral administration of naltrexone or TA-0910 alone did not exert any significant effects on alcohol, food or water intakes (Fig. 3 and Table 2).

**Experiment 3: chronic systemic administration**

Repeated single daily i.p. administration of the mixture for 10 consecutive days, but not the vehicle, significantly reduced alcohol intake in P rats, both at 6 \((P < 0.0001, \text{ Fig. 4A})\) and 24 h \((P < 0.004, \text{ Fig. 4B})\) without development of tolerance to the suppressant effect of the mixture on alcohol intake. Chronic administration of the mixture to P rats also significantly \((P < 0.03)\) increased the water intake at 6 h (Fig. 5A) but not at 24 h (Fig. 5B), whereas food intake was increased significantly \((P < 0.0001)\) following chronic administration of the mixture to these rats (Fig. 6).

**DISCUSSION**

The present study shows that a mixture composed of relatively low doses of three different kinds of alcohol intake-suppressing drugs can significantly reduce alcohol intake...
without altering food consumption in three different strains of alcohol-prefering rats. Two of the component drugs, fluoxetine and naltrexone, have been shown to reduce food intake and body weight in rats when administered separately at doses that individually suppress alcohol intake (Murphy et al., 1988; Overstreet et al., 1995; Rezvani et al., 1996; Gardell et al., 1997). The fact that the mixture of drugs was more efficacious in suppressing alcohol intake than any of the constituents alone, but did not suppress food intake, suggests that the serotonergic, dopaminergic, and opioidergic systems may interact synergistically or additively to reduce alcohol consumption but not food intake. Thus, the combination treatment may produce fewer or weaker non-specific side-effects, such as appetite suppression, which might be counter-productive in treating alcoholism.

The suppressant effects of fluoxetine and naltrexone are not specific to alcohol. Murphy et al. (1988) and Gardell et al. (1997) have shown that fluoxetine, in doses which reduce alcohol intake, prevents growth, and this drug is used to suppress appetite in humans. Naltrexone also has been shown to reduce body weight in rats (Gardell et al., 1997). These effects could be undesirable in chronic alcoholics, who are frequently malnourished. In the present studies, neither food

Table 1. Effects of a single systemic (i.p.) administration of the mixture and individual constituents on water and food intake in FH and HAD rats

<table>
<thead>
<tr>
<th>Intakes</th>
<th>Saline</th>
<th>Naltx</th>
<th>Fluox</th>
<th>TA-0910</th>
<th>Mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>14 ± 2.0</td>
<td>9 ± 3.0</td>
<td>10 ± 3.0</td>
<td>11 ± 5.0</td>
<td>12 ± 2.0</td>
</tr>
<tr>
<td>(g/kg/6 h)</td>
<td>47 ± 2.0</td>
<td>44 ± 3.0</td>
<td>49 ± 4.0</td>
<td>45 ± 3.0</td>
<td>46 ± 2.0</td>
</tr>
<tr>
<td>Food</td>
<td>6.0 ± 2.0</td>
<td>3.0 ± 1.0</td>
<td>5.0 ± 1.0</td>
<td>8.0 ± 4.0</td>
<td>7 ± 3.0</td>
</tr>
<tr>
<td>(g/kg/day)</td>
<td>52 ± 4.0</td>
<td>49 ± 6</td>
<td>48 ± 2.0</td>
<td>47 ± 6.0</td>
<td>51 ± 5.0</td>
</tr>
<tr>
<td>HAD rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>3.0 ± 1.0</td>
<td>3.0 ± 2.0</td>
<td>0.3 ± 0.3*</td>
<td>2.0 ± 1.0</td>
<td>4.0 ± 1.0</td>
</tr>
<tr>
<td>(g/kg/6 h)</td>
<td>47 ± 2.0</td>
<td>43 ± 3.0</td>
<td>42 ± 2.0</td>
<td>42 ± 3.0</td>
<td>41 ± 6.0</td>
</tr>
<tr>
<td>Food</td>
<td>52 ± 4.0</td>
<td>49 ± 6</td>
<td>48 ± 2.0</td>
<td>47 ± 6.0</td>
<td>51 ± 5.0</td>
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<tr>
<td>(g/kg/day)</td>
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</table>

Naltx = naltrexone, 2 mg/kg; Fluox = fluoxetine, 1 mg/kg; TA-0910, 0.2 mg/kg.
Values are means ± SEM (n = 10–15 for FH and eight for HAD rats).
nor water intake was reduced at 24 h by a single injection of the mixture or of its constituent drugs; however, when fluoxetine was given orally to HAD rats, it significantly reduced both alcohol and water intakes, indicating a non-specific effect. We reported previously that the administration of a single large dose (0.75 mg/kg) of TA-0910 into P rats increased food but not total calorie intake (Rezvani et al., 1992). It is possible that the presence of TA-0910 in the mixture may have counteracted any suppressing effect that fluoxetine and naltrexone together may have had on food intake, resulting in a net outcome of no change in food intake. Our results suggest that this combination treatment is relatively more potent than its individual constituent drugs in reducing alcohol intake, and more selective than larger doses of fluoxetine or naltrexone, which reduce alcohol intake. However, since food intake was not measured at 6 h, it is not clear whether food intake was decreased during this period but was compensated for in the remainder of the 24-h test period.

Although the mechanisms underlying the suppressant effect of the mixture of drugs on alcohol intake were not addressed by the present study, a review of current literature suggests that the mixture might exert its effect by interacting with central dopamine (DA), serotonin (5-HT), and opioids, each

Fig. 4. Effects of repeated i.p. administration of saline or the mixture of drugs (naltrexone + fluoxetine + TA-0910) on alcohol intake at 6 and 24 h in P rats.
Rats had free 24-h access to water, food, and a solution of 10% alcohol. The i.p. doses were the same as those given in the single experiments of Fig. 1. $F(17,1) = 62.8, P < 0.0001$ for 6-h data and $F(17,1) = 11.5, P < 0.004$ for 24-h data. *$P < 0.05$ and **$P < 0.01$ vs the corresponding saline values.

Fig. 5. Effects of repeated i.p. administration of saline or the mixture of drugs (naltrexone + fluoxetine + TA-0910) on water intake in P rats.
Rats had free 24-h access to water, food, and a solution of 10% alcohol. Drug administration details are as in Fig. 4. $F(17,1) = 5.5, P < 0.03$ for 6-h data and $F(17,1) = 2.4, P = 0.14$ for 24-h data. *$P < 0.05$ and **$P < 0.01$ vs the corresponding saline values.

Fig. 6. Effects of repeated i.p. administration of saline or the mixture of drugs (naltrexone + fluoxetine + TA-0910) on food intake in P rats.
Rats had free 24-h access to water, food, and a solution of 10% alcohol. Other details are as in Fig. 5. $F(17,1) = 25.9, P < 0.0001$. *$P < 0.05$ and **$P < 0.01$ vs the corresponding saline values.
of which may be involved in alcohol-seeking behaviour in animals and humans (see Introduction). The mesolimbic DA system has been implicated in the reinforcing properties of abused substances, including alcohol (DiChiara and Imperato, 1988; Koob et al., 1994). Based on these findings, it is speculated that the mixture may exert its suppressant effect on alcohol intake by modulating, at least in part, the dopaminergic system.

There is evidence that each component of the mixture stimulates the reward system by enhancing DA release in the mesolimbic pathway. Behavioural studies indicate that TA-0910 stimulates DA release in the nucleus accumbens (Yamamura et al., 1991). The development of a partial cross-tolerance between TA-0910 and the DA agonist bromocriptine with respect to the attenuating effect on alcohol intake in P rats (Mason et al., 1994) and the antagonism of the suppressant effect of TA-0910 on alcohol intake by the DA D2 antagonist eticlopide (Mason et al., 1997) further support a dopaminergic mechanism in the suppressant effect of TA-0910 on alcohol intake. Fluoxetine has been demonstrated to release DA in the prefrontal cortex of freely moving rats by stimulating local 5-HT₁ receptors (Tanada et al., 1995). There is also evidence of interaction between the opioidergic and dopaminergic systems, including anatomic co-localization of endogenous opioids and DA in the brain which reflects the interplay between these two systems. It has also been shown that microinjection of the selective µ-opioid receptor antagonists D-Pen-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH₂ and β-funaltrexamine into the ventral tegmental area produces increases in extracellular DA and DA metabolite concentrations in the ventral striatum (Devine et al., 1993). However, there are also conflicting reports that peripheral administration of opioid antagonists blocks DA release (Benjamin et al., 1993). Thus, it is unclear whether administration of naltrexone in the mixture increases mesolimbic DA transmission. Nevertheless, in preliminary experiments, we found that the mixture of the three drugs was more effective in reducing the 6-h alcohol intake than a combination of equivalent doses of TA-0910 and fluoxetine, suggesting that, at the dose we used, naltrexone does not counteract the effects of fluoxetine and TA-0910 and may enhance their suppressive effects on alcohol intake by an as yet unknown mechanism(s). Therefore, the suppressant action of the mixture on alcohol intake may indeed result from enhancement of DA release in the mesolimbic system that, by substituting for alcohol-mediated enhancement of DA release, reduces the motivation to drink.

It is also possible that drug–drug interactions play a role in the effect of the mixture in reducing alcohol intake. For example, one compound in the mixture may influence the pharmacokinetics of another compound, thus affecting its action on alcohol intake. However, this appears unlikely, because we used small doses of each drug in the mixture and the effect of the mixture on alcohol intake was apparent as early as 2 h following intake. Comparing the blood levels of the drugs and their active metabolites when given alone with those obtained when the mixture is given is needed to resolve this issue.

Recently, several groups have examined the effects of different combinations of drugs on alcohol intake with mixed results. Gardell et al. (1997) have shown that the suppressing effect of a combination of naltrexone (5 mg/kg) and fluoxetine (5 mg/kg) on alcohol intake is no different from those of either drug in Sprague–Dawley rats. However, in a preliminary study, Zink et al. (1997) reported that naltrexone and fluoxetine act synergistically to decrease alcohol intake in P rats. Similar findings have been reported with a combination of naltrexone and ondansetron, a 5-HT₁ receptor antagonist, in mice and rats (Le and Sellers, 1994). Since the effects of these combinations on food and water intakes have not been reported, we are unable to compare all of the effects of these combinations with our results. Concurrent administration of amperozide, a 5-HT₂ receptor antagonist, and naltrexone has also been shown to suppress volitional drinking of alcohol in HAD rats, without side-effects on food and water intakes. The suppressing effect of this combination on alcohol intake was greater than that of the individual drugs (Lankford and Myers, 1996).

In a pilot clinical study, Williams and Mason (1997) have shown that a combination of nalmefene and sertraline is more effective than sertraline and placebo in alcohol-dependent patients who failed to respond to nalmefene alone, suggesting the benefit of combination pharmacotherapy for the treatment of alcohol dependence. In another small clinical study, Salloum et al. (1998) combined naltrexone with a selective serotonin reuptake inhibitor (SSRI) for the treatment of patients diagnosed as currently alcohol-dependent and depressed. The naltrexone–SSRI combination reduced drinking from 49 drinks per week to six drinks per week. In addition, depressive symptoms improved. Farren et al. (1997) have also examined the effects of the combination of a SSRI (sertraline, 50 and 100 mg/day) and naltrexone (50 mg/day) in the treatment of alcoholism. Using the Obsessive Compulsive Drinking Scale (Anton et al., 1996) the patients on combination therapy tended to report lower levels of craving for alcohol at the end of 10 weeks of treatment, than in the naltrexone only group. It should be mentioned that, although these findings are promising, they should be considered preliminary as the sample size was small in all of these clinical studies.

In summary, the present results demonstrate that combination pharmacotherapy can be more potent and in some cases more specific in reducing alcohol intake than monopharmacotherapy in alcohol-prefering rats. These results show that a mixture of low doses of naltrexone, fluoxetine, and TA-0910, is more potent than any of the individual drugs in suppressing alcohol intake, without producing a significant effect on 24-h food intake. These promising preclinical findings suggest that the strategy of combination pharmacotherapy should be tested in alcoholics.

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