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Communications to the Editor

Sustained Decrease in Cocaine-Maintained Responding in Rhesus Monkeys with 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazinyl Decanoate, a Long-Acting Ester Derivative of GBR 12909

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Cocaine abuse continues to be a serious public health problem, for which effective treatments are sought. Since a hallmark feature of abused drugs is their ability to support self-administration (drug-seeking) behavior in animals,[1] preclinical evaluations of potential pharmacotherapies for treatment of cocaine abuse have focused on this behavior. Recent studies have shown that the high-affinity dopamine (DA) reuptake inhibitor GBR 12909 (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine)[2] can selectively decrease cocaine self-administration, without affecting comparable performances maintained by food, in rhesus monkeys.[3] Subsequent studies[4] showed that repeated treatments with lower doses could sustain these behaviorally selective effects. Together with the observation that GBR 12909 attenuates cocaine-induced activation of mesolimbic dopamine neurons, as measured by *in vivo* microdialysis,[5] these data suggest that DA reuptake inhibitors may be useful pharmacological adjuncts in the treatment of cocaine abuse in humans. To the extent that the desired effect of a potential medication would be a long-term decrement in drug-seeking behaviors, it was of interest to explore methods to extend the duration of these effects. Previous studies have shown that one method for producing a long-acting agent is to esterify a polar hydroxyl-containing molecule with a medium to long chain alkanoic acid, affording a nonpolar oil-soluble molecule suitable for depot injection (the high partition coefficient favors the oil phase, resulting in the continuous release of a small proportion of the compound into the plasma, until depleted). Several successful depot preparations have been developed, with pharmacological half-lives of 30 days or more.[6,7] While assessing the abilities of a series of different GBR 12909 analogs to inhibit DA reuptake and decrease cocaine-maintained responding, some agents were identified as suitable candidates for chemical derivatization as decanoate esters. We chose **4** as the most viable candidate for derivatization and depot formulation based in part on its *in vitro* biological activity (the measured values for binding to both the dopamine transporter (DAT) and serotonin transporter (SERT), along with its ability to inhibit the reuptake of [^{3}H]DA and [^{3}H]-5HT, were essentially identical with those for GBR 12909) and in part on behavioral data. This report details some promising preliminary results in the monkey.

Seven adult, male rhesus monkeys, weighing between 7.5 and 9.0 kg, served as subjects. Each had been previously trained under various schedules of food and cocaine self-administration.[3,4] Food (three 1 g banana pellets) was delivered by a dispenser in front of the monkey. Cocaine was delivered through the momentary activation of a syringe driver connecting the drug supply to a subcutaneous vascular access port.[8] Responding was maintained under a multiple fixed ratio (FR) 30-response food, FR30 cocaine (10 μg/kg/inf), time-out (TO) 10-min schedule.[3,4] Availability of food or cocaine alternated during brief periods of a 2-h session. In each period, a maximum of 10 reinforcer deliveries could be produced. Availability of each reinforcer was constrained by a 60-s limited hold. Periods of food and drug availability were separated by a 10-min TO, and sessions always began with a food component. Once responding was stable (±20% over at least 8−10 con-

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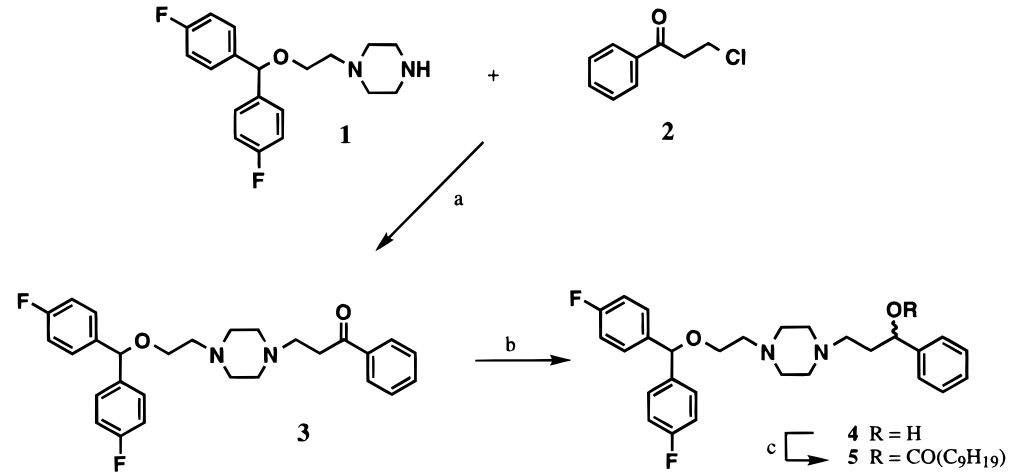
Scheme 1[a]



[a] (a) Acetone, 25 °C; (b) LAH, THF, 25 °C; (c) *n*-$C_9H_{19}COCl$, $CHCl_3$, 25 °C.

secutive sessions), monkeys were injected with 0, 1, 3, or 6 mL of **5** solution[9] and immediately run in a daily experimental session. Two monkeys were studied per dose, except for the 1-mL dose. Behavioral data were collected as the session average rate of responding for each component (food or cocaine) during individual daily sessions and compared to control rates occurring before treatment. Drug effects are described as the mean of individual effects (percent of control rates for both food- and cocaine-maintained responding) as a function of dose of **5**. Data for the first 24 days of treatment were satistically analyzed by repeated measures ANOVA and subsequently partitioned by two-factor repeated measures ANOVA.

Decanoate **5** was synthesized as shown in Scheme 1. Monosubstituted piperazine **1**[2a] was substituted with 3-chloropropiophenone (**2**) affording the ketone **3**[2b−d] in 88% yield after recrystallization as the bis-maleate salt, mp 165−166 °C (MeOH). Ketone **3** underwent facile reduction with lithium aluminum hydride, affording racemic **4** in quantitative yield as the bis-HCl salt, mp 216−218 °C (*i*-PrOH). Benzylic alcohol **4**[2b−d] was then treated with a 50% excess of decanoyl chloride in dry ethanol-free chloroform, affording the decanoate ester **5**, which was purified by formation of the bis-maleate salt, mp 154−155 °C (MeOH), and conversion back to the free base under mild, ammonia-free conditions (5% aqueous $NaHCO_3$). All new compounds gave NMR and mass spectra consistent with their assigned structures and gave C, H, N analyses within ±0.4% of their calculated values. Ester **5** was formulated for use by adding an equal weight of sesame oil (Sigma) to its ethereal solution, concentrating at reduced pressure, and then evacuating at 0.1 Torr until constant mass was reached. The formulated solution was calculated as being a 49.9% (w/w) solution of **5** in sesame oil.

Prior to treatment absolute control rates of responding (mean, coefficient of variation) were comparable for food- (3.696 resp/s, ±9.99%) and cocaine- (4.026 resp/s, ±13.6%) maintained responding. Three-factor ANOVA determined a significant main effect of dose ($F = 11.031$, $p = 0.016$), event ($F = 13.558$, $p = 0.0059$), and days of treatment ($F = 7.905$, $p = 0.0208$). Figure 1 shows the mean effect of treatment at each dose over the first 24 days immediately following a single injection. Noninjection control values were stable over this treatment

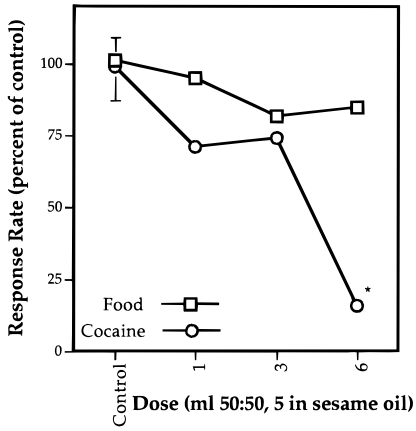


Figure 1. Mean effects of single injections of **5** (doses expressed as total milliliters when given as a 50% (w/w) solution in sesame oil) on rates of responding maintained by food or cocaine in rhesus monkeys. Effects are expressed as the mean percent of control rate, for food- or cocaine-maintained responding, over the course of the 24-day treatment period ($n = 2$). *Effects at 6 mL were determined significant by ANOVA.

period with food- and cocaine-maintained responding averaging 99.9% and 100.4% of control, respectively. The lowest dose of **5** had no effect on food-maintained responding (97% of control) and slightly decreased (76.2% of control) cocaine-maintained responding, although a downward trend in drug-maintained responding was clearer during the second and third week following the injection and recovered to baseline levels on subsequent days. An intermediate dose (3 mL) of **5** had a slight overall effect (82% of control) on food-maintained responding and decreased cocaine-maintained responding to about 74% of control over the entire treatment period. The were no differences in effect on food- and cocaine-maintained responding at these lower doses. In contrast, the highest dose of **5** tested (6 mL) had no effect on food-maintained responding and decreased cocaine-maintained responding to 25.3% of control over the entire treatment period. Figure 2 shows a small but observable effect of **5** on cocaine-maintained responding during the first 5 days after the injection. A robust statistical difference ($F = 55.919$, $p = 0.017$) in the effect of **5** on food- and cocaine-maintained responding occurred over the remaining treat-

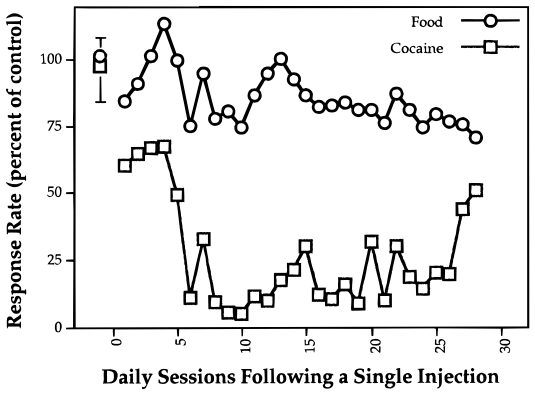


Figure 2. Effects of the 6-mL dose of **5** on rates of responding maintained by food or cocaine, for 28 sessions following a single treatment in rhesus monkeys. Effects are expressed as the mean percent of control rates for food- or cocaine-maintained responding ($n = 2$).

ment period, followed by a recovery in cocaine-maintained responding toward control levels approximately 30 days after the initial treatment.

The current results show that a single treatment with a relatively selective DA reuptake inhibitor, formulated to be long-acting, resulted in a sustained and selective effect on cocaine-maintained responding for almost 30 days. These results are qualitatively and quantitatively similar to those obtained with both acute[3,4] and repeated[4] daily administration of shorter-acting DA reuptake inhibitors, except only a single injection was required. Thus, drug-seeking behavior can be suppressed for periods assumed to be concordant with the pharmacological half-life of the decanoate preparation. These results are of particular interest because they appear to be consistent with those expected of a long-term medication for drug abuse, in that drug-seeking was selectively decreased for a relatively long time. An interesting observation of the current effects is that the decanoate required several days to obtain full effect. This observation is of interest because it suggests the slow onset of similar agents may limit their abuse potential. Previous studies have shown that by decreasing delivery rates of self-administered cocaine, responding for drug declines. This decrement in the reinforcing effects of cocaine, presumably mediated by delayed reinforcement, is likely to be a desired effect of formulating an slow-onset, long-acting, agonist-based medication.

Although the hazards of performing pharmacological studies on racemic compounds are well-known[10] this racemic compound displayed remarkable ability to selectively decrease cocaine-seeking behavior in monkeys. This observation, combined with the potent *in vitro* biological data for the parent hydroxy compound **4**, suggests that our ongoing studies to determine the relationship between chirality and the pharmacological profile for **4** and related compounds will prove to be of substantial interest. Of additional interest is the pharmacological profile of compound **5** itself. Initial experiments indicate that **5** potently inhibits DA binding, but these studies could not distinguish among inhibition produced by **5**, **4** formed by the action of membrane-associated esterases *in vitro*, or their combination. Further studies to dissociate these factors are in progress. Yet other studies are planned to determine minimal blood levels of such preparations to decrease drug-seeking behavior. This information should facilitate determination of minimum receptor occupancy for decreases in drug-seeking behavior by noninvasive methods such as PET or SPECT. Additional studies should address issues related to whether the self-administration dose−effect function changes in the presence of **5**. Some studies have suggested that in the presence of acute doses of an agonist, the unit dose−effect function for cocaine may shift to the left,[11] while others have only found evidence for a downward shift.[3,12] The ability to maintain a relatively constant effect over days would allow for a more effective means to assess such possibilities. Finally, the well-established use of long-acting decanoate formulations of antipsychotic agents for treating poorly compliant patients suggests that a decanoate formulation of a DA reuptake inhibitor might also be useful for treating poorly compliant cocaine-dependent patients. Positive results would validate this preclinical approach to developing high-affinity DA uptake inhibitors as medications for cocaine dependence.[13]

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Supporting Information Available: Experimental details and binding data for compounds **3**−**5** (5 pages). Ordering information can be found on any current masthead page.

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