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BRIEF COMMUNICATION

Self-Administration of the High-Affinity Cocaine Analog 2β-Carbomethoxy-3β-(4-Fluorophenyl)Tropane[1]

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SPEALMAN, R. D., J. BERGMAN AND B. K. MADRAS. *Self-administration of the high-affinity cocaine analog 2β-carbomethoxy-3β-(4-fluorophenyl)tropane.* PHARMACOL BIOCHEM BEHAV **39**(4) 1011–1013, 1991.—Self-administration of the high-affinity cocaine analog 2β-carbomethoxy-3β-(4-fluorophenyl)tropane (CFT) and cocaine were compared in squirrel monkeys responding under a second-order schedule of IV drug injection. Both CFT and cocaine maintained self-administration in all subjects. As the dose of either drug was increased, the rate of responding first increased and then decreased. Although the two drugs had qualitatively similar effects, CFT was approximately six times more potent than cocaine. This potency relation corresponds closely with the potency relations reported for CFT and cocaine in studies of dopamine uptake inhibition and binding at cocaine recognition sites. The results are consistent with the view that the reinforcing effects of cocaine-like drugs are mediated at cocaine recognition sites associated with the dopamine uptake system, and suggest that radioligand probes based on CFT may be suitable markers for these sites.

2β-Carbomethoxy-3β(4-fluorophenyl)tropane Cocaine analog Cocaine Self-administration Cocaine recognition sites Squirrel monkeys

2β-CARBOMETHOXY-3β-(4-FLUOROPHENYL)TROPANE [CFT, also designated WIN 35,428; see (6)], is a structural analog of cocaine with high affinity for cocaine recognition sites (14, 15, 17–19). Recently, a radiolabeled form of this compound, [^{3}H]CFT, has been used to characterize the binding properties and regional distribution of cocaine recognition sites in human and nonhuman primate brains (5, 13, 15). The rationale for selecting [^{3}H]CFT as a marker for cocaine recognition sites is based not only on its high binding affinity, but also on the high potency of CFT for producing cocaine-like behavioral effects. In this regard, CFT has been found to be at least three times more potent than cocaine in stimulating locomotor activity in mice or schedule-controlled responding in squirrel monkeys (6,21), in producing rotational behavior in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra (8) and in substituting for cocaine in pigeons or rats trained to discriminate cocaine from vehicle (10,23).

The prominent behavioral effects of CFT in these studies suggest that, like cocaine, CFT may have the capacity to maintain self-administration behavior. Information on this point would be of value both for determining the profile of behavioral effects shared by cocaine and CFT, and for evaluating the role of cocaine recognition sites in the reinforcing effects of cocaine-like drugs. We now report that CFT maintains robust self-administration behavior in squirrel monkeys with a potency that corresponds to its affinity at cocaine recognition sites.

METHOD

Subjects

Three adult male squirrel monkeys (*Saimiri sciureus*), weighing 0.8–0.9 kg, were studied in daily experimental sessions (Monday–Friday). Between sessions, the monkeys lived in individual home cages where they had unrestricted access to food and water. Prior to this experiment, monkeys S-78 and S-305

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had been trained to respond under a second-order schedule of drug injection identical to the one described below, and had been studied with a range of doses of cocaine (3). The third monkey (S-347), previously had served in studies of the effects of benzodiazepine-related drugs on schedule-controlled behavior, but had not been used in experiments for approximately 6 months before the present study began. Each monkey was prepared with a chronic venous catheter using the surgical procedures described by Herd et al. (9). Under halothane anesthesia and in aseptic conditions, one end of a polyvinyl chloride catheter (inside diameter: 0.38 mm; outside diameter: 0.76 mm) was passed by way of a jugular or femoral vein to the level of the right atrium. The distal end of the catheter was passed SC and exited in the midscapular region. Catheters were flushed with 0.9% saline solution and sealed with stainless-steel obturators when not in use. The monkeys wore nylon mesh jackets at all times to protect the catheters.

Apparatus

Experiments were conducted in a ventilated, sound-attenuating chamber, provided with white noise to mask extraneous sounds. Within the chamber, monkeys were seated in a Plexiglas chair and faced a panel on which were mounted a response lever and colored lights. Venous catheters were connected to a motor driven syringe located outside the chamber. Each operation of the syringe motor lasted 200 ms and delivered a volume of 0.2 ml.

Procedure

Self-administration was studied using a second-order schedule of IV drug injection similar to the one described by Bergman et al. (3,4). In the presence of a white light, completion of a fixed ratio (FR) of responses (10 for monkeys S-347 and S-305; 30 for monkey S-78) during a 10-min fixed interval (FI) produced a 1-s change in illumination from white to amber (brief stimulus). Completion of the first FR after the FI elapsed produced both the brief stimulus and an IV injection of drug or vehicle. A 1-min timeout period, during which the lights were off and responses had no scheduled consequences, followed each injection. Sessions ended after completion of 5 cycles of the second-order schedule (i.e., after the fifth injection).

At the beginning of the study, responding was maintained by IV injections of 0.29 μmol/kg (0.1 mg/kg) cocaine HCl in all three monkeys. Once responding became stable from day-to-day, vehicle (0.9% saline solution) was substituted for cocaine. Subsequently, a range of doses of the naphthalenedisulfonate salt of CFT (0.017–0.17 μmol/kg; 0.01–0.1 mg/kg) was studied in each monkey. Each dose was studied for a minimum of four consecutive sessions and until there were no increasing or decreasing trends in response rate over the last three sessions. For purposes of comparison, a range of doses of cocaine (0.029–2.9 μmol/kg; 0.01–1.0 mg/kg) was studied using the same procedure either before [monkeys S-78 and S-305; see (3)] or after (monkey S-347) experiments with CFT were conducted. Rates of responding for individual subjects were computed each session by dividing total responses by elapsed time (exclusive of timeout periods). To facilitate comparison with previous studies, the doses of CFT and cocaine estimated to maintain half the maximum response rate (ED_{50}) were calculated for individual subjects as described previously (4).

RESULTS

Intravenous injections of 0.29 μmol/kg cocaine initially maintained self-administration in all three monkeys, with mean response rates of 0.60–1.12 responses/s among the individual subjects (Fig. 1, unconnected symbols). During subsequent sessions in which saline was substituted for cocaine injections, mean response rates fell to 0.07–0.25 responses/s (shaded areas in Fig. 1).

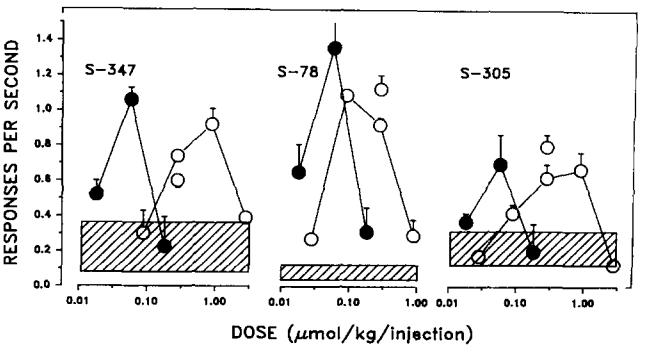

FIG. 1. Effects of dose of CFT (filled circles) and cocaine (unfilled circles) on responding under the second-order schedule of IV drug injection for individual subjects. Abscissae: dose, logarithmic scale, ordinates: response rate. Points are means based on the last three sessions of each condition; brackets show ±SD except where contained within the symbol. Unconnected circles show responding maintained by the training dose of cocaine (0.29 μmol/kg/injection). Shaded areas show means ± SD when saline was substituted for cocaine. Cocaine dose-response curves for monkeys S-78 and S-305 are reproduced from Bergman et al. (4).

Following the period of saline substitution, self-administration redeveloped and was maintained by IV injections of CFT in all three monkeys (Fig. 1, filled circles). The rate of responding maintained by CFT was a biphasic function of dose, with maximum response rates of 0.70–1.36 responses/s maintained by an intermediate dose of 0.051 μmol/kg. At this dose, temporal patterns of responding were characteristic for this type of second-order schedule; a period of little or no responding at the beginning of each 10-min FI typically was followed by sustained responding, which was interrupted by brief pauses upon completion of each FR unit. For the group of three monkeys, the dose of CFT estimated to maintain half the maximum response rate (ED_{50}) was 0.022 μmol/kg (range: 0.019–0.023 μmol/kg for individual monkeys).

Rates of responding maintained by IV injections of cocaine also were a biphasic function of dose in all three monkeys (Fig. 1, unfilled circles) and patterns of responding maintained by optimum doses were comparable to those maintained by CFT. Cocaine was, however, consistently less potent than CFT in each monkey, the average ED_{50} being 0.14 μmol/kg (range: 0.058–0.23 μmol/kg for individual subjects).

DISCUSSION

The results show that CFT can maintain robust self-administration behavior in squirrel monkeys under a second-order schedule of IV drug injection. Overall, the performances maintained by an optimal dose of CFT were similar to those maintained by optimal doses of cocaine (present study) as well as related drugs studied under a similar second-order schedule (4). Although CFT and cocaine were comparably effective in maintaining self-administration, CFT was considerably more potent. The potency of CFT in the present study (about six times that of cocaine) is similar to the potency of the related phenyltropane analog WIN 35,065-2 and greater than the potency of other cocaine-like drugs observed in previous self-administration experiments (4,22).

As in the present study, CFT has been found to be more po-

tent than cocaine in stimulating locomotor activity in rats or schedule-controlled behavior in monkeys (6,21), and in substituting for cocaine in rats or pigeons trained to discriminate cocaine from vehicle (10,23). The greater potency of CFT under these different experimental conditions supports the view that the reinforcing effects of cocaine-like drugs involve neurochemical mechanisms in common with those that mediate their psychomotor-stimulant and discriminative-stimulus effects. The additional findings that CFT is more potent than cocaine in inhibiting binding of [^{3}H]cocaine or [^{3}H]CFT and in blocking uptake of [^{3}H]dopamine in vitro (8, 14, 15, 17) suggest further that these common mechanisms involve cocaine recognition sites associated with the dopamine transport system.

A more complete understanding of cellular mechanisms underlying self-administration of cocaine is likely to emerge from integrated behavioral and neurochemical studies to characterize functional properties of cocaine recognition sites. Pursuit of these goals has been hampered, however, by the relatively low affinity of [^{3}H]cocaine as a radioligand probe [see discussion in (15)]. Other proposed radioligands for cocaine recognition sites such as [^{3}H]GBR 12935 and [^{3}H]mazindol, while of higher affinity, do not appear to be fully satisfactory alternatives. Both ligands, for example, have binding profiles and regional distributions in the brain that differ from that of [^{3}H]cocaine (1, 2, 7, 11, 12, 16). Furthermore, neither GBR 12909 (a close congener of GBR 12935) nor mazindol fully displace [^{3}H]cocaine or [^{3}H]CFT from cocaine recognition sites in the monkey brain (14,15), and mazindol fails to maintain consistent self-administration behavior (4). CFT, on the other hand, has a profile of neurochemical and behavioral effects, including IV self-administration, that closely parallels the profile for cocaine. These findings, coupled with the high affinity of CFT, suggest that radiolabeled forms of this compound or related cocaine analogs may be particularly suitable markers for recognition sites associated with the reinforcing effects of cocaine-like drugs.

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