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In vitro and in vivo effects of cocaine and selected local anesthetics on the dopamine transporter

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Abstract

The effects of selected local anesthetics on in vitro and in vivo measurements of dopamine transporter activity were determined to investigate the role of local anesthetic activity in the neuronal actions of cocaine. Cocaine inhibited [^{3}H]2-β-carbomethoxy-3-β-(4-fluorophenyl)tropane 1,5-naphthalenedisulfonate (CFT) binding and [^{3}H]dopamine uptake with estimated K_i and IC_{50} values of 0.6 μM and 0.7 μM, respectively. Of the local anesthetics tested, only dimethocaine showed full displacement of CFT binding (0–30 μM tested) and full inhibition of dopamine uptake (0–100 μM tested). Dimethocaine was only slightly less potent than cocaine with an estimated K_i of 1.4 μM and an IC_{50} value of 1.2 μM for [^{3}H]CFT binding and dopamine uptake. At a maximum concentration of 100 μM, the ester containing local anesthetics procaine, tetracaine, piperocaine and the amide containing local anesthetic dibucaine and bupivacaine partially inhibited dopamine uptake by 47–70%. The ester containing local anesthetic propoxycaine and the amide containing local anesthetics prilocaine, etidocaine, procainamide, and lidocaine inhibited dopamine uptake by 8–30% at 100 μM. A 10 min administration of cocaine, dimethocaine, or procaine in the dialysis solution produced dose-dependent, reversible increases in endogenous dopamine efflux from the striata of awake rats. Cocaine and dimethocaine produced similar 12-fold increases in dialysate dopamine at concentrations of 0.1 mM and 1 mM respectively. Procaine (10 mM) produced a 6-fold increase in dialysate dopamine while lidocaine (1 mM) produced a reproducible and reversible decrease (30%). These results show that the cocaine-like actions of certain local anesthetics such as dimethocaine and procaine result from their direct actions of dopamine uptake inhibitors.

Keywords: Local anesthetic; Dopamine uptake; Microdialysis

1. Introduction

The mood enhancing effects of cocaine in humans are thought to be related primarily to its ability to block the actions of the dopamine transporter. This inhibitory action as measured in vitro is well correlated with the self-administration potency of cocaine and various cocaine analogs in animals (Ritz et al., 1990). However, cocaine is also a potent local anesthetic and previous studies have shown that some local anesthetics have reinforcing effects in animals (Ford and Balster, 1977; Johanson, 1980; Woolverton and Balster, 1982). In addition, drug discrimination studies have demonstrated that some local anesthetics will substitute for cocaine in rats trained to discriminate cocaine from saline (Silverman and Schultz, 1989; Graham and Balster, 1993). Cocaine has also been shown to substitute for procaine in rats trained to recognize procaine from saline (Woolverton and Balster, 1982). Other local anesthetics like lidocaine, however, do not consistently produce cocaine-like reinforcing and discriminative stimulus effects (Woolverton and Balster, 1979; Huang and Wilson, 1986). The ability of some local anesthetics to produce cocaine-like effects suggests the possibility that the effects of cocaine on sodium channels as reflected in its own local anesthetic effects contribute to its in vivo pharmacological actions (Gifford and Johnson, 1992). On the other hand, some local anesthetics have been shown to have dopaminergic effects and may act at sites on the dopamine transporter similar to those of cocaine (Ritz et al., 1990; Silverman, 1990). To provide further information on the cocaine-like dopaminergic effects of local anes-

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thetics, we examined the effects of a number of these drugs for inhibition of dopamine uptake in striatal synaptosomes, binding to sites on the dopamine transporter labelled by [^{3}H]2-β-carbomethoxy-3-β-(4-fluorophenyl)tropane 1,5-naphthalenedisulfonate (CFT), and their ability to increase dopamine efflux in vivo using microdialysis.

2. Materials and methods

2.1. Synaptosomal dopamine uptake inhibition

Male Sprague-Dawley rats (250–300 g; Flow-Dominion Labs) were killed and the corpus striata was removed and placed in ice-cold 0.32 M sucrose (pH 7.4). Pairs of striata were homogenized with ten up and down strokes (300 rpm) using a Thomas A Teflon to glass homogenizer. The homogenized preparation was centrifuged at $3000 \times g$ for 10 min at 4° C and the supernatant was carefully decanted to a fresh tube. After centrifugation at $12000 \times g$ (4° C), the P2 pellet was resuspended in ice-cold incubation medium (136 mM NaCl, 5 mM KCl, 1.3 mM $MgCl_2$, 10 mM glucose, 10 mM Tris, pH 7.65 at room temperature) to a protein concentration of approximately 1 mg/ml (Bradford assay, BioRad. Calcium was omitted from the incubation medium to reduce release of endogenous dopamine which may compete with radiolabelled dopamine during the uptake period (unpublished observation). Synaptosomes were incubated for 10 min at 35° C prior to a 2 min exposure to a solution containing [^{3}H]dopamine (100 nM, Amersham) and the various drugs to be tested. Uptake was stopped after 2 min by rapid filtration through Whatman GF/B filters followed by two washes with ice-cold incubation medium. Radioactivity remaining on the filters was quantitated by liquid scintillation counting. For each experiment, a control uptake was performed with ice-cold synaptosomes to assess non-specific binding of radioisotope. This value averaged approximately 2.5% of control non-drug uptake at 35° C and was subtracted from all values to yield net uptake. All experiments were performed in duplicate and were repeated at least 3 times. Data represent mean ($\pm$S.E.M.) uptake as a percent of the control uptake. Inhibitory constants were calculated using the ALLFIT program.

2.2. [^{3}H]CFT binding

Male Sprague-Dawley rats (150–200 g) were killed by decapitation. Their brains were removed immediately following decapitation and striatal tissue (minimum of 225 mg) was placed in 10 ml of ice-cold buffer (50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, pH 7.4). Tissue was homogenized using a Tissumizer (Tekmar) and centrifuged at $40900 \times g$ at 4° C for 20 min. The supernatant was decanted and 10 ml of buffer was added and the tissue was centrifuged again. After pouring off the supernatant, the tissue was brought up to its reaction volume (25 mg tissue/ml buffer) and introduced into the reaction immediately. Displacement assays were performed using 30 nM [^{3}H]CFT and increasing concentrations of the selected local anesthetics. Non-specific binding was determined in the presence of 30 μM (−)-cocaine. After a 2 h incubation at 0° C, tissue binding was terminated by two rapid washes of ice-cold buffer onto Whatman GF/B filters using a Brandel 24-well cell harvester. Filters were placed in scintillation vials containing 10 ml of Boise II scintillation cocktail and radioactivity was counted in a Beckman LS 6000 scintillation counter. K_i values were determined using the ALLFIT program.

2.3. In vivo microdialysis of striatal dopamine

Adult male Sprague-Dawley rats were anesthetized with sodium pentobarbital (60 mg/kg i.p.) and guide cannulas were affixed with dental acrylic over the corpus striatum (coordinates, mm; bregma, −0.5, lateral, 2.7). The tip of the plastic guide cannula was trimmed so that it did not enter the area to be sampled from. Twenty-four hours later, a CMA 12 microdialysis probe (3 mm tip) was inserted using a special spacer to position the tip of the probe 6.5 mm ventral to the top of the skull. The probe was perfused for 24 h at 1 μl/min with artificial cerebrospinal fluid (145 mM NaCl, 2.7 mM KCl, 1.2 mM $CaCl_2$, 1.6 mM Na_2HPO_4, 0.19 mM NaH_2PO_4, pH 7.42) before sampling began. Dialysate exiting the probe was delivered to the sample loop of a CMA 140 automated sample injector. Samples were injected every 15 min into a BAS 480 liquid chromatograph. The BAS 480 liquid chromatograph was operated using a column splitter which delivered approximately 80 μl/min to a BAS Sepstik C18 column (3 μm ODS, 100×1 mm ID) which separated dopamine from its metabolites. The mobile phase consisted of 0.1 M monochloroacetic acid, 200 mg/l sodium octyl sulfate, and 3.5% (v/v) acetonitrile at a pH of 4.65. Under these conditions, dopamine eluted at approximately 9.5 min and was detected by a glassy carbon working electrode operated at 0.7 V relative to an Ag/AgCl reference electrode. The detection limit for dopamine was approximately 5 pg. Following establishment of a stable baseline, the perfusion solution was switched using a CMA 110 liquid switch to ACSF containing various concentrations of the drugs to be tested. The drug solution was perfused for 10 min before being switched back to non-drug containing perfusion solution. Dopamine peak areas were quantitated using the Rainin Dynamax Chromotography software running on a Macintosh computer. Data repre-

Table 1
Inhibition of striatal [^{3}H]dopamine uptake and [^{3}H]CFT binding by selected local anesthetics

Drug	Uptake inhibition [a] (% maximum)	IC_{50} (μM)	[^{3}H]CFT binding [b] (K_i, μM)
Cocaine	100	0.7	0.6
Dimethocaine	100	1.2	1.4
Dibucaine	63	13.0	> 30
Piperocaine	65	13.2	> 30
Chlorprocaine	70	26.2	> 30
Ketocaine	56	52.1	> 30
Procaine	55	58.4	> 30
Tetracaine	65	77.1	> 30
Bupivacaine	47	–	> 30
Propoxycaine	30	–	> 30
Prilocaine	30	–	> 30
Etidocaine	29	–	> 30
Procainamide	15	–	> 30
Lidocaine	8	–	> 30

[a] Inhibition of 50 nM [^{3}H]dopamine uptake in striatal synaptosomes. All drugs were tested over a concentration range of 0.1–100 μM.
[b] Inhibition of [^{3}H]CFT binding to striatal homogenates. All drugs were tested over a concentration range of 0.1–30 μM.

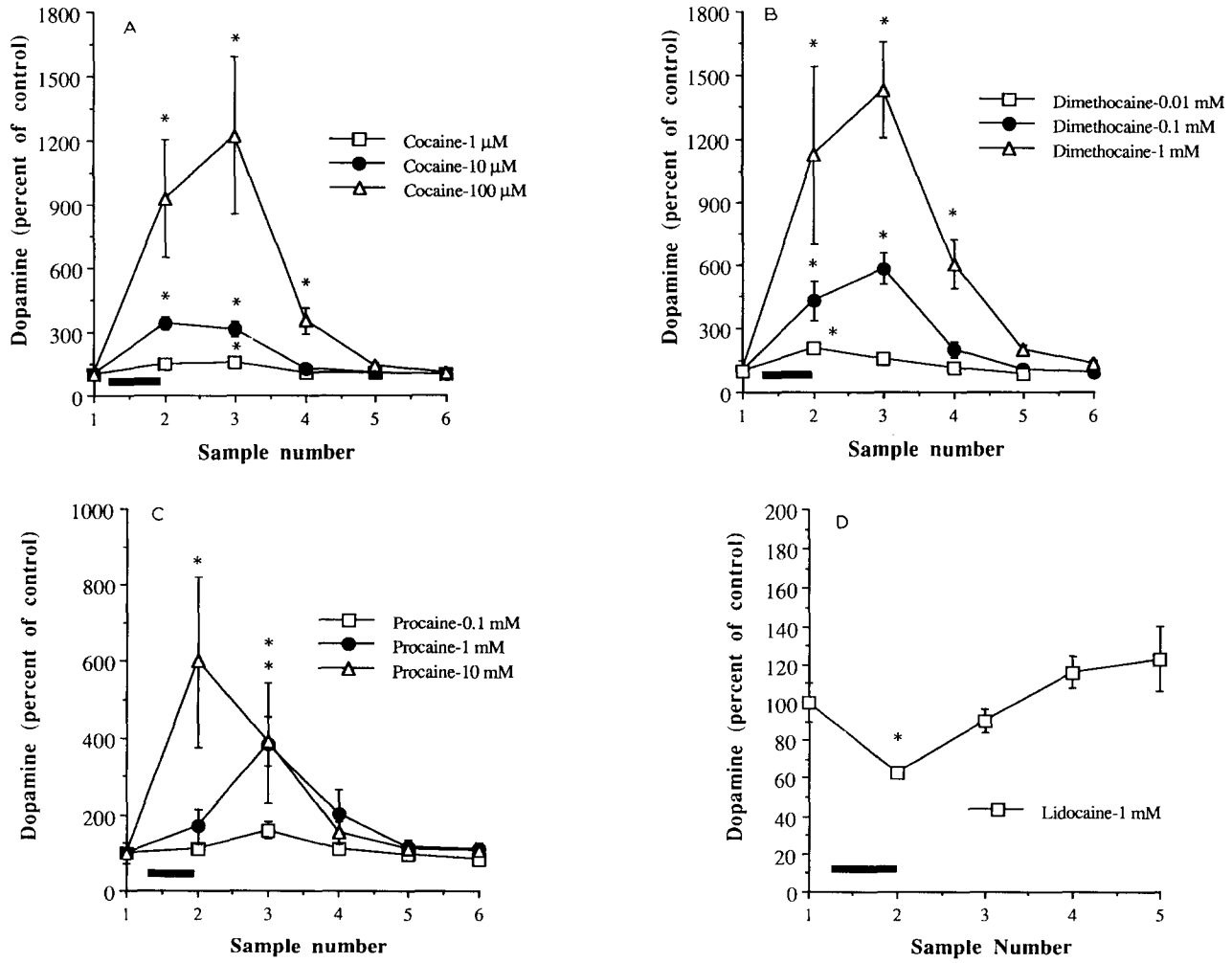

Fig. 1. A–D: Effects of cocaine (A), dimethocaine (B), procaine (C), and lidocaine (D) on striatal dopamine efflux as measured by in vivo microdialysis in awake rats. For each panel, drug was administered at the concentration shown for 10 min via the microdialysis probe. Dopamine contained in the dialysate was analyzed by HPLC and is expressed as a percent of the last basal sample which was assigned a value of 100%. Data represent the mean (±S.E.M.) from at least four (cocaine and dimethocaine) or three (procaine and lidocaine) different animals. * Value significantly different ($P < 0.05$; ANOVA) from corresponding pre-drug control level.

sent the mean percentage of control where the control sample represents the area of the sample (set at 100%) immediately preceding the sample containing the experimental drug. All drug effects were determined at least 3 times in three different animals and averaged to give the mean and standard error. The relative recovery of each probe was determined before implantation by perfusing the probe while it was suspended in a dopamine-containing solution. Probe recoveries averaged between 25 and 30% although the data presented were not corrected for individual probe efficiency. Data were analysed with ANOVA with repeated measures and Scheffe's F-test with a significance level of $P < 0.05$.

3. Results

3.1. Effects on binding and uptake

Table 1 shows the inhibition of synaptosomal dopamine uptake and displacement of [^{3}H]CFT binding by cocaine and 13 different local anesthetics. Cocaine was the most potent compound tested with an estimated IC_{50} and K_i for uptake inhibition and binding of 0.7 μM and 0.6 μM, respectively. The ester-containing local anesthetic dimethocaine was equi-effective as cocaine and nearly as potent with an IC_{50} and K_i of 1.2 μM and 1.4 μM, respectively. The Hill coefficients for the displacement of [^{3}H]CFT by cocaine and dimethocaine were 1.2 ($r = 0.98$) and 0.91 ($r = 0.99$), respectively indicating a single site of binding. Of the remaining 12 local anesthetics tested, only dibucaine, piperocaine, chloroprocaine, ketocaine, procaine, bupivacine, and tetracaine showed appreciable block of uptake inhibition at the highest concentration tested, 100 μM. The magnitude of this inhibition was less than that observed for cocaine and dimethocaine and ranged from 47 to 70%. The IC_{50} values derived from these data showed that dibucaine and piperocaine were slightly more potent (approximately 13 μM) than chloroprocaine (26 μM) while ketocaine, procaine, and tetracaine had IC_{50} values ranging from 50 to 77 μM, respectively. None of the local anesthetics except dimethocaine showed appreciable displacement of [^{3}H]CFT binding at the highest concentration tested, 30 μM. The remaining local anesthetics tested (propoxycaine, prilocaine, etidocaine, procainamide, lidocaine) showed only modest uptake blocking activity with lidocaine being the least potent. As a class, six out of the seven ester-containing local anesthetics inhibited uptake by at least 50% at the highest concentration tested (100 μM) while only two out of the six amide-containing compounds (dibucaine and bupivacaine) showed appreciable inhibition of uptake at 100 μM.

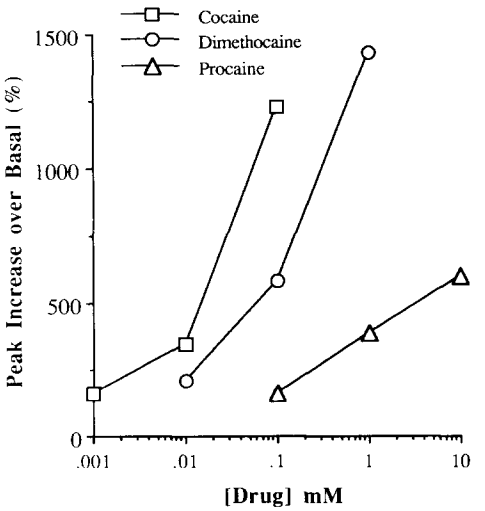

Fig. 2. Comparison of effects of cocaine, dimethocaine, and procaine on striatal dopamine efflux as measured by in vivo microdialysis in awake rats. The peak increase in striatal dopamine efflux achieved following drug administration is plotted at each concentration tested for cocaine, dimethocaine, and procaine. The EC_{500} values were calculated to be 15 μM (cocaine), 57 μM (dimethocaine), and 3.5 mM (procaine).

3.2. In vivo microdialysis

The effects of cocaine, dimethocaine, procaine, and lidocaine on endogenous striatal dopamine efflux from awake rats were measured using in vivo microdialysis to examine the effects of local anesthetics on the dopamine transporter in the whole animal. As expected from their in vitro effects, cocaine, dimethocaine, and procaine produced a rapid and reversible increase in dialysate dopamine when perfused separately through the probe for 10 min (Fig. 1A–C). In contrast, lidocaine (1 mM) produced a transient decrease in dopamine efflux (Fig. 1D). The increases in striatal dopamine efflux produced by cocaine, dimethocaine, or procaine were dose-dependent and displayed a rank order of potency consistent with that predicted from results observed in the in vitro uptake and binding assays. This is illustrated in Fig. 2 in which the peak increase in extracellular dopamine is plotted against the concentration of each drug tested. Although it is clear that a plateau was not reached at the maximal concentration tested for each drug, EC_{500} values (concentration required to increase levels 500% over basal) were calculated to be 15 μM, 57 μM, and 3.5 mM for cocaine, dimethocaine, and procaine, respectively.

4. Discussion

4.1. Dimethocaine

Local anesthetics are not generally recognized as being indirect dopamine agonists, with the obvious exception of cocaine. In support of this is the fact that

while cocaine is capable of altering rodent locomotor activity in a biphasic fashion (stimulation prior to depression), the local anesthetics (procaine, tetracaine, benzocaine, lidocaine, prilocaine) inhibit motor activity. Additionally, it has been concluded that since the rank order of potencies of cocaine analogs (norcocaine, etc.) and local anesthetics in depressing locomotion was similar to that for interaction with sodium channels, then the inhibition probably is due to a local anesthetic action (Reith et al., 1985). This is further supported by the findings of MacNeal et al. (1985) who determined the ability of a series of local anesthetics to displace labelled batrachotoxin from cerebral cortical membranes as a measure of their affinity for the voltage-dependent sodium channel (MacNeal et al., 1985). For example, the IC_{50} value reported for cocaine in that study was 49 μM which is nearly 100 times less potent as its dopamine uptake blocking activity shown in the present study. Conversely, while local anesthetics such as tetracaine, bupivacaine, and etidocaine only significantly inhibited dopamine uptake in this study at 100 μM, these compounds were among the most potent in inhibiting batrachotoxin binding with IC_{50} values in the 3–5 μM range.

Thus, while most local anesthetics do not appear to have a high affinity for the dopamine transporter, a variety of studies including the present one suggest that some of these compounds possess significant indirect dopaminergic agonist activity. This evidence is most clear for dimethocaine. We found that it was fully as efficacious and nearly as potent as cocaine in blocking dopamine uptake in striatal synaptosomes and that it potently competed for binding to the transporter. These results are consistent with earlier binding studies using [^{3}H]mazindol in rat striatal tissue (Ritz et al., 1990). In addition, dimethocaine was equally effective and only 4-fold less potent than cocaine for increasing dopamine efflux in the striatum. These results are in agreement with behavioral studies showing cocaine-like effects of dimethocaine. Both cocaine and dimethocaine can induce active rotation directed ipsilaterally to the lesioned side of animals receiving unilateral lesions of the substantia nigra, indicating indirect dopamine agonist activity (Silverman, 1990). Additionally, repeated administration of either cocaine or dimethocaine induced sensitization to their effects on turning behavior (Silverman, 1990). In drug discrimination studies, dimethocaine fully substitutes for cocaine in both rats (Graham and Balster, 1993) and squirrel monkeys (R.L. Mansbach and R.L. Balster, unpublished data). Dimethocaine is also an effective reinforcer in i.v. drug self-administration studies in rhesus monkeys (Woolverton and Balster, 1982). The potency relationship between cocaine and dimethocaine in these in vivo studies, with cocaine only being about 2–5 times more potent than dimethocaine, is also consistent with results from the biochemical studies reported here. Taken together, it is apparent that the cocaine-like behavioral effects of dimethocaine can be explained by its efficacy and potency as a dopamine uptake inhibitor.

4.2. Lidocaine

It is equally evident from the results of this study that other local anesthetics are less efficacious than cocaine and dimethocaine as dopamine uptake inhibitors and for producing cocaine-like behavioral effects. Lidocaine, for example, lacks both biochemical and behavioral dopaminergic effects. We found that it did not compete for binding to the dopamine transporter, produced only an 8% inhibition of dopamine uptake in striatal synaptosomes at the maximally tested concentration of 100 μM, and produced decreases rather than increases in dopamine efflux in the striatum. Lidocaine also produces only decreases in locomotor activity in mice (Reith et al., 1985), fails to produce ipsilateral turning in the nigrastriatal-lesioned rat (Silverman, 1990) and produces at best only partial substitution for cocaine in drug discrimination studies in pigeons (De la Garza and Johanson, 1985) and rats (Huang and Wilson, 1982; Graham and Balster, 1993). It completely lacks reinforcing effects in rhesus monkeys (Woolverton and Balster, 1979) and fails to produce cocaine-like physiological and subjective effects in humans (Fischman and Schuster, 1983).

4.3. Procaine

The other local anesthetic for which considerable data on its dopaminergic effects exist is procaine, although the results are less clear than they are for dimethocaine and lidocaine. In drug discrimination studies with procaine, partial substitution for cocaine has been observed in a number of studies (McKenna and Ho, 1980; De la Garza and Johanson, 1983, 1985; Jarbe, 1984; Silverman and Schultz, 1989; Graham and Balster, 1993). Cocaine and amphetamine produce quite robust substitution in rats trained to discriminate procaine (Woolverton and Balster, 1982) and procaine has been reported to have some amphetamine-like discriminative stimulus effects in pigeons (Zacny and Woolverton, 1989). Procaine has also consistently been shown to produce reinforcing effects in i.v. drug self-administration studies in rhesus monkeys (Ford and Balster, 1977; Hammerbeck and Mitchell, 1978; Woolverton and Balster, 1979; Johanson, 1980; Beardsley and Balster, 1993). To complicate the picture further, however, the dopamine antagonist haloperidol has been reported to be unable to block the reinforcing and discriminative stimulus effects of procaine (Silverman and Schultz, 1989), and procaine has recently

been found to lack completely cocaine-like discriminative stimulus effects in squirrel monkeys (R.L. Mansbach and R.L. Balster, unpublished data). Rats can also be trained to discriminate between equipotent doses of cocaine and procaine (Graham and Balster, 1993). One explanation for these inconsistent results is that procaine, although having some dopaminergic effects, is less efficacious for these effects than cocaine or dimethocaine. Direct support for this hypothesis is provided in our data, where procaine was only able to produce only half-maximal inhibition of dopamine uptake in striatal synaptosomes at the highest concentration tested (100 μM) and produced increases in striatal dopamine as measured by microdialysis that were about 50% of those produced by cocaine and dimethocaine. Procaine is also much less potent than cocaine for dopaminergic effects, with a potency ratio relative to cocaine ranging from > 50-fold for binding and in vitro uptake inhibition to over 200-fold in the microdialysis study. Its affinity for displacing labelled batrachotoxin was determined to be 110 μM (MacNeal et al., 1985). Therefore, when procaine is given systemically in whole-animal studies, it is likely that concentrations necessary to achieve dopaminergic effects are difficult to produce and/or that there is a poor separation of dopaminergic effects and effects mediated by actions at sodium channels.

There are some data from in vivo studies which support the idea that procaine is less efficacious than cocaine for effects presumably mediated by dopaminergic mechanisms. Unlike cocaine, procaine does not increase motor activity in mice (Reith et al., 1985) and rats (Wiechman et al., 1981) and it fails to produce rotational behavior in rats with lesions in the substantia nigra (Silverman, 1990). A number of drug self-administration studies in rhesus monkeys have attempted to compare the reinforcing efficacy of cocaine and procaine. In choice studies, monkeys prefer cocaine to procaine (Johanson and Aigner, 1981) and procaine reinforcement is more sensitive to the decreasing effects of alternative food reinforcement than is cocaine reinforcement (Nader and Woolverton, 1991). On the other hand, the relative reinforcing efficacy of cocaine and procaine could not be distinguished in a study examining their sensitivity to effects of delay of reinforcement (Beardsley and Balster, 1993). Because the efficacy of procaine to increase dopaminergic neurotransmission is less than for cocaine and because it may have a poorer separation of dopaminergic and local anesthetic effects, it seems likely that the efficacy of procaine to produce cocaine-like effects in vivo will depend greatly on the test procedure.

4.4. Other local anesthetics

An important goal of the present study was to examine a number of other local anesthetics to determine if other cocaine-like dopaminergic agonists could be identified. With the exception of dimethocaine, none of the 13 drugs tested was either very potent or very efficacious for binding to the dopamine carrier or inhibiting dopamine uptake. There was a tendency for ester-linked local anesthetics (e.g. piperocaine, chloroprocaine, chloroprocaine, tetracaine, propoxycaine) to show greater efficacy for dopamine uptake inhibition than the amide-liked drugs (e.g. lidocaine, procainamide, etidocaine), although the amides dibucaine and bupivacaine were not distinguishable from most of the esters. Since only dimethocaine showed robust dopaminergic effects, it is not possible from this study to accurately determine the structural features required. In general, these results are consistent with the relatively little information about the behavioral effects of local anesthetics other than dimethocaine, procaine and lidocaine. Chloroprocaine and tetracaine, which had procaine-like efficacy and were at least as potent as procaine as dopamine uptake inhibitors, have been reported to have reinforcing effects similar to procaine in rhesus monkeys, whereas lidocaine, procainamide and propoxycaine, which were much less efficacious and potent than procaine, failed to serve as reinforcers (Woolverton and Balster, 1979, 1982; Johanson, 1980). On the other hand, piperocaine, which was more potent and efficacious than procaine as a dopamine uptake inhibitor, did not have reinforcing effects (Woolverton and Balster, 1982), yet piperocaine is even less efficacious than lidocaine in producing procaine-like discriminative stimulus effects in rats. This local anesthetic merits further study to reconcile this apparent discrepancy.

In conclusion, the results of this study confirm the hypothesis that the cocaine-like effects of local anesthetics result from their direct actions as dopamine uptake inhibitors. They also confirm that dimethocaine is a potent and efficacious dopaminergic agonist, explaining its previously reported prominent cocaine-like effects. This is the first report directly comparing the relative efficacies of a number of other local anesthetics as dopamine agonists. Some, like procaine, have intermediate efficacy, whereas others, like lidocaine, are without dopaminergic effects. Nonetheless, dimethocaine remains the only local anesthetic with comparable potency and efficacy to cocaine. Dimethocaine should continue to serve as a useful probe for neural substrates of cocaine abuse.

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