Metabolite Involvement in Bromocriptine-Induced Prolactin Inhibition in Rats

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ABSTRACT

Bromocriptine (BCT) is a dopamine D2 receptor agonist used for the treatment of Parkinson’s disease and hyperprolactinemic disorders. After oral administration, BCT is metabolized into mono- or dihydroxylated metabolites. To study how these metabolites influence parent drug pharmacodynamics, we administered BCT to rats intravenously (1 mg/kg i.v.) and orally (10 mg/kg p.o.) and measured the inhibition of prolactin secretion. Despite similar areas under the curve for BCT, the duration of the effect was 36 h after oral and only 18 h after intravenous administration. Pharmacokinetic/pharmacodynamic models were used to correlate the concentration of BCT in the effect compartment with the lowering of prolactin. One of these models (effect compartment model) showed that the effective concentration (EC50) at the site of action was much lower after oral (0.56 nM) than after intravenous administration (3.68 nM). In contrast, the EC50 values based on BCT metabolite data were in the same range for both administrations. These observations suggested the activity of one or more BCT metabolites. To confirm this hypothesis, hydroxylated metabolites of BCT (produced in vitro by rat liver microsomes) were administered i.v. (100 μg/kg) in rats. We found that monohydroxylated BCT was able to lower prolactin secretion like BCT. Dihydroxylated metabolites, as well as monohydroxylated metabolites, were effective in reducing in vitro prolactin secretion. Because we demonstrated that the concentration of hydroxylated metabolites after oral administration is 55-fold that of BCT, it can be concluded that BCT activity in the pituitary after oral administration is mediated by its metabolites.

BCT (2-bromo-α-ergocryptine) is a semisynthetic derivative of the ergot alkaloid family possessing dopamine agonist properties (Kebabian and Calne, 1979). Because of its inhibitory effect on prolactin secretion this drug has been used successfully for the treatment of prolactin-producing tumors and other hyperprolactinemic disorders, including idiopathic hyperprolactinemia and postpartum lactation (Thorner et al., 1977). It has also been useful in the treatment of acromegaly (Wass et al., 1977) and at higher doses in the treatment of Parkinson’s disease (Kopin, 1993).

When given orally to animals or humans, BCT is extensively metabolized by a hepatic first-pass effect. The main metabolites observed in the circulation are hydroxylated BCT and 2-bromolyssergic acid (Maurer et al., 1982, 1983). Hydroxylated BCT metabolites have been implicated as possible active agents in the BCT-induced circling behavior of rodents (Reavill et al., 1980), hypothermia in rats (Silbergeld et al., 1977) and behavioral effects in cats (Gonzalez-Lima et al., 1987). However, other authors failed to confirm these findings (Keller and Da Prada, 1979; Markey et al., 1979; Schran et al., 1985) and demonstrated that the duration of the hypothermic effect was better correlated with the concentrations of parent drug rather than with concentration of BCT plus metabolites. The presence and action of pharmacologically active metabolites in the central nervous system is clearly controversial, and this issue has not yet been resolved.

Several observations indicate that the effect of BCT in human pituitary is not correlated with the concentration of parent drug. In fact, it is known that prolactin inhibition persists when no BCT remains in the circulation (Katz et al., 1991). This was attributed to a prolonged action of the drug.

ABBREVIATIONS: BCT, bromocriptine; i.v., intravenous; p.o., per os; EC50, equivalent concentration for 50% of the maximum effect; I.D. internal diameter; O.D. overall diameter; V, volume; Cmax, maximal concentration; Tmax, time for the Cmax; Ccp, concentration in the central compartment; Cce, concentration in the effect compartment; n, Hill factor; AUC, area under the curve; Kr, rate of drug transfer between plasma and the effect site; Kne, rate of elimination from the effect site; E, effect; Emax, maximum effect; Kn, and Kout, rate of prolactin input and output from the central compartment, respectively; PRL, prolactin; NADPH, nicotinamide adenine dinucleotide phosphate, reduced form; NADP, nicotinamide adenine dinucleotide phosphate; HPLC, high-performance liquid chromatography.
at the pituitary level rather than to a possible action of metabolites (Woolf, 1981).

To study the possible involvement of BCT metabolites at the pituitary level, we used a pharmacokinetic-pharmacodynamic model to correlate the concentration of BCT with its effect on in vivo prolactin secretion inhibition. We then produced hydroxylated metabolites by in vitro incubation of BCT with rat liver microsomes and demonstrated either in vitro or in vivo their dopaminergic activity on pituitary cells.

**Materials and Methods**

**Animals.** Male Sprague-Dawley rats were obtained from Iffa Credo (St-Germain sur l’Abresle, France). They were maintained on a 12-h light/dark cycle with light from 7:00 a.m. to 7:00 p.m., in a temperature (21–22°C) and humidity (50 ± 10%)-controlled room. Rats fed commercial rat chow (UAR, Villemonois sur Orge, France), and tap water was available ad libitum. The rats were used after a 1-week acclimation period, at which time their body weights ranged from 250 to 300 g. All studies on animals comply with the French law on rules for animal experimentation, Decree 87–848, 19 October 1987.

**Surgical procedures.** The rats were anesthetized with flunthanol (Pitman Moore, Meaux, France). An incision was made at the left and right groin, and, respectively, the saphenous vein and femoral artery were exposed. A polyethylene catheter (PE 10, I.D., 0.28 mm; O.D., 0.68 mm; Clay Adams supplied by Becton Dickinson, Sparks, MD) was inserted into each vessel and held in position with a silk suture. The catheters were flushed with physiological serum containing 10% heparin to avoid coagulation, and their distal ends were occluded. The free end of each catheter was then threaded under the skin on the back of the animal with a metal probe and exteriorized at the dorsal part of the neck between the ears, thus avoiding contact with the animals’ feet or mouth. Incisions on the left and right groin were sutured. The free end of the two catheters, emerging from the dorsum of the neck, were threaded through a metal spring 30 cm long. Animals were housed individually in metabolism cages with immediate free access to water, and were allowed to feed only after 1 day of recovery.

**In vivo studies.** The first animal study was designed to assess the effect of the plasma pharmacokinetics of BCT and its metabolites on the pharmacodynamic response, i.e., the lowering of plasma prolactin. BCT (Galenia State Corporation, Opava, Czech Republic) was prepared at a concentration of 1 mg/ml in water/methanol (95:5, V/V) immediately before administration. This solution was administered intravenously to six rats at 1 mg/kg through the saphenous vein catheter, or was given by gavage to six rats at a dose of 10 mg/kg. Control animals (n = 6) received vehicle alone. Blood samples were drawn through the arterial catheter at 0 (predose) and 0.08, 0.5, 1, 2, 4, 8, 12, 18, 24, 36, 48 and 72 h after injection of BCT. After centrifugation (3,500 × g, 5 min), plasma was frozen at −20°C until analysis. The volume of plasma collected was immediately replaced by physiological serum mixed with red blood corpuscles and injected through the femoral catheter to avoid a change in blood volume.

The second animal study was intended to compare directly the dopaminergic activity of BCT with that of its hydroxylated metabolites produced in vitro by rat liver microsomes. Six rats were anesthetized as described above and 2 days after the surgical operation each rat was given BCT, BCT metabolites and vehicle according a cross-over study designed as a Latin square. The interval between two administrations was 24 h. BCT or its metabolites were dissolved in water with 5% methanol at a concentration of 0.225 mg/ml immediately before the first administration and were administered at a dose of 100 μg/kg. Before the first administration and 4 h after each administration, animals were sampled as described above, and plasma prolactin was then assayed.

**In vitro experiments.** Anterior pituitary cell dispersion was obtained according to the methodology described by Hopkins and Farquhar (1973), in which 2 × 10⁶ cells/well were seeded into 12-well plates in Dulbecco’s Modified Eagle’s Medium (Gibco supplied by Life Technologies, Cergy-Pontoise, France) containing 1.5 g/l NaHCO₃, 2 mM glutamine, 50 μM penicillin, 50 μg/ml streptomycin and 10% fetal calf serum for 2 days under a 95% air and 5% CO₂ atmosphere. The monolayers were rinsed with 1 ml of phosphate buffer saline (PBS) and preincubated in the same medium for 1 h. Incubation was then performed with or without dopamine, BCT, monohydroxylated (M1/M2) and dihydroxylated (M3 and M4) metabolites at 10⁻⁸ M. After 1, 2 and 4 h of incubation, 100 μl of medium were collected and frozen at −20°C until prolactin measurement.

**Binding studies.** Receptor binding studies were performed with rat striatum as described previously (Terai et al, 1989) by CEREP (Celle L’Evescault, France). The binding assay used 0.1 nM [³H]YM-09151–2 (DuPont NEN, Les Ulis, France) as radioactive ligand, and nonspecific binding was determined with 10 μM (+)-butaclamol. After incubation with BCT or hydroxylated metabolites, the membrane preparations were filtered in a vacuum filtration pump using Whatman GF/B filters. The filters were then rinsed three times with 4 ml of cold saline and placed in scintillation vials with Formula 989 (DuPont NEN, Les Ulis, France). The radioactivity trapped on the filters was counted in a liquid scintillation counter (LS6000 Beckman, Gagny, France). Competitive inhibition studies allowed the calculation of the binding affinity constants of BCT and its metabolites.

**Analytical methods.** Plasma samples were analyzed for BCT and its main metabolites by two enzyme immunoassays specific either for untransformed BCT or for BCT plus a pool of hydroxylated metabolites (Valente et al., 1996). The hydroxylated metabolites were detected with antibodies directed against the bromolysine part of the molecule. Unchanged BCT was detected by antibodies directed against the cyclopeptide structure of BCT. Enzymatic tracers were obtained by covalent coupling of BCT analogs to acetylcholinesterase from the electric eel Electrophorus electricus. The specificity of antibodies was checked by cross-reactivity studies. Both assays have a limit of quantification of 50 pg/ml. The concentration of metabolites in each sample was calculated by subtracting the concentration determined by the assay measuring only untransformed BCT from the concentration determined by the assay measuring both BCT and its metabolites. Prolactin was determined by an enzyme immunoassay previously developed and validated in our laboratory (Duhau et al., 1991).
effect site was considered as an additional compartment linked to the plasma compartment by a first-order process (of rate $K_\text{int}$). Drug removal was characterized by a first-order rate constant $K_\text{rem}$ which describes the temporal aspects of equilibrium between plasma concentrations and the concentration at the site of effect. In this model, $K_\text{rem}$ was assumed to be equal to $k_{\text{out}}$ (Unadkat et al., 1986). The concentration-response relation in the effect compartment was defined according to the sigmoid $E_{\text{max}}$ model:

$$E = E_{\text{max}}C^n_C(\frac{C}{C_{50}} + C^n_C)$$

where $E_{\text{max}}$ is the maximum effect attributable to the drug, $EC_{50}$, the concentration of the drug in the effect compartment producing 50% of the maximum effect and $n$ is the Hill coefficient governing the slope and the shape of the effect concentration curve.

Additionally, the indirect pharmacodynamic response model proposed recently by Dayneca et al. (1993) and Jusko and Ko (1994) was applied to our data. The pharmacodynamics of the prolactin responses for the average data from the six rats treated intravenously or orally were characterized by use of inhibition model I (Jusko and Ko, 1994):

$$\frac{dPRL}{dt} = k_{\text{in}}[1 - (C^n_C/EC_{50} + C^n_C)] - k_{\text{out}}PRL$$

where PRL is the prolactin concentration in plasma; $EC_{50}$, the drug concentration which produces 50% of maximum inhibition; $n$, the Hill factor for sigmoidicity; $C^n_C$, the drug concentration in the plasma compartment; and $k_{\text{in}}$ and $k_{\text{out}}$, the rate of prolactin input and output from the central compartment, respectively. Pharmacokinetic and pharmacodynamic were fitted simultaneously.

For both pharmacodynamic analyses and at each time, the placebo effect was subtracted from the observed effect. Goodness of the fit of the curves was determined by visual inspection, residual analysis and Akaike criteria.

**Preparation of metabolites.** Metabolites were obtained by rat liver microsomal incubations as described previously with minor modifications (Peyronneau et al., 1994). Male Sprague-Dawley rats were treated intraperitoneally with dexamethasone, a cytochrome P450 3A specific inducer. Rat liver microsomes were prepared as reported previously (Kremers et al., 1981) and stored at −80°C before use. BCT (10.5 mg in 1 ml of methanol) was incubated with rat liver microsomal suspension containing 200 nmol of cytochrome P450 and an NADPH-generating system (0.5 mM NADPH, 5 mM glucose 6-phosphate and 1 U/ml glucose-6-phosphate dehydrogenase) in 100 ml of a 0.1 M phosphate buffer, pH 7.4, for 30 min at 37°C. Incubation was stopped by addition of 150 ml dichloromethane, and stirred on ice for 10 min. The mixture was centrifuged and the organic phase was reduced by evaporation. Metabolites were purified by HPLC at room temperature on a C18 Ultrabase 5 μm column (250 × 7.5 mm; SFCC, Neuilly Plaisance, France). The mobile phase included 10% acetonitrile and 1 g/l ammonium carbonate in water (solvent A) and acetonitrile (solvent B). Elution was performed at a flow rate of 2 ml/min. A gradient of solvent B increased linearly from 0% to 100% in 45 min followed by 10 min of solvent A. BCT and metabolites were detected at 305 nm. HPLC/UV profiles were identical with those obtained previously (Peyronneau et al., 1994). Peak fractions corresponding to mono- and dihydroxylated metabolites (structures shown fig. 1) were collected and dried under vacuum. The quantity of metabolites was determined by UV spectrophotometry at 305 nm. Starting with an incubation of 10.5 mg of BCT, approximately 0.9 and 1.3 mg of mono- and dihydroxylated metabolites were recovered, respectively.

**Results**

To analyze the respective effects of BCT and its metabolites, we first chose to generate, through two different routes of administration, a pharmacokinetic situation for which the ratio of BCT metabolites/untransformed BCT was different and to observe the consequences on the pharmacological response. Because no metabolites of BCT were commercially available, such an approach was necessary before undertaking *in vitro* production of metabolites. Because of the 10% bioavailability of BCT (Maurer et al., 1982), we decided to administer BCT orally at a dose 10-fold greater than the dose used for i.v. administration.

The plasma concentration-time profiles shown in figure 2 indicate that the choice of these routes and doses allowed production of similar BCT concentrations after either oral or intravenous administration. In contrast, concentrations of BCT metabolites were much higher after oral administration because of the marked first-pass effect. Individual profiles were modeled according to a two-compartment model for metabolites profile after intravenous administration of BCT or a three-compartment model for other profiles. The pharmacokinetic parameters are given in table 1. The equations allowing the description of the mean drug profiles shown in figure 2 were: $C_p = 1.52e^{−0.056t} + 80.05e^{−0.65t} + 335e^{−2.94t}$ (BCT, i.v.), $C_p = 0.42e^{−0.016t} + 94.35e^{−0.2t} − 74.1e^{−0.4t}$ (BCT, p.o.), $C_p = 10.1e^{−0.022t} + 1190e^{−0.32t}$ (BCT metabolites, i.v.) and $C_p = 31.6e^{−0.01t} + 2976e^{−0.159t} − 2892e^{−1.21t}$ (BCT metabolites, p.o.). The areas under the curves for untransformed BCT after i.v. or oral administration were in the same range (299 vs. 329 ng/mlh), whereas the AUC for immunoreactive metabolites were approximately 5-fold greater (3,893 vs. 18,050 ng/mlh) after oral administration. The ratio of immunoreactive metabolites to untransformed BCT was 55 after oral administration.

Plasma prolactin profiles are depicted in figure 3. After administration by both routes, plasma prolactin levels decreased strikingly. However, the reduction was significantly longer for oral BCT. Although the BCT plasma concentrations at 24 h were the same after both routes of administration, prolactin had returned to the basal level after i.v. administration, and was still significantly reduced after oral administration. This observation led to the suggestion that the apparent change in prolactin inhibition after the oral dose, as compared with the intravenous dose, may be attributed to one or more immunoreactive BCT metabolites present at higher concentrations. To confirm this hypothesis, the relation between the drug concentration and the effect was evaluated by means of pharmacokinetic-pharmacodynamic models. With use of the effect-compartment model,
individual pharmacodynamic parameters for prolactin suppression were estimated from both unchanged BCT and BCT metabolites after administration by the two routes (table 1). An observed discrepancy between the mean apparent EC_{50} for BCT obtained after intravenous administration (3.68 nM) and oral administration (0.56 nM) suggested that, paradoxically, BCT was more active by the oral route than by the intravenous route. Metabolite data, however, revealed no statistical difference in EC_{50} for the two routes. These data were compared with those obtained with the indirect pharmacodynamic model proposed by Dayneka et al. (1993). Pharmacodynamic parameters were in the same range as those obtained with the effect compartment model. However, the indirect pharmacodynamic model was unable to detect the difference in EC_{50} values for BCT after intravenous or oral routes of administrations.

As described elsewhere (Valente et al., 1996), the enzyme immunoassay for metabolites is specific for a pool of metabolites sharing the bromolysergic structure of BCT rather than for a single compound. Therefore, to identify and quantify each of the immunoreactive metabolites, they were fractionated by HPLC and separately detected by enzyme immunoassay. Rat samples were taken 18 h after administration, a time at which BCT activity could be attributed to its metabolites, were pooled and chromatographed. The immunoreactive profile was compared with that obtained after chromatography of BCT metabolized by rat microsomes. As shown in figure 4, the immunoreactive peaks for the rat samples were representative of metabolites obtained after BCT incubation with rat microsomes. For the rat sample, untransformed BCT represented less than 5% of the total immunoreactivity. The identity of the metabolites has been confirmed by mass spectrometry (Peyronneau et al., 1994). The main immunoreactive (M1/M2) peak corresponded to a mixture of stereoisomers of 8'-hydroxybromocriptine. The two other peaks (M3 and M4) corresponded to stereoisomers of 8',9'-hydroxybromocriptine. It should be pointed out that M1/M2 metabolites were not been fully separated under the conditions used for chromatography, because each isomer undergoes partial transformation into the other isomer upon storage or during purification.

Metabolites were then produced from rat liver microsomes in sufficient quantity for in vitro and in vivo pharmacological studies. With membrane preparations of rat striatum, we showed that BCT and its metabolites were able to specifically displace the binding of [3H]YM-09151–2 with binding affinity constants in the same range, i.e., 70, 20, 13 and 21 nM for BCT, metabolites M1/M2, metabolite M3 and metabolite M4, respectively. In rat primary pituitary cultures, each metabolite was able to inhibit prolactin secretion with a potency similar to that of BCT or dopamine (fig. 5). They were then administered intravenously to rats at the dose of 100 μg/kg and their effects on prolactin secretion inhibition were compared with those of BCT or vehicle. As shown in figure 6, only the mixture of metabolites M1/M2 inhibited prolactin secretion. Compared with monohydroxylated, the absence of in vivo effect for metabolites M3 and M4 could be attributed to their faster total clearance as shown by their plasma kinetics after intravenous administration (fig. 7). The plasma profiles were described by first-order biexponential disposition with C_p = 2.09e^{-0.15t} + 57.8e^{-0.75t} (metabolites M1/M2), C_p = 0.46e^{-0.088t} + 7.59e^{-4.41t} (metabolites M3) and C_p = 0.74e^{-0.146t} + 31.50e^{-3.99t} (metabolites M4). The clearances were 0.37, 10.85 and 3.19 l/h/kg for metabolites M1/M2, M3 and M4, respectively.

**Discussion**

Several observations indicate that the effect of BCT on human prolactin secretion is not correlated with the concentration of parent drug. Indeed, there is evidence that prolactin inhibition persists when BCT is undetectable in the circulation (Thorner et al., 1980; Katz et al., 1991). This effect has been attributed to a prolonged action of the drug at the pituitary level rather than to a possible action of BCT metabolites. It has been demonstrated that in vitro, inhibition of prolactin release from isolated rat pituitary cells is maintained after withdrawal of BCT. This prolonged effect may be caused by a slow dissociation rate from the receptors or by continuous release of BCT from nonspecific sites such as membrane lipids (Wolf, 1981; Hanna and Shin, 1992).

To confirm or deny this hypothesis, we first proposed an integrated pharmacokinetic-pharmacodynamic model to determine the possible involvement of BCT metabolites in the time course of prolactin inhibition after i.v. or oral adminis-
The sustained inhibition of prolactin secretion observed for the oral route and the differences in BCT pharmacodynamic parameters between the two routes provided evidence for action of the metabolites at the pituitary level. We then demonstrated that hydroxylated metabolites bind to the dopamine D2 receptor and were able to lower in vitro prolactin excretion of primary pituitary cells to an extent similar to BCT. Finally, we have shown that monohydroxylated BCT metabolites have the same potency in vivo as BCT in lowering circulating prolactin levels. Under our experimental conditions, dihydroxylated metabolites were ineffective because their plasma concentrations were insufficient because of rapid clearance from the circulation. However, these metabolites are active in vitro and are observed at high concentrations after oral administration of BCT (fig. 4). They therefore should also contribute to the in vivo inhibition of prolactin secretion. Because the concentrations of metabolites are well above that of BCT after oral administration, it may be concluded that they contribute mainly to the hypoprolactinemic effect of BCT.

It remains to be determined whether the action of metabolites on the pituitary is also found in the central nervous system, in particular in the corpus striatum. Disagreement is apparent in published reports. By use of specific inhibitors of BCT hydroxylation, it has been demonstrated that some central nervous actions of BCT, such as hypothermia in rats or

<table>
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<th>Table 1</th>
<th>Pharmacokinetic and pharmacodynamic parameters of BCT and its metabolites after i.v. (1 mg/kg) or p.o. (10 mg/kg) dose of BCT</th>
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<td>Pharmacokinetic parameters</td>
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<td></td>
<td>Bromocriptine</td>
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<tr>
<td>AUC (ng/ml · hr)</td>
<td>299 ± 71</td>
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<td>Cmax (ng/ml)</td>
<td>403 ± 105</td>
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<td>Tmax (hr)</td>
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<td>Rate constants&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>0.85 ± 0.13</td>
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<td>0.08 ± 0.01</td>
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<td>Pharmacodynamic parameters</td>
<td>Effect-compartment model</td>
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<tr>
<td>CE&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>3.7 ± 1.0</td>
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<tr>
<td>K&lt;sub&gt;e0&lt;/sub&gt; (hr&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.17 ± 0.02</td>
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<tr>
<td>E&lt;sub&gt;max&lt;/sub&gt; (%)</td>
<td>90.1 ± 1.1</td>
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<tr>
<td>n (Hill)</td>
<td>1.94 ± 0.81</td>
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<td>Indirect pharmacodynamic model&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>CE&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
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<td>K&lt;sub&gt;out&lt;/sub&gt; (hr&lt;sup&gt;-1&lt;/sup&gt;)</td>
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<td>n (Hill)</td>
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<sup>a</sup> Mean ± S.E.M.<br>
<sup>b</sup> First sampling time.<br>
<sup>c</sup> Elimination rates except for values noted by<sup>d</sup>.<br>
<sup>d</sup> Absorption rate.<br>
<sup>e</sup> Based on mean profiles.
hallucinatory-like behavior in cats, are at least partly dependent on BCT metabolism (Silbergeld et al., 1977, Gonzalez-Lima et al., 1987). Contradictory reports, however, have shown that hypothermia and BCT-induced cerebral dopamine turnover were caused by BCT itself and did not require previous biotransformation into active metabolites (Keller and Da Prada, 1979; Schran et al., 1985). This points to the passage of BCT metabolites through the blood-brain barrier or to the metabolization of BCT by monooxygenases present in the brain. We recently used the microdialysis technique to show that the metabolites were undetectable in striatum after BCT administration to rats (Renouf-Granveau et al., in press, 1997). The metabolites should therefore not contribute significantly to the effect of BCT in the central nervous system.

The evidence that hydroxylated metabolites are active at the pituitary level in rats suggests that these metabolites may be active in humans. Studies on in vitro BCT hepatic biotransformations have shown that metabolite patterns are identical in rats and humans (Maurer et al., 1983; Peyronneau et al., 1994). So far, the respective concentrations of BCT metabolites in human plasma after clinical therapeutic doses have been only partially studied with carbon 14-labeled BCT (Schran et al., 1980). A very low BCT-to-metabolites ratio was observed. With the same immunoassays as presented here, we have shown in women given oral BCT that the ratio of immunoreactive metabolites to untransformed BCT is in the same range as that noted in our rat study (Valente, D., unpublished observation). Recently, the intravaginal route has been proposed as a substitute to avoid the
secondary effects of BCT noted with oral administration, such as nausea or vomiting (Ginsburg et al., 1992). Compared with the same oral dose, intravaginal administration results in higher BCT concentrations because of the absence of a first-pass hepatic effect. However, inhibition of prolactin secretion is much lower than that recorded after the same oral dose (Vermesh et al., 1988; Katz et al., 1991). These observations suggest that BCT metabolites contribute to the action of BCT at the pituitary level in humans.

In conclusion, previous work suggested that the duration and maintenance of the pharmacological effect of BCT at the pituitary level resulted mainly from slow dissociation from specific receptor sites and/or from continuous release from nonspecific binding sites. In contrast, the present results show that it is BCT metabolites that mainly contribute to the prolonged action of BCT in rats. Although confirmation in humans is required, this finding may have clinical implications because BCT has a large spectrum of established and potential therapeutic applications and is subject to continuous biopharmaceutical and pharmacological developments.

References


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