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TISSUE LEVELS AND SOME *IN VIVO* RESPONSES TO A MONOFLUORINATED ANALOGUE OF AMPHETAMINE IN THE MOUSE

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Abstract—The metabolism and some behavioral properties of each of the optical isomers of 2-amino-1-fluoro-3-phenylpropane hydrochloride (fluoroamphetamine, FAM) were examined and compared to those of the optical isomers of amphetamine (AM). Substitution of fluorine into the side-chain of AM increased the rate of elimination of drug from brain and modified the kinetics from a one- to a two-compartment model. Urinary excretion of unchanged *S*-(−)-FAM was reduced from that observed after *R*-(−)-AM, suggesting a more extensive metabolism. Fluorine substitution also modified the behavioral response to AM. Thus, each optical isomer of FAM produced paradoxical reductions in locomotor activity and body temperature.

Substitution of highly electronegative fluorine atoms into the aliphatic side-chain of amphetamine (AM) reduces basicity without appreciably increasing the steric bulk of the molecule. For these reasons, it has been suggested that such fluorinated amphetamines are appropriate to study the effects of changes in pK_a upon the metabolism or pharmacology of AM [1]. Thus, it has been reported [1–6] that substitution with fluorine reduces basicity and modifies the tissue distribution, metabolism and pharmacological properties of AM. Each of these studies was conducted with racemic mixtures and the only analogues for which pharmacological data was reported had pK_a values at or below 7. The effects of lesser changes in pK_a upon the tissue distribution and pharmacology of the individual optical isomers of AM, therefore, have not been studied extensively.

In this respect, we describe the tissue distribution and some of the more striking pharmacological responses observed after administration of each of the optical isomers of 2-amino-1-fluoro-3-phenylpropane hydrochloride (fluoroamphetamine, FAM) [7]. This simple monofluorinated derivative has several characteristics which make it ideal to study the effects of small changes in basicity upon the properties of AM. First, a fluorine atom does not have an appreciably larger atomic volume than does hydrogen and would not be expected to exert any profoundly different steric effect. Second, a single highly electronegative fluorine atom lowers the pK_a of these derivatives only to 7.9 [7]. Third, placement of the fluorine on the carbon atom most remote from the aromatic ring would not be expected to have significant effects upon the electronic character of the aromatic ring, and its introduction does not generate a second chiral centre.

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MATERIALS AND METHODS

S-(−)- and *R*-(+)-FAM were synthesized from the corresponding optical isomers of phenylalanine [7]. *S*-(+)- and *R*-(−)-AM were obtained as the sulfate salts from Health and Welfare, Canada. Gas chromatographic analysis after derivatization with *S*-(−)-*N*-trifluoroacetylprolyl chloride indicated optical purities in excess of 95% (Singh, Coutts and Pasutto, unpublished).

All experiments were conducted in male or female mice of the Balb-cCr strain (body weights 18–25 g). Drugs were administered by intraperitoneal injection dissolved in saline. Dose volume was 10 ml/kg. Doses were selected to provide the highest dose of 10 mg/kg of FAM free base.

Open field activity was monitored in a square field (60 × 60 cm) divided into a grid (15 × 15 cm). Activity scores were measured as the number of grid lines crossed by all 4 feet during a 3-min period. Rectal temperatures were read 30 sec after insertion of a small animal probe to a depth of 2 cm. Room temperature was maintained between 22 and 25° during all experiments.

Effects of R-(+)- *or* S-(−)-*FAM*. Male mice were divided among five groups (eight/group). Individual animals were placed into the open field apparatus and, after 1 hr, were injected with saline, *R*-(+)- or *S*-(−)-FAM (6.4, 16, 32 or 64 μmoles/kg). Activity was scored during 3-min periods immediately prior to any treatment and again after 30, 60, 90, 120, 180, 240 and 480 min.

Effects on rectal temperature were determined in male mice at a room temperature of 22–25°. Animals were divided into groups (five/group) and were injected with either *R*-(+)-FAM, *S*-(−)-FAM (6.4, 16, 32, 64 μmoles/kg) or saline. Rectal temperatures were determined 180 min after injection. To determine the duration of the thermic response to the

enantiomers of FAM, mice were injected with either saline or an enantiomer of FAM (16 μmoles/kg). Rectal temperatures were monitored prior to injection and again 30, 60, 90, 120, 180, 240 and 480 min after injection.

Brain levels of FAM and AM. Male or female mice (four per group) were injected with either of the optical isomers of FAM (64 μmoles/kg) and were killed after 30, 45, 60, 90, 120, 150 or 180 min. Brains were rapidly removed, blotted dry, weighed and homogenized in cold perchloric acid (0.4 N, 5 ml) and were immediately assayed as described below. Other male mice (four/group) were injected with either of the optical isomers of AM (64 μmoles/kg) and were processed in an identical manner.

Distribution of S-(−)-*FAM.* Male mice (three to four/group) were injected with *S*-(−)-FAM (64 μmoles/kg) and were decapitated after 15, 30, 60 or 90 min. Trunk blood was collected onto sodium citrate (10–20 mg) and was immediately centrifuged to provide measured volumes of plasma. Brains and intraperitoneal fat were collected, blotted dry, weighed and homogenized in cold perchloric acid (0.4 N, 5 ml).

Analysis of FAM or AM in brain, plasma or fat. Tissue levels of FAM or AM were assessed according to a method based upon that of Cristofoli *et al.* [8]. Each tissue was processed identically except for plasma which was spiked with internal standard (300 ng) prior to addition of perchloric acid. Internal standard (*p*-chloroamphetamine) was added (300 ng for FAM, 2000 ng for AM) to plasma or to the perchloric acid homogenates of brain or fat. Plasma was then diluted with an equal volume of perchloric acid. Tissue homogenates or diluted plasma were centrifuged (12,000 *g*, 10 min, 4°) and supernatant fractions were decanted, basified by addition of solid sodium carbonate, and extracted with chloroform (2 × 5 ml). Combined chloroform layers were back-extracted with aqueous hydrochloric acid (1.2 N, 2 ml). Acid layers were basified with solid sodium carbonate, and pentafluorobenzoyl chloride (0.005 ml) was added. Reaction mixtures were shaken at room temperature for 20 min and were then extracted with ethyl acetate (3 ml). Ethyl acetate layers were decanted and evaporated to dryness under a gentle stream of nitrogen (38°). Residues were dissolved in toluene (0.1 ml) and were washed with ammonium hydroxide (5%, 0.2 ml). One microlitre portions of the washed toluene layers were injected onto a gas chromatograph (Perkin Elmer, model Sigma 3) equipped with a fused silica capillary column (Se-54, 8M). Helium carrier gas was delivered at a head pressure of 75 kilopascals. An initial oven temperature of 100° was held for 1 min and then increased by 6°/min to 250°. Compounds were quantified by comparison of peak height ratios (test substance/internal standard) to standard curves constructed by plotting peak height ratios, obtained by analysis of homogenates spiked to contain known amounts of drug and internal standard.

Urinary excretion of R-(−)-*AM and* S-(−)-*FAM.* Male mice were divided between two groups. Five mice received *R*-(−)-AM (64 μmoles/kg) and four *S*-(−)-FAM (64 μmoles/kg) by intraperitoneal injection. Mice were then placed individually into a glass beaker equipped with a wire mesh flooring. Water was freely available. After 24 hr, mice were removed and beakers were washed with distilled water (10 ml). Parent drug in these diluted urine samples was determined according to the assay procedure described for FAM in tissues.

Statistical analysis. Data are presented as means ± SEM. Differences from control were determined by a two-tailed Student's *t*-test. Half-lives of FAM or AM were determined by linear regression after appropriate application of curve shaving techniques [9].

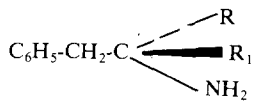
RESULTS

Structures of AM and its monofluorinated derivatives employed in this study are provided in Fig. 1. Structures of the mono- and difluorinated derivatives employed by Fuller *et al.* [1, 4–6] are included for comparative purposes.

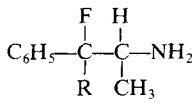
Prior treatment of mice with *R*-(+)-FAM resulted in a dose-dependent biphasic effect upon mouse locomotor activity (Fig. 2). At a low dose (16 μmoles/kg), locomotor activity was significantly ($P < 0.05$) reduced from that of saline-treated animals during the period from 90 to 240 min after injection. As the dose of *R*-(+)-FAM was increased to 32 or 64 μmoles/kg, a trend appeared by which locomotor suppression was preceded by a brief period of increased activity. This initial stimulant effect became statistically significant ($P < 0.05$) at the 64 μmoles/kg dose level. Stereotypes were not observed after treatments with these doses of *R*-(+)-FAM. Treatments with *S*-(−)-FAM also lowered mouse locomotor activity in a dose-dependent, delayed manner. No obvious differences were observed between the abilities of each of the FAM enantiomers to produce this effect. However, the brief period of locomotor activation observed after treatment with the highest dose of *R*-(+)-FAM was not observed after treatment with an equimolar dose of *S*-(−)-FAM. The optical isomers of AM, tested under similar conditions and at equimolar doses, either failed to modify locomotor activity (*R*-(−)-AM) or produced only increased locomotor activity and stereotypes (*S*-(+)-AM) (data not shown). At times corresponding to decreased locomotion, mice appeared to be mildly sedated but were easily aroused by a light touch or hand-clap. Twenty-four hours after treatment, mice appeared normal and were indistinguishable from saline-treated mice. No mice succumbed during the 24 hr following injection with either of the FAM enantiomers.

Rectal temperatures decreased after administration of either optical isomer of FAM in similar delayed, dose-dependent fashions (Fig. 3). Time–courses of effects upon rectal temperature (Fig. 4) were similar to those of decreased locomotor activity (Fig. 2) and again did not differ significantly between enantiomers. The enantiomers of AM tested in parallel either failed to modify (*R*-(−)-AM) or increased (*S*-(+)-AM) rectal temperature (data not shown).

Levels of parent drug present in brain tissue of male mice treated with equimolar doses (64 μmoles/kg) of each optical isomer of AM or FAM are represented in Fig. 5. These data indicate that brain



	R	R′	pK_a	% Protonated at pH 7.4	Ref.
R-(−)-AM	H	CH_3	9.5	99	1
S-(+)-AM	CH_3	H	9.5	99	1
R-(+)-FAM	CH_2F	H	7.9	76	7
S-(−)-FAM	H	CH_2F	7.9	76	7



	R	pK_a	% Protonated at pH 7.4	Ref.
β-Monofluoroamphetamine	H	8.4	90	1
β,β-Difluoroamphetamine	F	7.0	27	1

Fig. 1. Structures of amphetamines.

levels and elimination kinetics of the isomers of FAM differ from those of AM. Thus, with AM, brain levels achieved after administration of each of the optical isomers were similar, and elimination followed simple first-order kinetics. Elimination half-lives were 42 and 47 min for *S*-(+)- and *R*-(−)-AM respectively. In contrast, brain levels of FAM were always lower ($P < 0.05$) than those of the corresponding isomers of AM, and brain levels of *S*-(−)-FAM, measured 30 and 45 min after injection (3806 ± 602 and 1530 ± 231 ng/g respectively; N = 4) were lower ($P < 0.05$) than those produced by injection with *R*-(+)-FAM (7615 ± 218 and 3437 ± 489 ng/g respectively; N = 4). At times later than 45 min brain levels of each of the optical isomers of FAM did not differ ($P > 0.05$) from each other. Also, and in contrast with the monoexponential disappearance of AM from brain tissue, the disappearance of each isomer of FAM from brain could be resolved into two major components, the initial phase between 30 and 90 min being more rapid. Application of the method of residuals [9] indicated that, during this initial phase, elimination half-lives of each isomer of FAM were approximately 10 min. At times later than 90 min, elimination half-lives were calculated to be 52 and 65 min for *R*-(+)- and *S*-(−)-FAM respectively.

In female mice (Fig. 6), elimination of each isomer of FAM from brain tissue was again multiphasic, and levels of *S*-(−)-FAM (1397 ± 148 ng/g, N = 8) measured 45 min after injection were lower ($P < 0.05$) than those produced by injection of the *R*-(+)-isomer (2724 ± 332 ng/g, N = 10). Elimination of *S*-(−)-FAM from brain tissue of female mice

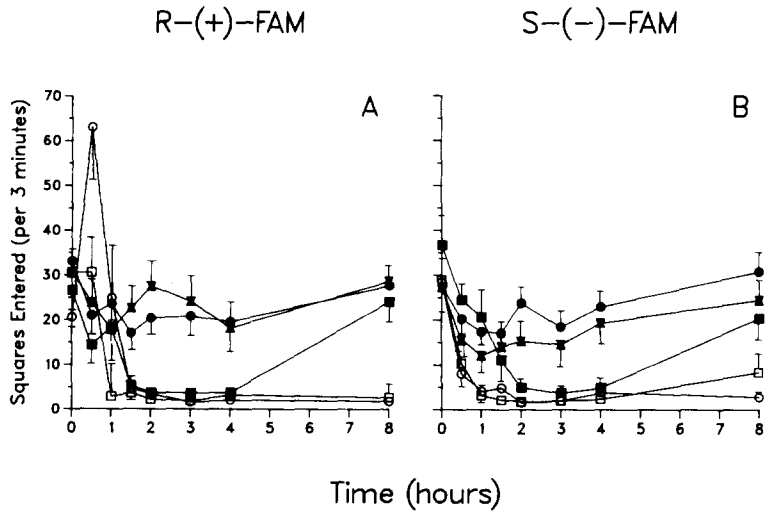


Fig. 2. Effects of *R*-(+)-AM (panel A) and *S*-(−)-FAM (panel B) upon locomotor activity (eight animals per group, mean quadrants entered ± SEM, except where SEM < symbol; (●) saline; ▮ 6.4 μmoles/kg; (■) 16 μmoles/kg; (□) 32 μmoles/kg; and (○) 64 μmoles/kg).

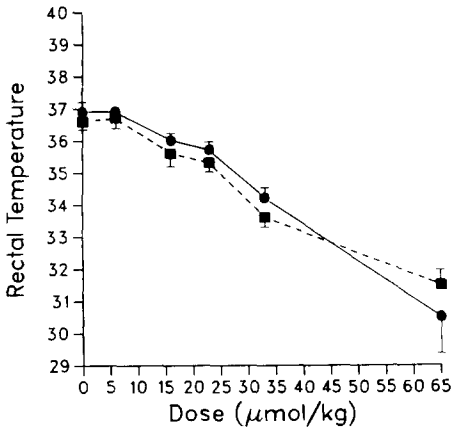


Fig. 3. Dose-dependent reduction in rectal temperature after *R*-(+)-FAM (●) or *S*-(−)-FAM (■) (five animals per group, mean rectal temperature ± SEM; temperatures measured 180 min after dosing).

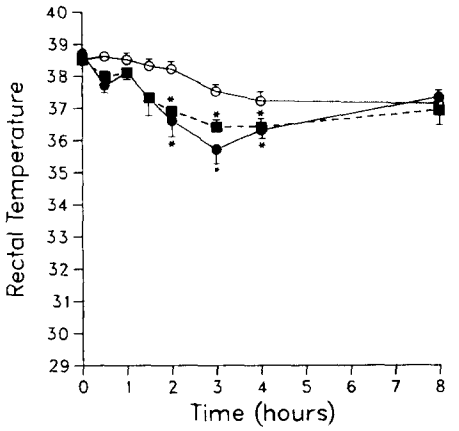


Fig. 4. Time–course of effect after enantiomers of FAM (16 μmoles/kg) on rectal temperature (mean temperatures ± SEM, six animals/group; (○) saline; (●) *R*-(+)-FAM; and (■), *S*-(−)-FAM). An asterisk indicates reduction ($P < 0.05$) from saline.

was similar to that previously observed in males and calculated half-lives were 11 and 43 min for the rapid and slower elimination phases respectively. Elimination of *R*-(+)-FAM from brain tissue of female mice was more rapid than that of the *S*-(−)-isomer in that sex or of either isomer in males. Half-lives of *R*-(+)-FAM disappearance from brain tissue of female mice were calculated to be 7 and 24 min for the rapid and slower elmination phases respectively.

Data describing levels of *S*-(−)-FAM in brain, plasma and fat of male mice are presented in Table 1. These data indicate that levels of *S*-(−)-FAM in

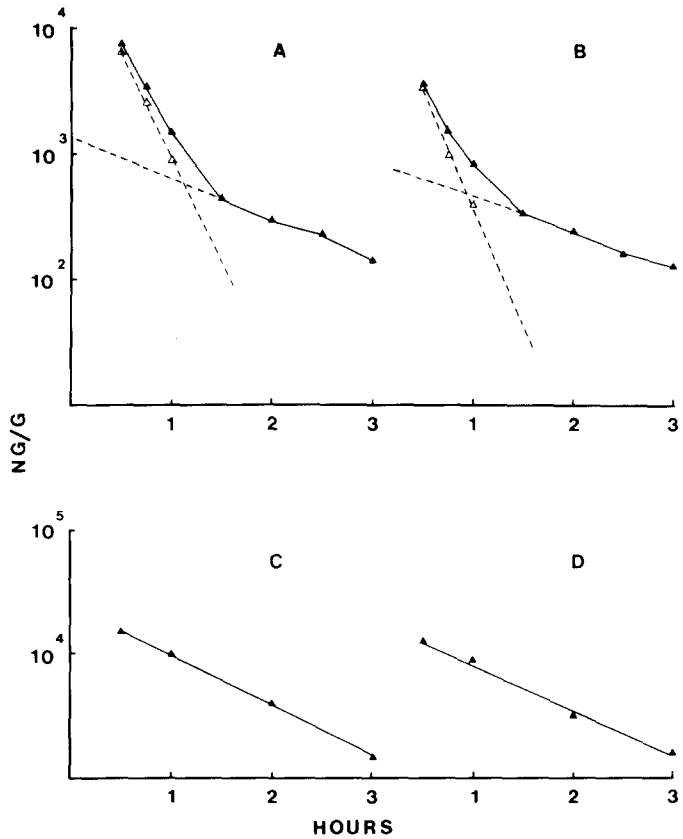


Fig. 5. Concentrations of *R*-(+)-FAM (panel A), *S*-(−)-FAM (panel B), *S*-(+)-AM (panel C), and *R*-(−)-AM (panel D) (ng/g ± SEM, N = 4) in brain tissue of male mice after intraperitoneal injection of each drug (64 μmoles/kg) (residual values denoted by open triangles and broken lines).

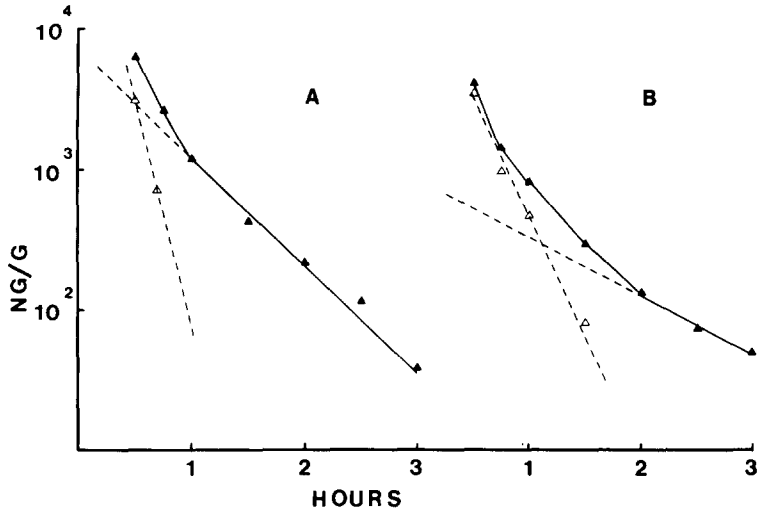


Fig. 6. Concentrations of *R*-(+)-FAM (panel A) and *S*-(−)-FAM (panel B) (ng/g ± SEM, N = 4–10) in brain tissue of female mice after intraperitoneal injection of each drug (64 μmoles/kg) (residual values denoted by open triangles and broken lines).

Table 1. Levels of *S*-(−)-FAM in various tissues of male mice after treatment with *S*-(−)-FAM (64 μmoles/kg)

	Levels (ng/g*) of *S*-(−)-FAM at indicated times (min)			
	15	30	60	90
Brain	1505 ± 90	3963 ± 636	688 ± 62	329 + 73
Plasma	612 ± 65	1127 ± 102	271 ± 65	90 ± 18
Fat	331 ± 30	1614 ± 239	384 ± 34	271 ± 76

Values are means ± SEM, N = 4.
* Expressed in ng/ml for plasma.

each tissue were greatest approximately 30 min after dosing and declined thereafter from each tissue in parallel fashions.

Urinary excretion of unmetabolized *S*-(−)-FAM and *R*-(−)-AM were monitored in male mice*. These experiments showed that only 2.7 ± 0.3% (N = 4) of the *S*-(−)-FAM dose was recovered in urine during the 24 hr following injection. Recovery of *R*-(−)-AM under similar conditions was 20.3 ± 3.8% (N = 5) of dose.

DISCUSSION

Our data, in general, support previous observations on other fluorinated amphetamines [4–6] that reductions in pK_a modify the accumulation and/or elimination of AM by brain tissue. Comparison of our data with previous reports suggests, however, that this effect may occur after lesser changes in basicity in the mouse than in the rat. Thus, for example, Fuller *et al.* [1] reported that rat brain levels of parent drug measured 1 hr after treatment with equimolar doses of β-monofluoroamphetamine (pK_a 8.35; Fig. 1) or of AM (pK_a 9.45) are not different. However, brain levels of β,β-difluoroamphetamine (pK_a, 6.97; Fig. 1) measured under similar conditions have been shown to be markedly lower than those of AM [1]. Similarly, Cristofoli *et al.* [8] demonstrated that, in the rat, a dose of *R*-(+)-FAM (pK_a 7.9, Fig. 1) similar to that employed in the present study yields brain levels that are both higher and more persistent than those now reported in the mouse. This difference has been confirmed independently in our laboratory. These comparisons suggest that, in the rat, substrate basicity must be reduced in excess of 1.4 pK_a units to significantly modify the accumulation and/or elimination of AM-like compounds by brain. Our data suggest that similar changes occur in the mouse when basicity is decreased by less than 1.4 pK_a units.

As noted above, a primary result of fluorine substitution into the side chain of AM would be to decrease basicity and, as a result, increase the amount of drug existing in a non-protonated form at physiological pH (Fig. 1). This decreased degree of protonation might be expected to alter metabolism via pathways involving the basic nitrogen of AM. In this respect, Fuller *et al.* [6] have demonstrated that β,β-difluoro-substitution in AM does increase deamination by rat liver microsomes, *in vitro*. A similar promoting effect in our experiments may explain the more rapid clearance of FAM, relative to AM, from the brain of the mouse, a species known to metabolize AM principally by deamination [10]. This possibility is supported by our observation that virtually no unmetabolized *S*-(−)-FAM could be recovered in the urine of injected mice, whereas 20.3 ± 0.8% of an *R*-(−)-AM dose was recovered in urine.

Our data also suggest other differences between the kinetics of AM and FAM in mouse brain. Most significantly, elimination of FAM occurred in a

* *S*-(−)-FAM and *R*-(−)-AM were chosen for comparison since the absolute stereochemistry of these compounds is identical. Different *R*- or *S*-designations reflect only the change in substituent priority which results from replacement of CH_3 with CH_2F.

biphasic manner, whereas elimination of AM was readily described by a monoexponential equation. This suggests that FAM, but not AM, might be distributed *in vivo* into two distinct pharmacokinetic compartments. On first principles, this biphasic loss of FAM from brain might be interpreted to indicate that, as a consequence of a reduced degree of protonation at physiological pH, penetration of FAM into fat, or some other depot tissue, might be increased and that the initial rapid loss of FAM from brain may represent a redistribution phenomenon. However, since levels of *S*-(−)-FAM in fat closely paralleled those in brain or plasma, it is clear that we have not been able to identify fat as a depot site. This observation agrees closely with the conclusions of Fuller and Molloy [4] who demonstrated that fat also does not act as a depot tissue for β-monofluoroamphetamine in the rat. In view of the fact that only very little *S*-(−)-FAM was recovered in mouse urine, rapid metabolism cannot be excluded as the mechanism by which FAM is cleared from mouse brain.

In addition to this biphasic quality, the metabolism of FAM may also be isomer- and sex-related. These dependencies were most obvious with regard to two points. First, brain levels of *R*-(+)-FAM measured 30 or 60 min after injection were higher than those of *S*-(−)-FAM in both sexes. Second, in females, both phases of *R*-(+)-FAM elimination were more rapid than those of either *R*-(+)-FAM in males or *S*-(−)-FAM in females.

S-(+)-AM, but not *R*-(−)-AM, typically produced responses characterized by elevated rectal temperature and behavioral stimulation. These responses are consistent with literature reports [11]. In comparison, both enantiomers of FAM produced long-term reductions in rectal temperature and locomotor activity. *R*-(+)-FAM differed only slightly from *S*-(−)-FAM in that the initial portion of the response to *R*-(+)-FAM had some characteristics of *S*-(+)-AM and increased locomotion was observed 30 min after *R*-(+)-FAM administration at the highest dose level. This initial effect of *R*-(+)-FAM may relate to the demonstrated ability of this enantiomer to promote dopamine release *in vitro* [12].

Several explanations for the surprisingly weak stimulant properties of *R*-(+)-FAM in the mouse are possible. In an examination of the stimulant properties of β,β-difluoroamphetamine [5], Fuller *et al.* noted that the dose–response curve was shifted to the right from that of AM but that maximum achievable stimulation was not reduced. They therefore suggested that the reduced potency of β,β-difluoroamphetamine as a locomotor stimulant was most probably due to a more rapid clearance of the drug from brain relative to AM. A similar effect may account for the low stimulant potency of *R*-(+)-FAM in mice. This conclusion is consistent with previous observations that, in the rat [8], brain levels of *R*-(+)-FAM persist longer than presently observed in the mouse, and the response to *R*-(+)-FAM in the rat is characterized mainly by elevated temperatures and stereotypes [13].

Drug metabolism may also play an important role in development of the hypothermia and reduced locomotion observed in the mouse after treatments with the enantiomers of FAM. Thus, the very long duration of hypomotility and hypothermia seen after FAM is inconsistent with the very short half-life of this substance in mouse brain. This may suggest that either a lasting effect has been produced or a long-lived metabolite(s) may account for the observed effects. The latter explanation may be more tenable since FAM effects had disappeared completely by 24 hr after dosing, and, as pointed out above, hyperthermia and behavioral stimulation predominate in the rat [13], consistent with the more persistent brain levels of parent drug in that species [8].

Other reports [14, 15] have demonstrated that *meta*-substitution of AM, by bulky groups as in fenfluramine, reduce affinity for the neuronal uptake system and, as a consequence, lead to decreased potency as stimulants of locomotor activity. By analogy it is possible that substitution by fluorine may also reduce transport of FAM to the intraneuronal site affected by AM, leading to decreased stimulant potency. This explanation is not, however, compatible with either the demonstrated ability of *R*-(+)-FAM to release dopamine from rat striatum, *in vitro*, or the production of hyperthermia and stereotypes in the rat [13]. Finally, the relatively slight effect of substitution with a single fluorine atom upon steric bulk also does not support an analogy between FAM and fenfluramine.

Although it is clear that the ability to reduce locomotion and rectal temperature was not restricted to one or the other enantiomer of FAM, it is not presently possible to assess the exact degree of isomer specificity. This difficulty derives from the suggestion that these effects may be due to a metabolite(s) derived possibly to different degrees from each enantiomer of FAM. To clarify this question the metabolism of FAM is presently being studied.

In conclusion, our data demonstrate that side-chain subsitution by fluorine into AM resulted in a compound (FAM) which produced *in vivo* effects atypical of AM. Thus, FAM enantiomers produced lower absolute brain levels, were cleared from brain more rapidly, and produced behavioral/pharmacological responses apparently opposite to those observed after treatments with AM enantiomers.

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