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Effects of Isradipine, a Dihydropyridine-Class Calcium Channel Antagonist, on D-Methamphetamine-Induced Cognitive and Physiological Changes in Humans

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D-methamphetamine is abused for its euphoric effects and stimulatory action on cognitive function. Its abuse can, however, be associated with massive hypertension resulting in strokes, ruptured aneurysms, or myocardial infarction. We examined the utility of isradipine, a dihydropyridine-class calcium channel antagonist, in treating d-methamphetamine induced hypertension and evaluated its effects on cognitive function, both of which are mediated by dopaminergic mechanisms. D-methamphetamine dose-dependently increased all vital signs (systolic, diastolic, and mean arterial pressure, and pulse rate) parameters. Isradipine significantly reduced d-methamphetamine-induced increases in diastolic and mean arterial pressure; however, this potentially beneficial therapeutic effect was offset by a significant reflex rise in pulse rate. D-methamphetamine also improved attention, accuracy of reasoning ability, and performance on computerized cognitive function tasks. D-methamphetamine's cognitive improving effects were not altered significantly by isradipine. Isradipine increased the false responding rate but was without significant effect on any other attentional task, or on reasoning ability, or performance. Isradipine does not appear to enhance cognitive function in healthy humans.

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KEY WORDS: *Methamphetamine; Isradipine; Hypertension; Calcium channel blockers; Attention; Cognition; Humans*

Massive hypertension, often resulting in cerebrovascular accidents, is a major cause of morbidity and mortality among d-methamphetamine addicts (Beebe and Walley 1995; Derlet and Horowitz 1995; U.S. Department of Health and Human Services 1998). Specifically, d-methamphetamine-induced hypertension and tachycardia have been associated with deaths or debilitating injury from ruptured berry aneurysms (Davis and Swalwell 1996), intracerebral hemorrhage (Selmi et al. 1995; Shibata et al. 1988; Yen et al. 1994), and aortic dissection (Davis and Swalwell 1994). Indeed, d-methamphetamine's hypertensive effects, and the associated complications, may render it more toxic than cocaine because of its longer half-life (Davis and Swalwell 1996). The hypertensive and tachycardic effects of d-methamphetamine (Mendelson et al. 1995) have been attributed to its ability to increase dopamine (DA) (Bennett et al. 1998; Fleckenstein et al. 1997; Hanson et al. 1998) and norepinephrine (NE) turnover (Fischman 1987).

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D-methamphetamine's vascular complications in addicts have been illustrated by emergency room reports and series of case studies (Substance Abuse and Mental Health Services Administration 1997). However, much less is known about d-methamphetamine's effects in healthy individuals participating in human laboratory studies. Few doses of d-methamphetamine have been studied in the human laboratory, and the use of a multiple-dosing strategy has been the exception (Martin et al. 1971; Mayfield 1973). The dose-related effects of d-methamphetamine in the laboratory are, therefore, not well characterized. This information is essential for the systematic development of putative therapeutic medications for treating d-methamphetamine's vascular complications.

Isradipine, a dihydropyridine-class calcium channel antagonist, has demonstrated utility in the treatment of both hypertension and intracerebral hemorrhage (Mosby 1997). Isradipine's anti-hypertensive (Brogden and Sorkin 1995) and negative inotropic (Leslie 1993) effects are due to a combination of calcium influx inhibition into arteriolar and myocardial smooth muscle (Apostolakos and Varon 1996) and a reduction of DA release. Indeed, DA infusions have been used successfully to treat the peripheral vasodilatation and hypotension associated with overdose or toxicity to calcium channel antagonists (Pearigen and Benowitz 1991; Ramoska et al. 1993). While these data suggest that isradipine may be a useful therapeutic agent for the treatment of d-methamphetamine-induced hypertension, our literature search revealed no existing electronically-indexed studies in animals or humans directly testing this interaction. Thus this study is timely in its exploration of isradipine as a potential treatment for d-methamphetamine-induced hypertension.

D-methamphetamine increases achievement on computerized tasks of performance and attention (Harvey 1987; Spiegel 1979) by enhancing catecholamine (Cole and Robbins 1987, 1992) (especially DA) release (Drachman 1977). Dihydropyridine-class calcium channel antagonists (DCCCA) may improve learning and performance in animals (Quevedo et al. 1998). In addition, there is clinical evidence that DCCCA may improve age-associated and Alzheimer-related memory impairment in humans (Heidrich et al. 1997; Yamada et al. 1996). Nimodipine, another DCCCA, may also improve learning and memory in schizophrenic patients (Schwartz et al. 1997). In sum, these studies support a cognitive enhancing role for DCCCA (Jerzy et al. 1997) in some psychiatric conditions. Importantly, however, the effects of DCCCA on cognitive function have not been established in cognitively unimpaired humans. It is also plausible that d-methamphetamine-induced increase in cognitive function could be reversed by isradipine, presumably via its anti-DA effects (Ginsberg et al. 1991; DeVries and Beart 1984).

In the present study, we tested two hypotheses. The first hypothesis was that d-methamphetamine administration to healthy male and female volunteers in the human laboratory would produce dose-dependent increases in blood pressure, and that this would be antagonized by isradipine pre-treatment. The second hypothesis was that d-methamphetamine's cognitive-enhancing effects would be diminished by isradipine pre-treatment.

MATERIALS AND METHODS

Subjects

We studied 18 healthy male and female volunteers (females = 7) between the ages of 19 years and 48 years (mean age = 31.1 years) recruited by advertisement from a local newspaper. Subjects had no history of pre-existing physical (including cardiovascular) disease, mental illness, substance abuse or dependence. Subjects were not studied if they had any prior use of opiates, cocaine or psychostimulants including methamphetamine, and this was confirmed by a urine drug screen on the morning of each test day. All subjects provided written informed consent approving their participation in the study.

Laboratory Conditions

We conducted this study in a testing room about 12 ft x 13 ft in size. Subjects sat upright in a comfortable chair and were attached via leads to an Escort 300 Patient Monitor (E300 PM; Medical Data Electronics™).

Functional parameters for vital signs (blood pressure and heart rate) were as follows: (a) blood pressure (range: 40 mm Hg to 300 mm Hg; accuracy: ±1% or 1 mm Hg; sensitivity: 5uV/V/mm Hg); and (b) pulse (accuracy ±2% or ±2 beats/min). Recordings were conducted as scheduled over the preceding minute. Closed circuit TV was used for subject monitoring. Subjects were informed that that they were being observed by the camera as a safety precaution. The computerized cognitive function tasks were completed on an IBM-compatible workstation fitted internally with a timer card, and connected to a printer.

Experimental Measures of Performance, Attention, and Reasoning

Rapid Visual Information Processing Task. The Rapid Visual Information Processing Task (RVIPT) (see Johnson et al. 1996) is a test of attention. In the RVIPT, subjects monitored digits which were presented sequentially on a computer screen at a rate of 100/min for 7.5 min Subjects were instructed to detect and respond to targets of three consecutive odd or even digits as quickly as possible. Independent measures were made

of both the speed and accuracy of decision making. These measures were recorded for each 250 trial block: hits = correct responses within 600 ms; delayed hits = responses which occurred between 600 ms and 1200 ms after the target; false alarms = incorrect responses; and reaction time for both hits and delayed responses.

Logical Reasoning Task. The Logical Reasoning Task (LRT) (Baddeley 1968), is a test of conceptual ability. The subject was shown a series of sequences of the letters "A" and "B" one at a time. Each sequence was followed by a question asking if the correct order (i.e., "T" for true or "F" for false) of the sequence was: "A follows B," "B follows A," "A precedes B," " B precedes A," "A is preceded by B," "B is preceded by A," "A is followed by B," and finally "B is followed by A." In all, 32 questions were asked in random order. Mean response time (seconds), percent correct, and percent correct/time were calculated.

Finger Tapping Task. The Finger Tapping Task (FTT) (see Riedel et al. 1995) is a manual test of motor speed. Subjects were required to finger-tap a response button as quickly as possible during a short period of time (60 s). The number of taps per second was used as a measure of psychomotor speed. The test was conducted using the preferred hand.

Treatments and Medication Preparation

Subjects received each of the following six treatments in a double-blind, double-dummy, placebo-controlled crossover design: (a) placebo + placebo; (b) low-dose d-methamphetamine (0.21 mg/kg) + placebo; (c) high-dose dmethamphetamine (0.42 mg/kg) + placebo; (d) isradipine (0.21 mg/kg) + placebo; (e) low-dose d-methamphetamine + isradipine; and (f) high-dose d-methamphetamine + isradipine. The sequence of the six treatments was determined by a diagram-balanced Latin Square controlling for both sequence and order effects. There was a 2–7 day interval between treatments.

Isradipine or d-methamphetamine tablets, obtained from Sandoz Corporation and Abbott Desoxyn respectively, were crushed to provide the mg/kg dosing and mixed with cornstarch to completely fill a royal blue size 0 capsule (Shinogi Qualicaps, Whitsett, NC). Placebo capsules were identical in both color and size, and contained only cornstarch.

Experimental Sessions

Prior to testing, subjects were familiarized with the experimental room and conditions. Subjects were trained in the use of psychological rating scales, and practiced to reach criterion (i.e., less than 10% test-retest variability) on the computerized performance and attention tasks.

On test days, subjects arrived at 07:00 h having fasted from 22:00 h the previous night. Subjects were only allowed to proceed with testing if no measurable amount of alcohol was recorded on breath testing, and his/her urine tested negative for the presence of drugs. At 07:15 h, leads from the vital signs monitoring device were attached. Subjects were allowed 15 min to relax. Vital signs recordings commenced at 07:30 h, and these were followed by the computerized tasks of cognitive function. Isradipine (0.21 mg/kg) or its matching pla-

Table 1. Analysis of Covariance Results for the Change in Vital Signs in 18 Male and Female Healthy Volunteers Who Received D-methamphetamine (0.21 mg/kg or 0.42 mg/kg, orally) with or without Isradipine (0.21 mg/kg, Orally)

	Main Effects and Interactions						
Cognitive Function Tests	**IS (F: *p*)**	**METH (F; *p*)**	**T (F; *p*)**	**IS x METH (F; *p*)**	**IS x T (F; *p*)**	**METH x T (F; *p*)**	**IS x METH x T (F; *p*)**
RVIPT							
Mean total hits	0.66; NS	7.34; **	15.63; NS	1.20; NS	0.31; NS	13.64; ***	0.19; NS
Mean false hits	0.67; NS	0.8; NS	0.19; NS	0.04; NS	5.73; *	3.15; *	0.78; NS
Mean delayed hits	0.95; NS	0.19; NS	6.62; *	0.72; NS	1.09; NS	2.62; NS	0.20; NS
Mean reaction time	1.07; NS	2.76; NS	10.90; **	0.34; NS	0.61; NS	9.69; **	0.20; NS
LRT							
Percent correct	0.27; NS	0.43; NS	0.05; NS	0.32; NS	1.00; NS	0.49; NS	1.97; NS
Percent correct/time	3.41; NS	0.12; NS	1.79; NS	1.02; NS	0.74; NS	4.38; *	0.92; NS
Time	5.53; *	0.25; NS	2.06; NS	0.67; NS	1.00; NS	1.81; NS	1.69; NS
FTT							
Total hits	0.28; NS	1.10; NS	14.59; **	0.71; NS	0.9; NS	4.37; *	0.22; NS

IS = isradipine; METH = d-methamphetamine; T = time.
NS = $p > .05$; *$p < .05$; **$p < .01$; ***$p < .0001$.
For table, df = 1, 15 (IS); 2, 30 (METH), 2, 30 (IS X METH X T). Two subjects with incomplete data were excluded from the ANCOVA.
RVIPT = Rapid Visual Information Processing Task, a measure of attention.
LRT = Logical reasoning Task, an evaluation of reasoning ability.
FTT = Finger Tapping Task, an index of performance.

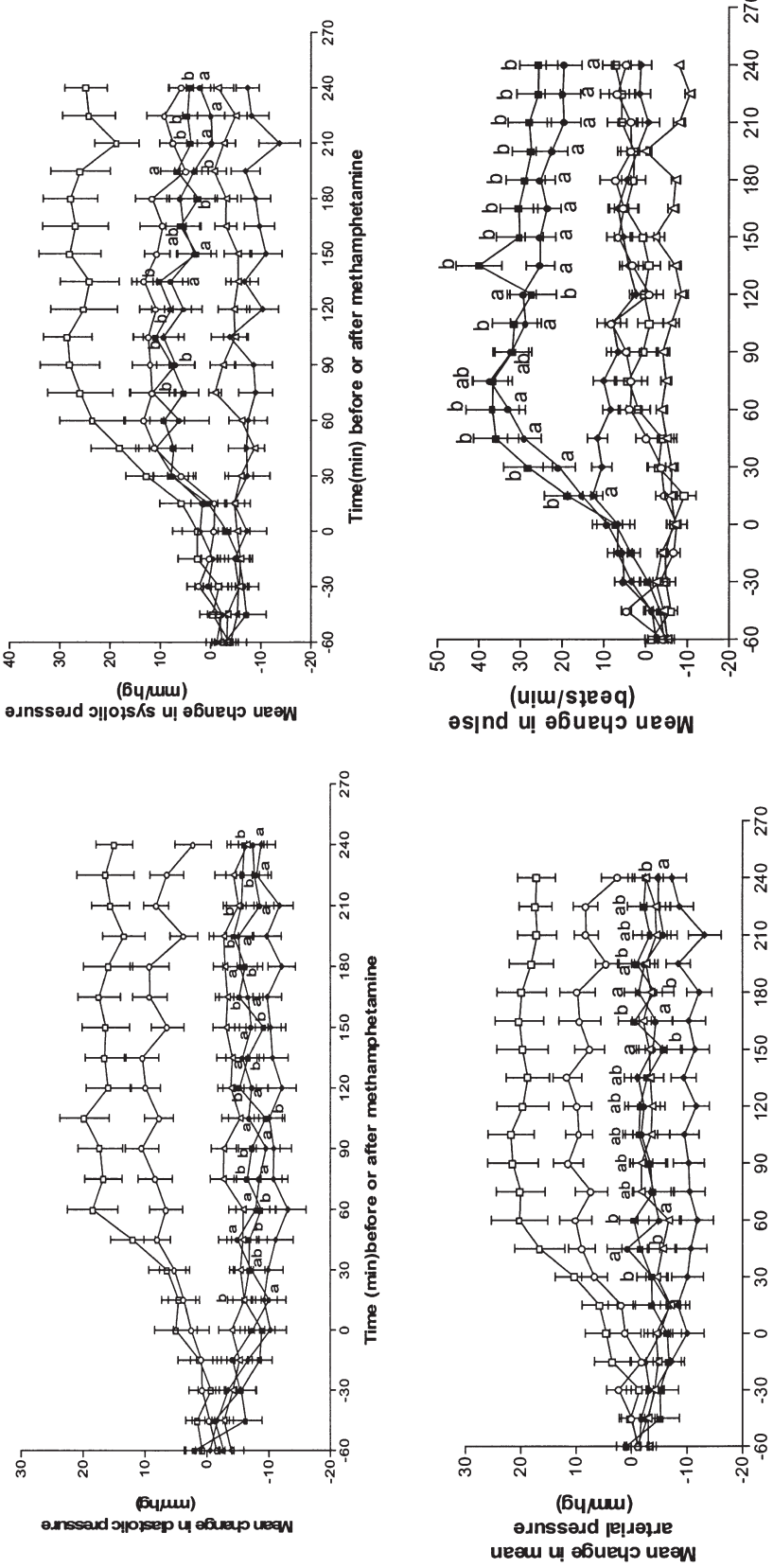

Figure 1. Mean ± SE change from baseline in vital signs, following the administration of d-methamphetamine (0.21 mg/kg or 0.42 mg/kg, orally) with and without isradipine (0.21 mg/kg, orally) to 18 healthy male and female volunteers. There were six treatment conditions: (a) placebo + placebo (Δ); (b) low-dose d-methamphetamine (0.21 mg/kg, orally) + placebo (○); (c) high-dose d-methamphetamine (0.42 mg/kg, orally) + placebo (□); (d) isradipine (0.21 mg/kg, orally) + placebo (◆); (e) low-dose d-methamphetamine + isradipine (●); and (f) high-dose d-methamphetamine + isradipine (■). Baseline was time −30 min. Isradipine or matching placebo was administered at time 0 min. D-methamphetamine or its matching placebo was administered at time +30 min. Significant post-hoc differences between: low-dose d-methamphetamine and low dose d-methamphetamine+ isradipine are denoted by an 'a', whereas high dose d-methamphetamine and high-dose d-methamphetamine + isradipine are represented by a 'b'.

cebo was administered at 08:00 h. At 08:30 h, d-methamphetamine (0.21 mg/kg or 0.42 mg/kg) or its matching placebo was administered. Vital signs were recorded at 15 min intervals for up to 240 min post d-methamphetamine. After 120 min post d-methamphetamine, computerized tasks of attention, logical reasoning, and performance were repeated—about the time peak d-methamphetamine level was expected following its oral ingestion (Angrist et al. 1987). Subjects were discharged at the end of each experimental day following a health check.

Recordings of vital signs and cognitive function at 07:30 h were treated as baseline. Between sessions, baseline means were used as covariates in the analytic procedure which was a repeated measures analysis of covariance (ANCOVA). The ANCOVA examined for the main effects of d-methamphetamine or isradipine x time, or their interaction (isradipine x d-methamphetamine x time), on the outcome measures of vital signs and cognitive function.

To minimize type I errors, the: (a) ANCOVAs reported had Greenhouse-Geisser corrections; and (b) post-hoc dependent t-tests were only used to test for differences within a medication condition if there was an interaction between either or both of the main treatment effects and time.

RESULTS

In Table 1 and Figure 1, which display the vital signs results, it can be seen that d-methamphetamine significantly increased the systolic pressure, diastolic pressure, mean arterial pressure, and pulse. Isradipine pre-treatment significantly decreased the systolic pressure, diastolic pressure, and the mean arterial pressure. Isradipine increased pulse rate. For all vital signs measures, there was a significant effect of time. In addition, d-methamphetamine-induced increases in diastolic pressure and mean arterial but not systolic pressure were attenuated significantly by isradipine (i.e., there was a significant isradipine x d-methamphetamine interaction). In contrast, the d-methamphetamine-induced increase in pulse was significantly accentuated by isradipine pre-treatment. There were also significant 3-way interactions (isradipine x d-methamphetamine x time) on diastolic pressure, mean arterial pressure, and pulse but not systolic pressure.

In Table 2 and Figure 2, which display the results of the cognitive function tasks, it can be seen that d-methamphetamine increased the mean hits, and decreased the mean false hits and the mean reaction time on the RVIPT. On the Logical Reasoning Test, d-methamphetamine significantly improved percent correct/time ratio (i.e., accuracy). There was no effect of d-methamphetamine on Finger Tapping scale. Isradipine alone was without significant effect on performance using the RVIPT except that there was an increased rate of false responding. While there was a main effect of isradipine to increase the time spent and reduce accuracy on the reasoning ability task (i.e., LRT), neither of these effects interacted with time. Isradipine had no significant interaction with d-methamphetamine with or without the effect of time on any cognitive task.

DISCUSSION

Few contemporary studies have examined d-methamphetamine's dose-related relationship between vital signs and cognitive functions in the human laboratory (Perez-Reyes et al. 1991). In addition, this is the first study to look for a potential pharmacological interaction between d-methamphetamine and DCCCA on cardiovascular and cognitive function.

D-methamphetamine was associated with dose-dependent increases in all vital signs measures. As predicted, isradipine was effective at reducing the hypertensive effects of d-methamphetamine, particularly diastolic

Table 2. Analysis of Covariance Results for the Change in Cognitive Function Tasks in 18 Male and Female Healthy Volunteers Who Received D-Methamphetamine (0.21 mg/kg or 0.42 mg/kg, orally) with or without Isradipine (0.21 mg/kg, Orally)

	Main Effects and Interactions						
Vital Signs	**IS [F; *p*]**	**METH [F; *p*]**	**T [F; *p*]**	**IS x METH [F; *p*]**	**IS x T [F; *p*]**	**METH x T [F; *p*]**	**IS x METH x T [F; *p*]**
Systolic pressure	13.95; **	18.95; ***	16.61; ***	1.80; NS	4.14; ***	7.76; ***	1.35; NS
Diastolic pressure	46.99; ***	19.93; ***	3.50; ***	3.94; *	12.17; ***	4.67; ***	1.82; **
Mean arterial pressure	38.70; ***	21.70; ***	6.95; ***	4.70; *	8.40; ***	6.45; ***	1.41; *
Pulse rate	98.95; ***	30.02; ***	26.16; ***	15.74; ***	25.03; ***	10.51; ***	3.03; ***

IS = isradipine; METH = d-methamphetamine; T = time.
NS = $p > .05$; * $p < .05$; ** $p < .01$; *** $p < .0001$.
For table, df = 1, 17 (IS); 2, 34 (METH), 20, 340 (IS X METH X T). One subjects with incomplete data was excluded from the ANCOVA.

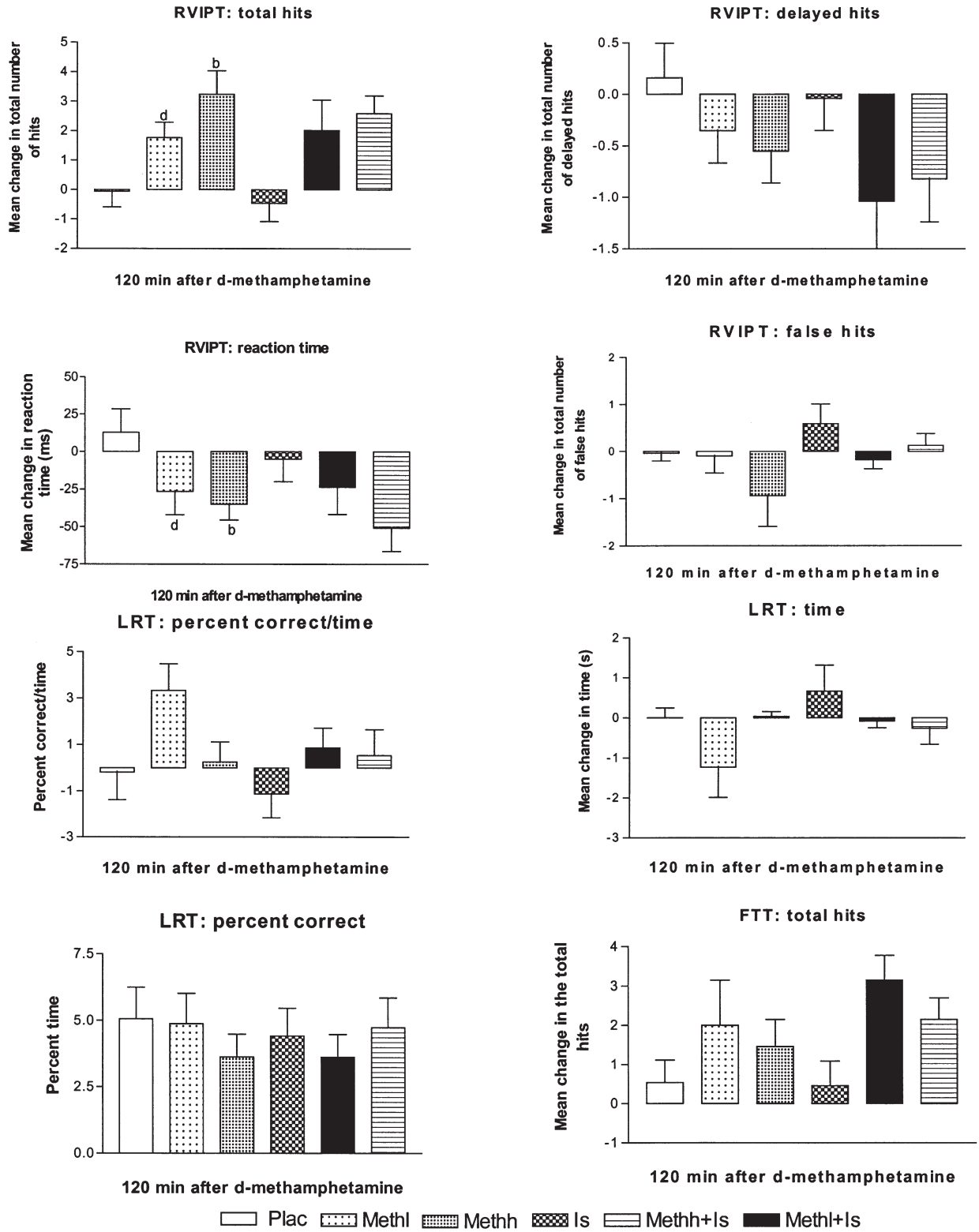

Figure 2. Peak ± SE change from baseline in attention, reasoning ability, and performance following the administration of d-methamphetamine (0.21 mg/kg or 0.42 mg/kg, orally) with and without isradipine (0.21 mg/kg, orally) to 18 healthy male and female volunteers. There were six treatment conditions: (a) placebo + placebo; (b) low-dose d-methamphetamine (0.21 mg/kg, orally) + placebo; (c) high-dose d-methamphetamine (0.42 mg/kg, orally) + placebo; (d) isradipine (0.21 mg/kg, orally) + placebo; (e) low-dose d-methamphetamine + isradipine; and (f) high-dose d-methamphetamine + isradipine. Baseline was time −30 min. Isradipine or matching placebo was administered at time 0 min. D-methamphetamine or its matching placebo was administered at time +30 min. Peak action of d-methamphetamine was registered at +120 min. Significant post-hoc differences between: ii) low-dose d-methamphetamine and placebo are denoted by an 'a'; ii) high dose d-methamphetamine and placebo are represented by a 'b'; and iii) high dose d-methamphetamine and low dose d-methamphetamine are identified by a 'c'. The tests administered were: rapid visual information processing task (RVIPT); logical reasoning task (LRT); and the finger tapping task (FTT).

pressure. D-methamphetamine's hypertensive effects appear more pronounced than those we obtained with cocaine (Johnson et al. 1999), presumably because it has a greater duration of action on increasing monoamine levels. Isradipine's anti-hypertensive effect is presumably the result of its anti-DA actions. Interestingly, isradipine's relatively greater anti-hypertensive effect following d-methamphetamine in this experiment, compared with our previous work on cocaine (Johnson et al. 1999), was probably a function of the relatively higher dose (10 mg, orally vs. approximately 15 mg for a 70 kg individual) rather than a differential pharmacological effect. We did, however, consider the possibility that isradipine's apparently exaggerated pharmacological effect may be mediated by d-methamphetamine's complex interactions with N-methyl-D-Aspartate receptors; however, these effects have primarily been described in neural tissue (Abekawa et al. 1997; Snyder 1992). For instance, d-methamphetamine may facilitate nitric oxide production, which may have been accentuated by isradipine-mediated reduction in extracellular calcium. Both of these effects combine to enhance vasodilatation (Kirsten et al. 1998; Salmone et al. 1996).

Despite the significant counter-regulatory increase in heart rate, which is consistent with other studies where single oral doses were administered to healthy volunteers (Carrara et al. 1994) this regimen was well tolerated with no reported physical symptoms. Since, however, an important potential indication for isradipine may be in the treatment of psychostimulant dependence (Johnson et al. 1997), consideration should be given to use of the slow-release form. This is because the slow-release preparation may be more cardio-protective in treating d-methamphetamine-induced hypertension since advantage could be taken of its beneficial hypotensive effects while avoiding the reflex tachycardia (van Zweiten and Pfaffendorf 1993). This presumption remains untested but worthy of empirical study using a multiple dosing strategy between d-methamphetamine and isradipine among addicts in a clinical setting. Hypertensive crises may, however, require rapid correction with the standard rather than slow-release preparation of isradipine. Notably, isradipine's effectiveness at reducing methamphetamine-induced hypertension occurred at pharmacological doses; hence, these results may not be entirely translatable to hypertensive crises due to much higher doses of methamphetamine ingestion in an abuser.

We re-evaluated the cardiovascular risks of administering d-methamphetamine in human laboratory studies. D-amphetamine has been used extensively as a pharmacological probe to model a variety of psychiatric conditions (e.g., mania) over several decades. In contrast, human laboratory studies with d-methamphetamine have been relatively rare, and there is inadequate dosing information. Such studies can certainly be anticipated, especially in the addictions where there is renewed interest in developing treatment medications for dependence to, or the toxic effects of, d-methamphetamine. Given the robust pharmacological response elicited by approximately 15 mg, orally of d-methamphetamine in a 70 kg individual, we suggest that this should perhaps be the 'ceiling' dose tested for profiling other possible interactive medication effects. Characterizing the pharmacological effects of even lower d-methamphetamine doses in the human laboratory would, therefore, merit further study.

Studies of animals performing complex cognitive tasks or of patients with Alzheimer's disease support the memory-enhancing effects of DCCCA. It is, however, plausible that these improvements are relatively modest and can only be demonstrated in particular diseased populations. Additionally, these memory-enhancing effects of DCCCA might be mediated by non-catecholamine systems. For instance, rises in acetylcholine induced by the DCCCA, nimodipine, have been associated with enhancements of spatial memory in rats (Levy et al. 1991). Similarly, when rhesus monkeys with calcium imbalance are treated with nimodipine there is a significant improvement in short-term memory (LeVere and LeVere 1994). Thus, it may be that prominent cognitive improvement with DCCCA can only be demonstrated in humans with either reduced acetylcholine function (e.g., in Alzheimer's disease) or an abnormality of calcium utilization associated with reduced neuronal plasticity.

The effects of DCCCA on attention are not well established in healthy individuals. Nevertheless, there is preliminary evidence that patients who received nimodipine, compared with controls, experienced no improvement in attention (Besson et al. 1988). It would also appear that nimodipine may only be beneficial in improving the attention of elderly individuals with calcium imbalance (Baer and Gispen, 1996). We found that the effects of isradipine on attention were modest with only an increased rate of false responding on the RVIPT. This attention-sparing profile of isradipine does enhance its suitability as a treatment agent for psychostimulant dependence (Johnson et al. 1998a) or toxicity (Johnson et al. 1998b) since addicts are often non-compliant with taking medications perceived to have mood lowering or sedative properties, or both.

Consistent with the animal literature where DCCCA were shown not to impair raw performance (Quevedo et al. 1998), isradipine treatment in our healthy humans volunteers was not associated with any performance decrement. In any event, further studies are needed to more fully characterize isradipine's cognitive effects with and without d-methamphetamine administration in both healthy individuals and those dependent upon psychostimulants.

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