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III. Serotonin-selective Arylpiperazines with Neuroendocrine, Behavioral, Temperature, and Cardiovascular Effects in Humans

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I. Introduction

THE principal focus of this review is the neuropharmacology of a group of selective serotonergic agents, the *l*-arylpiperazines, which have been studied clinically. In the past decade, multiple 5-HT* receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_2, 5-HT_3, 5-HT_4) have been identified; some of these have been cloned, sequenced, and studied in isolated systems (Fozard, 1989; Frazer et al., 1990; Paoletti et al., 1990; Peroutka, 1991; Sanders-Bush, 1988; Schmidt and Peroutka, 1989; Whittaker-Azmitia and Peroutka, 1990). In addition, discrete 5-HT subsystems involving different brainstem 5-HT-containing neurons of the raphe nuclei have increasingly become recognized. Although it has been known for some time that there were differences between the characteristics of the 5-HT neurons of the caudal raphe nuclei, which project into the spinal cord, and those of the rostral raphe nuclei, which innervate the brain, newer evidence indicates that there are important functional as well as anatomical differences among the different rostral raphe nuclei and their projection systems which provide dual innervation of different brain regions, sometimes with opposing functional effects (Azmitia, 1987; Blier et al., 1990; Hillegaart and Hjorth, 1989; Jacobs et al., 1974; Kosofsky and Molliver, 1987; Mamounas and Molliver, 1988; Murphy, 1991; Sinton and Fallon, 1988; Tork, 1990; Van de Kar and Lorens, 1979).

Considerable interest in evaluating the functional status of the multiple 5-HT receptor systems and the allied anatomical subsystems in humans has followed the development and increasing clinical use of two groups of serotonergic drugs. First, highly selective 5-HT uptake inhibitors (including fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram, and alaproclate) are proving to be not only effective antidepressants but also of therapeutic use in other disorders such as OCD, alcoholism, obesity, bulimia, panic disorder, and the chronic pain syndrome (Coccaro and Murphy, 1990; Fuller and Wong, 1990; Peroutka et al., 1989; Sleight et al., 1991) . Second, a series of highly selective 5-HT_{1A} partial agonists, the azapirones (including buspirone, ipsapirone, gepirone, tandospirone, and MDL-73005) possess antianxiety, antidepressant, and possibly other clinically useful actions (Editorial, 1988; Glaser, 1988; Robinson et al., 1989; Sleight et al., 1991; Traber and Glaser, 1987). The therapeutic effectiveness of these serotonergic agents and new basic science studies of 5-HT subsystems and 5-HT receptor subtypes have stimulated studies of 5-HT function in these disorders and in other neuropsychiatric disorders thought to involve serotonergic abnormalities including Alzheimer's disease, schizophrenia, sexual dysfunction, migraine, and several substance abuse disorders (Coccaro and Murphy, 1990; Glennon, 1990; Sandler et al., 1991). Of related interest, some drugs of abuse such as 3,4-methylenedioxyamphetamine have neurotoxic effects on 5-HT neurons, and other drugs of abuse including LSD, cocaine, and alcohol, modulate serotonergic functions (Cunningham and Lakoski, 1990; McKenna and Peroutka, 1991; Wolf and Kuhn, 1991).

One direct approach to evaluate the functional status of brain 5-HT receptors and subsystems in humans is to quantitate various responses elicited by centrally acting 5-HT receptor subtype-selective agonists. Other indirect approaches, such as measurements of the 5-HT metabolite, 5-hydroxyindoleacetic acid, in cerebrospinal fluid or responses to serotonergic agents without receptor-selective actions, such as L-tryptophan, 5-HTP, clomipramine, or fenfluramine, have been used to evaluate individual differences in total serotonergic function. However, any alterations found with these strategies necessarily reflect the summed effects of many processes and not independent subsystem changes; these measures may be useful if gross abnormalities in 5-HT synthesis or transport are present or if a change in the total numbers of 5-HT neurons has occurred, but they may be insensitive to other more discrete abnormalities (Cowen, 1990; Murphy, 1990b, 1991; Murphy et al., 1990).

Most of the studies in which 5-HT receptor subtype-selective agonists have been used as probes to perturb and evaluate CNS 5-HT functions have been accom-

*Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; LSD, lysergic acid; 5-HTP, 5-hydroxytryptophan; CNS, central nervous system; *m*-CPP, *meta*-chlorophenylpiperazine; MK-212, 6-chloro-2-(l-piperazinyl)pyrazine; 5,7-DHT, 5,7-dihydroxytryptamine; TFMPP, trifluoromethylphenylpiperazine; 2-MPP, 1-(2-methoxyphenyl)piperazine ; ACTH, adrenocorticotropic hormone; OCD, obsessive-compulsive disorder; 8-OH-DPAT, 8-hydroxy-2-(di-N-propylamino)tetralin; CRH, corticotropin-releasing hormone; DOI, 1-(2,5-dimethoxyphenyl)-2-aminopropane; 5-MEODMT, 5-methoxydimethyltryptamine.

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plished in the last 5 years, and two principal groups of agents have been used in single-dose studies: (*a*) several phenylpiperazines and related agents, including *m*-CPP and MK-212, and (*b*) several azapirones, including ipsapirone, buspirone, and gepirone.

Different physiological responses to these agonists have been measured, including plasma neuroendocrine changes, temperature, and behavioral changes. Animal studies have indicated that alterations in responses to these agents may reflect differences in CNS serotonergic receptor densities or other direct or indirect, adaptive changes induced by surgical lesions or by selective serotonergic neurotoxins, such as 5,7-DHT, *p*-chloroamphetamine, or 3,4-methylenedioxyamphetamine, or by treatment with 5-HT synthesis inhibitors (e.g., *p*-chlorophenylalanine), chronic treatment with tricyclic antidepressants (which induce changes in 5-HT receptors and related adaptational events), and differences based on gender, age, and genetic factors (Chase and Murphy, 1973; Murphy, 1990a,b, 1991).

In this paper we briefly summarize the studies using these serotonergic agents in humans. We also compare some of the most relevant information concerning these agents from studies in vitro and in animals. A less detailed review of azapirone data from nonhumans is included, because a number of these agents are in widespread clinical use and study, and reviews of many aspects of their behavioral actions and general pharmacology are available (Editorial, 1988; Dourish et al., 1987; Eison et al., 1986; Eison and Temple, 1986; Glaser, 1988; Goa and Ward, 1986; Hamon et al., 1990; Robinson et al., 1989; Lucki and Wieland, 1990; Taylor 1988, 1990; Traber and Glaser, 1987; Yocca, 1990).

II. *m*-Chlorophenylpiperazine and Other Substituted Phenylpiperazines

During the last two decades, a number of substituted piperazines including quipazine, *m*-CPP, TFMPP, MK-212, and 2-MPP were identified as 5-HT mimetic agents in rodents (Clineschmidt et al., 1977; Fuller et al., 1978; Maj et al., 1979; Page et al., 1959). Although a number of these compounds have been studied in humans, none have been developed as therapeutic agents. *m*-CPP, which is a metabolite of the antidepressant, trazodone, has been the most extensively investigated phenylpiperazine in humans. Its primary use has been as a probe of the functional status of brain 5-HT function, part of the so-called challenge strategy of using drugs with relative CNS neurotransmitter selectivity to attempt to evaluate the role of different CNS neurotransmitters, and of changes in their functional status, in patients with neuropsychiatric disorders and in the CNS responses to pharmacological treatment of these disorders.

A. Single-Dose Studies of m-Chlorophenylpiperazine in Humans

1. Studies of m-chlorophenylpiperazine in healthy normal subjects. *m*-CPP given to healthy human volunteers elicits changes in neuroendocrine measures, temperature, blood pressure, self-ratings of mood, and sleep. Plasma prolactin, cortisol, and ACTH elevations have regularly been observed after administration of *m*-CPP either orally or intravenously (Charney et al., 1987, 1988; Kahn et al., 1988a,b, 1990a,b; Mueller et al., 1985a,b, 1986; Murphy et al., 1989a; Zohar et al., 1987). Plasma growth hormone increases followed intravenous (Charney et al., 1987) but not oral (Mueller et al., 1986), *m*-CPP administration. Plasma norepinephrine, β-endorphin/lipotropin, and systolic and diastolic blood pressure were increased by intravenous *m*-CPP (Murphy et al., in preparation; Pigott et al., in preparation). Temperature increases after *m*-CPP administration have been found in several (Mueller et al., 1985a, 1986; Murphy et al., 1989a; Zohar et al., 1987), but not all (Kahn et al., 1990b), studies. No changes in sexual interest or penile erections were reported after *m*-CPP (Murphy et al., 1989a). Increases in self-rated anxiety, activation/euphoria, functional deficit, and physical symptoms such as nausea, dizziness, and sweating have also been reported, particularly after higher oral doses (0.5 versus 0.25 mg/kg) or after intravenous doses (0.1 mg/kg) of *m*-CPP (Charney et al., 1987, 1988; Kahn et al., 1990b; Mueller et al., 1985a,b; Murphy et al., 1989a). Reductions in electroencephalographically monitored total sleep, rapid eye movement sleep, and slow-wave sleep were found in a study comparing *m*-CPP with placebo (Lawlor et al., 1991).

The increases in plasma levels of prolactin, cortisol, and ACTH and physical symptoms after orally administered *m*-CPP have been found to be dose dependent (Kahn et al., 1990a; Mueller et al., 1985b; Murphy et al., 1989a). In one study in which oral administration of *m*-CPP (0.5 mg/kg) was compared with intravenous administration (0.1 mg/kg), no statistically significant differences in peak plasma prolactin or cortisol levels were found, although self-rated increases in anxiety, altered self-reality, depression, and functional deficit were greater after intravenous than oral administration (Murphy et al., 1989a).

The 5-HT_1/5-HT_2 antagonist metergoline (4 mg, orally) completely blocked the prolactin, cortisol, and temperature responses and significantly attenuated the ACTH response to orally administered *m*-CPP (Mueller et al., 1986). A second study in which both metergoline and methysergide (both 4 mg, orally) were used also demonstrated blockade of the prolactin response to 0.5 mg/kg *m*-CPP given orally; the cortisol increases were blocked by metergoline, whereas methysergide's attenuation of the cortisol increase was not statistically significant (Kahn et al., 1990b). The one study in which metergoline's effects on the responses to intravenous *m*-CPP were investigated found that prolactin, temperature, and blood pressure increases were significantly less after metergoline pretreatment, whereas a blocking effect

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could not be demonstrated for the cortisol, growth hormone, or norepinephrine responses (Pigott et al., in preparation). In these studies, metergoline or methysergide pretreatment did not alter plasma concentrations of *m*-CPP.

Several other factors have been shown to affect physiological or behavioral responses to *m*-CPP. Older subjects (mean age, 62 years) had considerably smaller increases in anxiety, activation/euphoria, depression, altered self-reality, and functional deficit than did younger subjects (mean age, 32 years) given 0.1 mg/kg of *m*-CPP intravenously; no similar age-associated differences were found in plasma prolactin or cortisol responses or in plasma *m*-CPP levels (Lawlor et al., 1989a,b). Exaggerated behavioral responses were observed when *m*-CPP was given at night (Lawlor et al., 1991). Female subjects had greater prolactin responses to *m*-CPP in one study (Charney et al., 1987) with trends toward such a difference in two other studies (Kahn et al., 1990a; Mueller et al., 1985a) but no difference in another study (Murphy et al., 1989a).

2. Studies of m-chlorophenylpiperazine in patients with neuropsychiatric disorders. Patients with some neuropsychiatric disorders had different responses to *m*-CPP when compared with healthy volunteer control subjects. Both neuroendocrine and behavioral response differences have been observed.

a. PANIC DISORDER. More patients with panic disorder (60%) had panic episodes when given *m*-CPP, 0.25 mg/kg, than did controls (0%), and the patients had significantly greater increases in self-ratings of anxiety, hostility, and physical symptoms than did the controls (Kahn et al., 1988b). Greater increases in plasma cortisol concentrations after *m*-CPP administration, unaccompanied by any difference in plasma *m*-CPP levels, were observed in patients with panic disorder studied by this same group (Kahn et al., 1988a). Pre-*m*-CPP anxiety ratings and the maximal anxiety responses to *m*-CPP were positively correlated with plasma cortisol responses to *m*-CPP (Kahn et al., 1988a). When patients with panic disorder were studied using intravenous *m*-CPP (0.1 mg/kg), 12 of 23 patients compared with 6 of 19 normal controls had panic attacks; neither this result nor changes in general anxiety ratings or cortisol, prolactin, or growth hormone responses differed statistically for the patients compared with the controls (Charney et al., 1987). Dose and mode of *m*-CPP administration would appear to be important factors governing responses to *m*-CPP, and Kahn and coworkers (1990a) suggested that a preferred strategy to explore an hypothesized hyperresponsive serotonergic state in panic disorder or other disorders is to use relatively low *m*-CPP doses that are subthreshold for normal controls.

b. OBSESSIVE-COMPULSIVE DISORDER. Like individuals with panic disorder, patients with OCD also responded to *m*-CPP, given orally, with greater increases in ratings of anxiety and other symptoms (Zohar et al., 1987). These patients did not have panic attacks, but a majority exhibited an exacerbation of OCD symptoms with *m*-CPP, but not placebo or fenfluramine, administration (Hollander et al., 1988; Zohar et al., 1987). Some indication that this OCD symptom exacerbation did not simply represent a nonspecific response to the anxiogenic effects of *m*-CPP comes from studies of patients with OCD that use anxiogenic agents. Unlike patients with panic disorder in whom panic attacks occurred when exposed to yohimbine, lactate, or carbon dioxide, patients with OCD did not manifest greater anxiety or panic attacks with these agents, nor did they manifest any exacerbation of OCD symptoms (Gorman et al., 1985; Griez et al., 1990; Rasmussen et al., 1987).

In another study, patients with OCD and healthy controls both developed marked increases in anxiety when treated with *m*-CPP (0.1 mg/kg), but not L-tryptophan or placebo given intravenously, but without any statistical difference in this response between patients and controls, and without any apparent exacerbation of OCD symptoms rated 90 min after *m*-CPP administration (Charney et al., 1988). A second study in which intravenous *m*-CPP (0.1 mg/kg) was administered within a shorter period (90 s versus 20 min) similarly found equivalent increases in anxiety and other symptoms in both patients with OCD and controls but also reported significant increases in OCD symptoms in the patients with OCD on ratings obtained 30 min after *m*-CPP treatment; this effect was brief and had largely dissipated after 60 or 90 min (Pigott et al., in preparation). As in the panic disorder studies, these data again suggest a relatively narrow dose range and an experimental paradigm-selective effect of *m*-CPP's behavioral effects in neuropsychiatric patient populations (Murphy et al., 1989b).

Neuroendocrine and temperature responses to *m*-CPP in patients with OCD compared with healthy controls have also been evaluated. Plasma cortisol, growth hormone, and norepinephrine and temperature responses were no different in the patients with OCD versus controls after intravenous *m*-CPP treatment (Charney et al., 1988; Pigott et al., in preparation); whereas plasma prolactin responses were blunted in female patients with OCD compared with female controls in one study (Charney et al., 1988). Blunted prolactin responses in patients with OCD compared with controls were also found in one study of orally administered *m*-CPP (Hollander et al., 1991) but not another study (Zohar et al., 1987). These variably blunted or unaltered physiological responses are in contrast to the quite marked behavioral responses to both oral and intravenous *m*-CPP in patients with OCD.

Several attempts have been made to determine whether the behavioral and other responses of patients with OCD might be modified by 5-HT antagonists or by

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therapeutic agents that improve OCD symptoms. Pretreatment with orally administered metergoline (4 mg), which by itself had no effects on OCD symptoms or anxiety (Pigott et al., 1991; Zohar et al., 1987), obliterated the increases in observer-rated OCD symptoms and anxiety as well as the subjective dysphoria and functional deficit state found after *m*-CPP (0.5 mg/kg orally) given alone (Pigott et al., 1991). *m*-CPP-induced plasma prolactin increases were also eliminated by metergoline pretreatment in these patients (Pigott et al., 1991). In another study, metergoline pretreatment also blocked the exacerbation of OCD symptoms found after intravenously administered *m*-CPP; plasma prolactin, temperature, and blood pressure increases produced by *m*-CPP were also blocked, but metergoline did not block the increases in plasma cortisol, growth hormone, or norepinephrine concentrations produced by *m*-CPP (Pigott et al., in preparation). In neither *m*-CPP/metergoline study in patients with OCD were *m*-CPP plasma levels altered by metergoline pretreatment.

Patients with OCD treated for an average of 4 months with the partially selective 5-HT uptake inhibitor, clomipramine, were found to have fewer behavioral responses to *m*-CPP, with no significant exacerbation of OCD symptoms after *m*-CPP treatment (Zohar et al., 1988). Temperature responses to *m*-CPP were also attenuated, but prolactin and cortisol increases were no different from non-clomipramine-treated patients with OCD. The patients receiving *m*-CPP in combination with continued clomipramine treatment had improved approximately 40%, raising the question of whether the altered behavioral response to *m*-CPP might be related to the altered clinical state rather than a primary pharmacological effect or biochemical adaptational change produced by clomipramine. This might be assessed by studying *m*-CPP responses in patients with OCD prior to and after successful behavioral therapy. Another factor complicating interpretation of the neuroendocrine (but not the behavioral or temperature) changes in response to *m*-CPP was a doubling of peak plasma concentrations of *m*-CPP found in the clomipramine-treated patients with OCD. If, as reviewed above, the cortisol and prolactin changes after *m*-CPP treatment were proportionate to plasma *m*-CPP concentrations, then an exaggerated neuroendocrine response rather than a lack of change would have been expected. Hence, it remains a possibility that *m*-CPP plasma level-adjusted neuroendocrine responses may actually have been attenuated in the clomipramine-treated patients.

Treatment with the more highly selective 5-HT uptake inhibitor, fluoxetine, also led to an attenuation of the exacerbation of obsessive-compulsive symptoms produced by orally administered *m*-CPP in patients with OCD (Hollander et al., 1991). This finding was all the more striking because fluoxetine treatment was associated with a 4-fold increase in plasma *m*-CPP concentrations. In this study, plasma prolactin and cortisol responses to *m*-CPP were enhanced during fluoxetine treatment, perhaps reflecting *m*-CPP's altered pharmacokinetics.

c. DEPRESSION. Patients with major depression who were given *m*-CPP orally had prolactin increases identical with those of normal controls (Kahn et al., 1990c). Plasma levels of *m*-CPP were also the same in both groups. The depressed patients reported significantly more physical symptoms after *m*-CPP treatment than did the controls, but neither group reported any significant changes on self-rated mood assessed by Profile of Mood State subscales.

Patients with seasonal affective disorder studied with intravenous *m*-CPP (0.1 mg/kg) while they were depressed had significantly greater increases in self-rated activation/euphoria and anxiety than did healthy volunteers (Jacobsen et al., 1989). Plasma cortisol and prolactin increases after *m*-CPP treatment were also significantly greater in the patients. These differences between patients and controls markedly diminished after the patients were treated with phototherapy and their depression had improved; at this time, both the patients and controls manifested moderate increases of similar magnitude in anxiety and other self-rated measures following *m*-CPP. In a follow-up study, patients with seasonal affective disorder who had become nonsymptomatic during the summer months exhibited negligible behavioral response differences to *m*-CPP compared with normal controls (Joseph-Vanderpool et al., in preparation).

In a study of longer-term *m*-CPP administration in humans, patients with major depressive disorder were treated with *m*-CPP (80 mg/day) in an off-on-off-on design of 2-week periods of active drug and placebo (Mellow et al., 1990). In this preliminary study, *m*-CPP appeared to lead to reductions in depression, anxiety, aggressivity, and hostility in some patients, with rebound increases in symptoms during placebo substitution.

d. SCHIZOPHRENIA. Patients with schizophrenia given *m*-CPP (0.1 mg/kg) intravenously became increasingly symptomatic, with statistically significant increases in psychosis ratings on the Brief Psychiatric Rating Scale (Seibyl et al., 1989; Owen et al., in preparation). Increased anxiety preceded the increase in positive schizophrenic symptoms; negative schizophrenic symptoms were unchanged (Seibyl et al., 1989). Visual hallucinations occurred after *m*-CPP, but not placebo, treatment in two patients (Seibyl et al., 1989). The prolactin, cortisol, and growth hormone concentrations and many of the behavioral effects of *m*-CPP were attenuated by pretreatment with the 5-HT antagonist, ritanserin, in one study (Seibyl et al., 1989). In another study, the neuroleptic, fluphenazine, had negligible effects on the responses to *m*-CPP, whereas the atypical neuroleptic, clozapine, which possesses more marked 5-HT_2 antago-

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nist properties (Nash et al., 1988), blocked *m*-CPP's cortisol increases and also attenuated the behavioral effects of *m*-CPP (Owen et al., in preparation).

e. ALZHEIMER'S DISEASE. In one study in which the responses to intravenous *m*-CPP (0.1 mg/kg) were compared in patients with Alzheimer's disease and age-matched elderly controls, significantly greater increases in anxiety, activation, depression, and other behavioral ratings were found in the patients with Alzheimer's disease (Lawlor et al., 1989c). Total Brief Psychiatric Rating Scale ratings and the Brief Psychiatric Rating Scale activation and thought disorder subscale ratings after *m*-CPP were also greater in the patients with Alzheimer's disease. Some of the patients manifested unusual perceptual changes not seen in the controls. Impairment of recent memory and knowledge memory after *m*-CPP treatment was also greater in the patients with Alzheimer's disease. Temperature increases were less in the patients, whereas plasma prolactin and cortisol increases and *m*-CPP plasma levels were no different, suggesting that some, but not all, 5-HT subsystems are affected in these patients.

f. ALCOHOLISM AND SUBSTANCE ABUSE. Patients with chronic alcoholism who were abstinent for 3 weeks before they were given *m*-CPP (0.08 mg/kg) intravenously reported significantly greater ratings of "feel high" and "crave alcohol" after *m*-CPP treatment than after placebo (Benkelfat et al., 1991). Male patients with antisocial personality disorder and substance abuse histories (mixed abuse of alcohol, cocaine, marijuana, and opiates) who were abstinent for 2 weeks had significantly reduced prolactin responses and significantly greater cortisol responses than did controls to orally administered *m*-CPP (0.5 mg/kg); no behavioral response data during the *m*-CPP study were reported (Moss et al., 1990).

g. CHRONIC PAIN. Patients with neuropathic pain given *m*-CPP (40 mg) did not report any greater analgesic effects than after placebo treatment; side effects were greater after *m*-CPP treatment (Kishore-Kumar et al., 1989).

h. BULIMIA AND MIGRAINE. Female patients with the eating disorder, bulimia, given *m*-CPP (0.5 mg/kg) orally had significantly smaller increases in plasma prolactin concentrations after *m*-CPP treatment than did controls, whereas cortisol increases and plasma *m*-CPP levels were no different; similar differences between patients and controls were not found for the prolactin responses to L-tryptophan (Brewerton et al., in press).

An unexpected occurrence in this study of young female patients with bulimia and controls was a high frequency of late-onset headaches (Brewerton et al., 1988; Fozard and Gray, 1989). Delayed headaches, occurring usually in the evening, 8 to 12 hours after *m*-CPP administration, had originally been reported in a few subjects in the first study of *m*-CPP in healthy volunteers (Mueller et al., 1985a). In the eating disorder study, 28 of 52 subjects (54%), including both bulimic patients and controls, reported severe headaches with the features of common migraine. None of these subjects had similar headaches after placebo or L-tryptophan (100 mg/kg) given intravenously.

The incidence of these headaches was significantly greater in those patient or control subjects with a personal or family history of migraine, with severe symptoms developing in almost all such predisposed individuals (18 of 20, 90%). Headache characteristics were described as essentially indistinguishable from naturally occurring headaches, including nausea (86%), photophobia (86%), throbbing (75%), unilaterally (32%), and involuntary vomiting (7%). Although no spontaneous prodrome typical of some migraine episodes was regularly reported, there was considerable similarity between some of the effects and side effects of *m*-CPP (mood lability, hot-cold sensations with sweating, feeling lightheaded, and cognitively slowed and impaired) and a clinical tabulation of the prodromal symptoms that precede spontaneously occurring migraine (Blau, 1987).

B. Relevant Studies of m-Chlorophenylpiperazine and Related Piperazines in Vitro and in Animals

m-CPP and a number of other related compounds, including TFMPP, MK-212, and quipazine, are most well known for their 5-HT agonist properties. Some of these substituted piperazines also have affinity for other neurotransmitter receptors, and some, including *m*-CPP, function as agonists at some 5-HT receptor subtypes, but antagonists at other 5-HT receptors. *m*-CPP is a constituent of the chemical structure of a group of drugs, some studied clinically, including trazodone, nefazodone, etoperidone, cloperidone, mefeclorazine, and mepiprazole; similarly, the TFMPP moiety is found in fluprazine, antrafenine, DU27725, and terciprazine; *m*-CPP or TFMPP have been identified as metabolites of some of these drugs in rodents and humans (Caccia et al., 1981, 1982, 1985; Fuller, 1986).

1. Receptor affinity profile and second messenger system effects. In rodent brain, *m*-CPP has highest affinity for 5-HT_{1C} sites, although its pK_d (−log mol/liter) for 5-HT_{1C} sites as determined in two studies (7.68, 7.78) is only approximately 10-fold greater than its affinity for 5-HT_2 (6.70), 5-HT_{1B} (6.47, 6.58), and 5-HT_{1A} sites (6.49, 6.61) (Hoyer 1988a, 1989). *m*-CPP also has affinity for α_2-adrenoceptor sites (Smith and Suckow, 1985). More recently, *m*-CPP has been reported to have lower affinity for 5-HT_{1D} sites (5.81) but relatively high affinity (7.00) for 5-HT_3 sites studied with [^{3}H]ICS 205–930 as the radioligand and considerably higher affinity when [^{3}H]quipazine was the ligand for 5-HT_3 sites, with K_i or IC_{50} values in the 20- to 50-nM range (Glennon et al., 1989; Hoyer 1989; Kilpatrick et al., 1987; Neijt et al., 1988; Peroutka, 1988). However, because [^{3}H]quipazine also binds to sites other than 5-HT_3, including the 5-HT transporter site, and specific [^{3}H]quipazine binding may

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not be present in human brain, further study is required (Glennon et al., 1989; Kilpatrick et al., 1990; Peroutka, 1988; Van Wijngaarden et al., 1990).

A limited study using human brain tissue ranked *m*-CPP affinities for different neurotransmitter receptor sites as follows [IC_{50} (nM)]: 5-HT_2 (360); 5-HT_{1A} (400); α_2-adrenergic (570); 5-HT_{1D} (1300); β-adrenergic (2,500); α_1-adrenergic (2,900); D_1 dopamine (7,000); D_2 dopamine (10,000); cholinergic muscarinic, benzodiazepine, 5-HT uptake site (all >10,000) (Hamik and Peroutka, 1989). However, *m*-CPP affinities for 5-HT_{1C} and 5-HT_3 sites were not assessed, and some of the radioligands used are now known to have relatively high affinity for sites other than those designated. For example, the α_2-adrenergic ligand used in this study, [^{3}H]rauwolscine, is now known to bind with high affinity for 5-HT_{1D} (20 nM) and 5-HT_{1A} (100 nM) sites, and the β-adrenergic ligand ([^{3}H]dihydroalprenolol), the α_1-adrenergic ligand ([^{3}H]WB 4101), and the D_1 dopamine ligand ([^{3}H]SCH 23390) used in this study have nanomolar affinities for the 5-HT_{1A}, 5-HT_{1C}, and/or 5-HT_2 sites (Hoyer, 1989).

In some of the earlier animal pharmacology literature, *m*-CPP was considered a relatively selective 5-HT_{1B} agonist, and in some cases extrapolation of this viewpoint was used to interpret the human pharmacology of *m*-CPP. This has more recently been discovered to be erroneous, because several studies have failed to find 5-HT_{1B} receptors in human brain (Heuring et al., 1986; Hoyer et al., 1986a). Although the 5-HT_{1D} receptor is thought to function as an autoreceptor at nerve terminals in humans, guinea pigs, and other species, as the 5-HT_{1B} receptor does in rodents, *m*-CPP's low affinity for 5-HT_{1D} receptors make rodent-human extrapolations of *m*-CPP's actions more tenuous (Engel et al., 1986; Maura et al., 1986; Waeber et al., 1988, 1989).

Investigations of *m*-CPP and TFMPP in vitro, using changes in second messengers as end points, reported that *m*-CPP and TFMPP were partial agonists at 5-HT_{1C} receptors of the rat choroid plexus, with efficacies relative to 5-HT of 90% and 50%, respectively (Conn and Sanders-Bush, 1987). In contrast, *m*-CPP and TFMPP were full 5-HT antagonists at rat cerebral cortex 5-HT_2 receptors (Conn and Sanders-Bush, 1987). In the choroid plexus preparation, 5-HT_{1C} responses to 5-HT were antagonized by ritanserin > metergoline = mianserin, with K_i values of 0.2 to 2 nM, clearly indicating that earlier pharmacological studies in which blockade by ritanserin was used as the criterion for a 5-HT_2-mediated effect may require reinterpretation to clarify whether 5-HT_{1C} or 5-HT_2 receptors were being acted upon (Sanders-Bush and Breeding, 1988, 1990).

In a detailed study comparing second messenger responses to *m*-CPP, TFMPP, 8-OH-DPAT, and other 5-HT agonists at different 5-HT_1 receptor subtypes, *m*-CPP behaved as a partial agonist at 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_{1D} sites, with efficacies relative to 5-HT of 40%, 60%, 65%, and 30%, respectively (Schoeffter and Hoyer, 1989). *m*-CPP's affinity for the 5-HT_{1C} site was slightly higher than that of 5-HT, whereas at the 5-HT_{1A} site, it had a >100-fold lesser affinity than that of 5-HT or 8-OH-DPAT. At the 5-HT_{1D} site, *m*-CPP was an antagonist of 5-HT's effects. TFMPP also had partial agonist effects at all four 5-HT_1 subtypes but no apparent 5-HT_{1D} antagonist effects (Schoeffter and Hoyer, 1989).

2. Electrophysiological effects. Compared with 5-HT, which hyperpolarizes and inhibits the spontaneous firing of dorsal raphe 5-HT neurons and also of hippocampal pyramidal cells, *m*-CPP and TFMPP produced only very weak effects when administered iontophoretically (Sprouse and Aghajanian, 1987, 1988). In the hippocampus, *m*-CPP's effects were nonadditive with the relatively weak effects of ipsapirone and 8-OH-DPAT; these 5-HT_{1A} agonists, in contrast, were equiactive as 5-HT in potently producing a slowing of neuronal firing rates in the dorsal raphe (Sprouse and Aghajanian, 1988).

When TFMPP was administered intravenously and cell firing recorded from 5-HT neurons in the dorsal raphe and median raphe, weak and inconsistent slowing effects on dorsal raphe-firing rates were observed with TFMPP doses up to 1 mg/kg (Sinton and Fallon, 1988). However, in the median raphe, TFMPP and a fused arylpiperazine, CGS 12066, potently increased cell-firing rates at low drug doses, with an inverted U-shaped dose-response curve. These effects were in contrast to those of the 5-HT_{1A} agonists, 8-OH-DPAT and ipsapirone, which dose dependently slowed firing rates of both dorsal and median raphe cells, although higher doses of 8-OH-DPAT (>20-fold) and ipsapirone (2-fold) were required in the median raphe. TFMPP and CGS 12066 were also the most potent agents in slowing the firing rates of dopamine neurons in the substantia nigra; their effects were not blocked by the dopamine antagonist, haloperidol, whereas the weaker slowing effects of 8-OH-DPAT were (Sinton and Fallon, 1988).

The electrophysiology of 5-HT_{1C} receptors has been explored rarely. Similarly, investigations of the possible effects of *m*-CPP on cation conduction changes mediated by 5-HT_3 receptors have not yet been reported.

3. Neurochemical effects. In addition to effects at 5-HT and possibly other neurotransmitter receptors, *m*-CPP and TFMPP inhibited [^{14}C]5-HT uptake (IC_{50}, 1.3×10^{-6} M) and [^{14}C]norepinephrine uptake (IC_{50}, 5.8×10^{-6} M) in rat brain synaptosomes and rat platelets (Fuller et al., 1981a,b; Garattini et al., 1976). One study demonstrated that *m*-CPP released 5-HT from rat hypothalamic slices studied in vitro (Pettibone and Williams, 1984). Similar effects of *m*-CPP were not observed in rat brain synaptosomal preparations or in vivo (Fuller et al., 1981a,b). Monoamine oxidase activity was partially inhibited by large doses (10 mg/kg) of *m*-CPP in vivo (Invernizzi et al., 1981) or high concentrations of TFMPP (10^{-4} M) in vitro (Fuller et al., 1981a).

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m-CPP and TFMPP, like other 5-HT agonists, produced a reduction in brain 5-HT turnover measured either as a reduction in the accumulation of 5-HTP after decarboxylase inhibition or as a reduction in steady-state concentrations of 5-hydroxyindoleacetic acid (Fuller et al., 1978, 1981a,b, 1986; Invernizzi et al., 1981; Rokosz-Pelc, 1980). One dose comparison study showed that 5-HT turnover was selectively reduced at 0.3 and 1 mg/kg, whereas at 10-fold higher doses (3 and 10 mg/kg), *m*-CPP increased brain concentrations of homovanillic acid and methoxy-4-hydroxyphenylglycol (Invernizzi et al., 1981).

4. Physiological effects at different serotonin receptor subtypes. *m*-CPP was originally reported to reduce food uptake, reduce locomotor activity, and produce hyperthermia and the hind limb flexor reflex in rodents (Maj and Lewandowska, 1980; Maj et al., 1979). These effects were prevented by pretreatment with 5-HT antagonists, including metergoline or cyproheptidine, but not adrenergic or dopamine antagonists, and thus were interpreted as representing postsynaptic, 5-HT-mediated events.

Subsequently, *m*-CPP and TFMPP were found to increase plasma corticosterone, ACTH, and prolactin concentrations and to deplete hypothalamic CRH in rats via 5-HT antagonist-susceptible mechanisms (Fuller and Snoddy, 1980; Fuller et al., 1981a,b, 1986; Hashimoto et al., 1982; Preziosi et al., 1983; Quattrone et al., 1981). In the periphery, *m*-CPP had negligible or weak agonist activity on contractile responses of the rat jugular vein or the rat uterus, but, rather, antagonized 5-HT's effects on these preparations, and also antagonized the diarrhea-producing effects of 5-HTP in mice (Cioli et al., 1984; Cohen and Fuller, 1983; Warrick et al., 1981).

Only more recently has it begun to be possible to more closely relate the effects of *m*-CPP and other related piperazines to actions at different 5-HT receptor subtypes. Progress in several different research areas has been important: (*a*) the development of more selective antagonists for some 5-HT receptor subtype, (e.g., ritanserin for 5-$HT_{2/1C}$ sites); (*b*) the recognition of the functional importance of additional 5-HT receptor subtypes and receptor families (e.g., 5-HT_{1C}/5-HT_2, which use phosphotidylinositol hydrolysis as a second messenger system, other 5-HT_1 subtypes which use adenylyl cyclase, and 5-HT_3 receptors which use ligand-gated ion channels for signal transduction); and (*c*) the cloning and sequencing of some of the 5-HT receptors (5-HT_{1A}, 5-HT_{1C}, 5-HT_2) (Sanders-Bush, 1988; Schmidt and Peroutka, 1989; Whitaker-Azmitia and Peroutka, 1990). A summary of the current views concerning *m*-CPP's mechanisms of action for some of its more prominent, clinically relevant effects follows.

a. TEMPERATURE. *m*-CPP and *p*-chlorophenylpiperazine were originally reported to produce hyperthermia in rabbits and rats acclimated to a 28°C environment; these effects were blocked by the 5-HT antagonist, cyproheptidine (Maj and Lewandowska, 1980). In mice, quipazine produced temperature elevations when given at an ambient temperature of 27°C but not at 20°C (Goodwin and Green, 1985). In other studies in mice, *m*-CPP and TFMPP produced dose-proportionate body temperature reductions in a 21°C environment that were attenuated by pindolol and cyanopindolol but not by cyproheptidine, methysergide, mianserin, metergoline, or 5-HT_3 antagonists or by adrenergic, cholinergic, or dopaminergic antagonists (Frances, 1988; Maj et al., 1988).

Dose-dependent hyperthermic responses were observed in rats given *m*-CPP (ambient temperature 25 ± 1.5°C) or MK-212 (ambient temperature 22 to 24°C) (Gudelsky et al., 1986; Wozniak et al., 1989a). Ketanserin, mianserin, spiperone, pizotifen, and pirenperone blocked MK-212-induced hyperthermia; methiothepin, pindolol, and xylamidine were ineffective (Gudelsky et al., 1986). *m*-CPP-induced hyperthermia in rodents was blocked by metergoline but not by ritanserin, pindolol, haloperidol, clonidine, or phenoxybenzamine; methiothepin and pindolol had temperature-elevating effects of their own (Wozniak et al., 1989a). Although the available antagonist studies are inadequate to identify 5-HT receptor subtypes involved in *m*-CPP's temperature effects, 5-HT_2 receptors were implicated in MK-212 hyperthermic responses (Gudelsky et al., 1986). However, in doses that attenuated 8-OH-DPAT-induced hypothermia, the 5-HT_2 agonist DOI had no effect on body temperature (Bill et al., 1990). Treatment with several antidepressants (imipramine, clomipramine, clorgyline) for either 3 or 22 days significantly attenuated the hyperthermic response to *m*-CPP (Wozniak et al., 1989a,b).

b. FOOD INTAKE. *m*-CPP and TFMPP produced dose-dependent decreases in food intake in rodents both when the animals had food available on a 24-hour basis (free-feeding paradigm) or when food availability was restricted to part of the day (food-deprived paradigm) (Aulakh et al., 1987; Cohen et al., 1983; Fuller et al., 1981a,b; Kennett and Curzon, 1988a,b; Kennett et al., 1987a; Samamin et al., 1980). Hypophagia was also produced by direct infusion of TFMPP, 5-HT, RU 24969, and norfenfluramine (but not 8-OH-DPAT) into the paraventricular nucleus of the hypothalamus, a likely site of action of this effect of 5-HT agonists (Hutson et al., 1988a; Shor-Posner et al., 1986).

m-CPP-induced hypophagia can be blocked by metergoline, mesulergine, mianserin, cyanopindolol, and propranolol but not by ketanserin, ritanserin cyproheptidine, (−)-pindolol, ICS-205930, MDL-72222, phentolamine, or idazoxan, a profile that has been interpreted as indicating that 5-HT_{1C} sites predominate in *m*-CPP's effect, although a 5-HT_{1B} component may also be involved (Kennett and Curzon, 1988a,b). This interpretation was supported by a high correlation between the affinities of these and other antagonists for 5-HT_{1C} ver-

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sus 5-HT_2 sites and the potency of these agents to block *m*-CPP's hypophagic effect (Kennett and Curzon, 1988a). Other studies have demonstrated that several 5-HT antagonists (metergoline, methysergide, cyproheptidine, and mianserin) can increase food intake in rodents (Curzon, 1990; Dourish et al., 1989; Fletcher, 1988). Different patterns of antagonist effects and other data also suggest that *m*-CPP's hypophagic effect is not simply a consequence of nonspecific malaise or the locomotor suppressant actions of *m*-CPP and TFMPP (Curzon, 1990; Kennett and Curzon, 1988a,b).

Rats treated with the monoamine oxidase-inhibiting antidepressant, clorgyline, or with lithium for 3 weeks no longer manifested a hypophagic response to *m*-CPP (Aulakh et al., 1989; Cohen et al., 1983), whereas similar long-term treatment with the tricyclic antidepressant, imipramine, led to an approximate 2-fold increase in *m*-CPP's hypophagic effects at *m*-CPP doses of 1.25 and 2.5 mg/kg (Aulakh et al., 1987). This latter action might represent a pharmacokinetic effect of tricyclics on *m*-CPP metabolism like that reported in humans (Zohar et al., 1988).

Intake of hypertonic saline was selectively reduced by *m*-CPP and MK-212 in rats; because water intake was unchanged, it was suggested that 5-HT_{1C} receptors may participate in the control of salt intake (Neill and Cooper, 1989). Some parallels with food intake are noteworthy, because 5-HT_{1A} agonists and benzodiazepines have been known for some time to increase salt intake and food intake (Cooper and Desa, 1987; Cooper et al., 1988; Dourish et al., 1985, 1986b).

c. NEUROENDOCRINE MEASURES. In studies of the hypothalamic-pituitary-adrenal axis, *m*-CPP produced dose-dependent increases in plasma corticosterone, ACTH, and CRH in rodents and in cortisol, ACTH, and CRH in rhesus monkeys (Aulakh et al., 1988b; Bagdy et al., 1989a; Calogero et al., 1989, 1990; Wozniak et al., 1989b). Other substituted piperazines, including TFMPP, MK-212, and quipazine also increased corticosterone and, in some cases, ACTH in rodents (Fuller and Snoddy 1979; King et al., 1989; Koenig et al., 1987; Krulich et al., 1979; Lorens and Van de Kar, 1987; Van de Kar et al., 1981). These responses have generally been reported to be blocked by metergoline and mesulergine, partially blocked by ritanserin, but not blocked by ketanserin, spiperone, or (−)-pindolol—data recently reinterpreted as most likely indicative of a 5-HT_{1C}-mediated effect as the primary mode of these neuroendocrine effects of *m*-CPP (Bagdy et al., 1989b; King et al., 1989).

5-HT-elicited release of CRH from explanted rat hypothalami was blocked by metergoline, ritanserin, and ketanserin (Calogero et al., 1989). CRH release can also be elicited not only by *m*-CPP but also by 8-OH-DPAT and DOI, suggesting that 5-HT_{1A} as well as 5-HT_{1C}/5-HT_2 receptors are capable of activating the hypothalamic-pituitary-adrenal axis, in keeping with other in vivo data (Calogero et al., 1989; Koenig et al., 1987; Lorens and Van de Kar, 1987). CRH release by 5-HT was unaffected by cholinergic or α-adrenergic blockade (Calogero et al., 1989).

m-CPP's effects on ACTH and corticosterone in rats were totally blocked by hyperimmune CRH rabbit serum and by dexamethasone pretreatment; in contrast, these responses to 8-OH-DPAT and DOI were only partially blocked by the anti-CRH serum, and, whereas dexamethasone markedly suppressed ACTH responses to 8-OH-DPAT and DOI, corticosterone responses were only diminished approximately 50% by dexamethasone (Calogero et al., 1990). These data were interpreted as indicating that *m*-CPP's activation of this endocrine axis is essentially exclusively via CRH without direct effects on the pituitary, whereas the other 5-HT agonists appear to act via actions on hypothalamic CRH and on pituitary ACTH release (Calogero et al., 1990; Di Renzo et al., 1988); however, as noted below, increased vasopressin elicited by *m*-CPP also may be involved.

Plasma β-endorphin was also increased by *m*-CPP, MK-212, and quipazine in rodents (Bagdy et al., 1991; Bruni et al., 1982; Koenig et al., 1987). The response to MK-212 was blocked by metergoline, ritanserin, ketanserin, and mianserin but not by spiperone or pindolol, results interpreted as suggesting a 5-HT_2 mechanism (Koenig et al., 1987). Unlike the β-endorphin response to 8-OH-DPAT which could be blocked by anti-CRH serum, *m*-CPP's response was little affected; as with DOI's effects, *m*-CPP-induced elevations of plasma β-endorphin were only partially reduced by pituitary stalk section, suggesting that some of *m*-CPP's effect on β-endorphin might be directly on the pituitary release of this hormone (Bagdy et al., 1991).

m-CPP elicited plasma prolactin elevations in rodents and rhesus monkeys (Aloi et al., 1984; Aulakh et al., 1988b; Clemens et al., 1978; Preziosi et al., 1983; Quattrone et al., 1981). TFMPP, MK-212, and quipazine also elicited prolactin elevations (Clemens et al., 1978; Krulich et al., 1979; Kuhn et al., 1981; Meltzer and Fleming, 1976; Van de Kar and Bethea, 1982; Van de Kar et al., 1989). Metergoline was an effective antagonist, whereas ketanserin and naloxone were not (Aloi et al., 1984; Meltzer et al., 1983; Preziosi et al., 1983). A shift to the left in the dose-response curve for *m*-CPP's effects on prolactin was found after destruction of 5-HT neurons by intraventricularly administered 5,7-DHT (Quattrone et al., 1981). Other studies have shown that neurons from the dorsal raphe and not the median raphe stimulate prolactin secretion (Van de Kar and Bethea, 1982).

m-CPP, TFMPP, MK-212, and quipazine all produced vasopressin release (Brownfield et al., 1988; Hashimoto et al., 1982; Iovino and Steardo, 1985; G. Bagdy et al., unpublished data). The MK-212-evoked vasopressin release was inhibited by LY53857, a 5-HT_2 antagonist (Brownfield et al., 1988). However, the failure of DOI,

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and of 8-OH-DPAT or RU 24969, to induce vasopressin release (G. Bagdy et al., unpublished data) suggests that vasopressin release may be 5-HT_{1C} mediated, although more comprehensive antagonist studies are needed.

TFMPP, MK-212, and quipazine increased plasma renin concentrations (Alper and Snider, 1987; Lorens and Van de Kar, 1987; Van de Kar et al., 1981). The renin responses to MK-212 and quipazine were blocked by LY53857 (Alper and Snider, 1987; Lorens and Van de Kar, 1987).

An increase in plasma growth hormone after intravenous *m*-CPP administration, which was blocked by metergoline, was observed in rhesus monkeys (Aloi et al., 1984); very few studies of the effects of other 5-HT agonists or antagonists on growth hormone have been conducted in rodents, and in the few reports available, highly variable results have been obtained (Murakami et al., 1986; Richards et al., 1980).

m-CPP decreased the plasma thyroid-stimulating hormone concentration, and this effect was blocked by metergoline pretreatment (Di Renzo et al., 1982). This was not a direct action on the pituitary, because pituitaries studied in vitro were unresponsive to a range of doses of *m*-CPP (Di Renzo et al., 1988).

d. CARDIOVASCULAR MEASURES. *m*-CPP, TFMPP, and quipazine were originally described as partial agonists at 5-HT receptors in the isolated rat jugular vein (Cohen and Fuller, 1983). The actions of *m*-CPP and TFMPP were predominantly those of an antagonist of 5-HT's contractile effect; both phenylpiperazines were very weak agonists. Pressor effects of *m*-CPP were first described by Bagdy and coworkers (1987) using pithed rats; *m*-CPP produced a dose-dependent doubling of mean arterial pressure which was blocked by metergoline and ritanserin, but not by prazosin, given in combination with yohimbine. Heart rate was also increased to a lesser extent by *m*-CPP. *m*-CPP's effects thus seem to be quite different from those of its parent molecule, trazodone, which is a potent 5-HT_2 receptor antagonist in the peripheral vasculature (Leff and Martin, 1986). Other phenylpiperazines (quipazine or TFMPP) reduced blood pressure in spontaneously hypertensive rats (Fuller et al., 1981c).

In intact, conscious rats, *m*-CPP increased blood pressure, heart rate, and plasma catecholamine levels (Bagdy et al., 1987, 1988, 1989a,b). The pressor effects were blocked by ritanserin and ketanserin; metergoline, xylamidine, and prazosin partially antagonized these effects. Ritanserin-pretreated rats developed inverted responses to *m*-CPP; in these rats, *m*-CPP reduced blood pressure and heart rate; these effects of *m*-CPP were blocked by metergoline (Bagdy et al., 1989b). Heart rate increases produced by *m*-CPP were antagonized by ketanserin, pindolol, and yohimbine. The 2-fold increases in plasma norepinephrine and >10-fold increases in plasma epinephrine produced by 2.5 mg/kg of *m*-CPP were dose dependently attenuated by ritanserin. The pressor effects of *m*-CPP thus appear to involve several mechanisms including a direct, initial vasoconstrictor effect and a delayed vasoconstriction which may likely be related to the release of catecholamines and, possibly, vasopressin and renin as well (Bagdy et al., 1989b).

e. LOCOMOTOR ACTIVITY. *m*-CPP, TFMPP, and MK-212 produced dose-dependent reductions in spontaneous ambulatory motor activity and rearing in rats studied in both caged and open field environments (Aulakh et al., 1989; Kennett et al., 1988a; Klodzinska et al., 1989; Lucki and Fraser, 1982; Lucki et al., 1989). Similar effects also followed injection of smaller concentrations of *m*-CPP into the third ventricle (Kennett and Curzon, 1988a). Motor coordination was impaired by *m*-CPP when trained or untrained rats were studied using a rotating drum but not when a stationary elevated bar was used (Kennett and Curzon, 1988a). Other motor phenomena observed with many other serotonergic agents acting at 5-HT_{1A}, 5-HT_2, and other sites, including the 5-HT behavioral syndrome, head twitches, or wet dog shakes in rodents and myoclonus in guinea pigs, were not observed in most of these studies with *m*-CPP and related compounds (Kennett and Curzon, 1988a; Lucki et al., 1989; Luscombe et al., 1982). Furthermore, *m*-CPP, TFMPP, and several other related agents blocked head twitches induced by 5-MEODMT, 5-HTP, and quipazine and thus appeared to act as full antagonists of these central 5-HT_2-mediated responses (Simansky and Schechter, 1988).

In two strains of mice (BALB and CD), *m*-CPP dose dependently reduced basal locomotor activity; only in the BALB mice was exploratory motor activity in a novel environment reduced by *m*-CPP (Maj and Lewandowski, 1980); a third mouse strain (C57BL/6) was unaffected by identical doses of *m*-CPP in the same experimental paradigms (Vetulani et al., 1982). In rhesus monkeys, *m*-CPP produced sedation (as indicated by eye closure and a relaxed posture) and a slowing in coordinated motor activities (Aloi et al., 1984; Szele et al., 1988).

Premature rat pups also responded to *m*-CPP with decreased "behavioral activation" (a composite of several locomotor activities) and decreased probing but increased mouthing and grooming behaviors, a behavioral pattern that was considerably different from that produced by 8-OH-DPAT, but generally similar to behaviors induced by DOI (Kirstein and Spear, 1988). Immature (5-day-old) rat pups, but not 20-day-old rats, also demonstrated increases in stereotyped mouthing and grooming behaviors after *m*-CPP treatment (Jackson and Kitchen, 1989). In 4-day-old rat pups, TFMPP also produced increased grooming behaviors, including face washing and head wiping, and also increased yawning, effects not duplicated by 5-HT_{1A} agonists or DOI; in 21-day-old animals, TFMPP lacked these effects, but it reduced ACTH-induced grooming and increased ACTH-

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induced stretching (Kirstein et al., 1990). Dose-dependent increases in purposeless chewing behavior after *m*-CPP, TFMPP, or quipazine treatment were reported in adult rats (Stewart et al., 1989).

Antagonists of *m*-CPP's locomotor slowing effects included methysergide and mianserin; metergoline was partially effective, whereas ketanserin, ritanserin, piramperone, cyproheptidine, ipsapirone, gepirone, ICS 205–930, pindolol, iodocyanopindolol, idazoxan, and other adrenergic, cholinergic, and dopaminergic agents were inactive (Kennett et al., 1988a; Klodzinska et al., 1989; Lucki et al., 1989; Lucki and Wieland, 1990). Purposeless chewing behavior induced by *m*-CPP was antagonized by pretreatment with mianserin, methiothepin, propranolol, and the anticholinergic drugs scopolamine and benzhexol but not by ketanserin, spiperone, ICS 205–930, or methylscopolamine (Stewart et al., 1989). Repeated administration of *m*-CPP or TFMPP to rats for 1 to 2 weeks led to an attenuation of the locomotor response to a test dose of *m*-CPP or TFMPP but no change in the ability of 8-OH-DPAT or 5-MEODMT to produce the 5-HT behavioral syndrome (Sills et al., 1985), results in keeping with other data that these effects are mediated by different 5-HT subsystems.

f. OTHER BEHAVIORAL MEASURES: CONDITIONED AVOIDANCE RESPONDING, DRUG DISCRIMINATION PARADIGMS, AND ANIMAL MODELS OF ANXIETY AND DEPRESSION. *m*-CPP, TFMPP, and MK-212 blocked conditioned avoidance responding in rats, pigeons, and monkeys studied with several different paradigms, unlike the increases in punished responding that have generally been reported after treatment with benzodiazepines or the 5-HT_{1A} agonists 8-OH-DPAT, buspirone, or gepirone (Brady and Barrett, 1985; Gleeson et al., 1989; Li et al., 1990; Marek et al., 1989; Martin et al., 1988, 1989; McKearney, 1989a, 1990). These putative anxiogenic responses to *m*-CPP were blocked by methysergide, metergoline, and mianserin but not by ketanserin or piramperone (Martin et al., 1988, 1989; McKearney, 1989a).

In tests of social interaction and of activity in a light/dark X maze, which make up two suggested animal models for anxiety, low doses (0.1 to 1.0 mg/kg) of *m*-CPP and TFMPP reduced total social interaction time and also activity in the light (Curzon et al., 1991; Kennett and Blackburn, 1990; Kennett et al., 1989). Total locomotion was only reduced by the highest dose of *m*-CPP. Administration of very small doses (1 to 4 μg/kg) of *m*-CPP intraventricularly or into the hippocampus, but not the amygdala, similarly reduced social interactions; injections of these doses of *m*-CPP into the hippocampus or the amygdala did not have a significant effect on overall locomotion (Kennett et al., 1989; Whitton and Curzon, 1990). These putative anxiogenic effects of *m*-CPP and TFMPP were blocked by mianserin, metergoline, and cyproheptidine but not by ritanserin, ketanserin, (−)-propranolol, or cyanopindolol; low, but not high, doses of ICS 205–930 also blocked these effects, as did chronic pretreatment with chlordiazepoxide (Kennett et al., 1989). In subsequent studies, single doses of chlordiazepoxide or of the 5-HT_3 antagonist, BRL 46470, significantly attenuated the effects of *m*-CPP in the light/dark X maze (Kennett and Blackburn, 1990).

The profile of antagonist effects on both the locomotor-slowing activity and especially on the anxiogenic like effects of *m*-CPP have been interpreted as implicating 5-HT_{1C} receptor mediation of these effects (Curzon and Kennett, 1990; Kennett and Curzon, 1988a; Lucki et al., 1989); however, some possible contribution from 5-HT_{1B} sites has been suggested (Lucki et al., 1989), and the antagonism of *m*-CPP's anxiogenic effects by 5-HT_3 antagonists (Kennett and Blackburn, 1990; Kennett et al., 1989) suggests multiple sites for these effects of *m*-CPP in rodents. Although these results are in keeping with other data indicating that various 5-HT_3 antagonists have anxiolytic actions in several animal models (Costall et al., 1990) and with data that *m*-CPP has a high affinity for 5-HT_3-binding sites in brain and other tissues (Glennon et al., 1989; Kilpatrick et al., 1987; Neijt et al., 1988), it is in apparent conflict with data that *m*-CPP is a full competitive antagonist at 5-HT_3 sites in some peripheral tissues (Ireland and Tyers, 1987; Kilpatrick et al., 1987).

Altered behavioral responses to *m*-CPP and other phenylpiperazines can be produced by pretreatment with neurotoxins and other drugs and by brain stimulation. For example, locomotor, prolactin, and penile erection responses to *m*-CPP were enhanced after the destruction of 5-HT neurons by 5,7-DHT (Berendsen et al., 1990b; Lucki et al., 1989; Quattrone et al., 1981); enhanced responses after 5,7-DHT treatment were similarly obtained with 5-HT_{1A} and 5-HT_{1C}/5-HT_2 agonists, including 8-OH-DPAT, DOI, and 5-MEODMT but not quipazine or RU 24969 (Dall'Olio et al., 1985; Nisbet and Marsden, 1984; Pranzatelli et al., 1990; Trulson and Jacobs, 1978). On the other hand, *m*-CPP's suppressant effects on locomotor activity were reduced by chronic pretreatment with the monoamine oxidase inhibitors, clorgyline, phenelzine, or nialamide; similar pretreatment with the antidepressants, desmethylimipramine or iprindole, was without effect in one study, whereas imipramine enhanced *m*-CPP's effects in another study (Aulakh et al., 1987; Cohen et al., 1983; Lucki et al., 1989).

m-CPP and TFMPP and two other *l*-arylpiperazines, 1-NP and PAPP, were full antagonists of the 5-HT_2-mediated head twitch response produced by 5-MEODMT or 5-HTP in mice and the head twitch produced by quipazine in rats (Simansky and Schechter, 1988). It is of note that quipazine and MK-212 elicited head twitching in rodents (Clements-Jewery et al., 1980; Malick et al., 1977), because both of these arylpiperazines were partial agonists, stimulating phosphatidylinositol hydrolysis in rat cortex, whereas *m*-CPP and TFMPP, in

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agreement with the behavioral findings, were full antagonists of 5-HT-induced phosphatidylinositol hydrolysis in cortex (Conn and Sanders-Bush, 1987). Whereas 1-NP and PAPP antagonized the 5-HT_{1A}-mediated behavioral syndrome produced by 5-MeODMT in rats and, at higher doses, produced this syndrome, *m*-CPP or TFMPP had neither of these effects (Simansky and Schechter, 1988). *m*-CPP, TFMPP, DOI, and quipazine, but not a putative 5-HT_{1B} agonist, CGS 12066B, potentiated another effect of 8-OH-DPAT, the elicitation of spontaneous tail flicks; the *l*-phenylpiperazines and DOI also potentiated the tail flick response to other 5-HT_{1A} agonists or partial agonists, including lisuride, buspirone, and flesinoxan, whereas the *l*-phenylpiperazines had no agonist effects alone on this measure (Bervoets et al., 1990).

In some behavioral studies in which TFMPP was used as the training drug in drug discrimination paradigms, dose-dependent responses equivalent to the TFMPP cue were found for *m*-CPP and the 5-HT-releasing drugs, fenfluramine and norfenfluramine, as well as RU 24969; in contrast, 2,5-dimethoxy-4-methylphenylisoprophlamine, DOI, 8-OH-DPAT, 5-MEODMT, 2,5-DMA, quipazine, and other drugs did not generalize to the TFMPP cue (Cunningham and Appel, 1986; Glennon et al., 1984; McKenney and Glennon, 1986; Schecter, 1988). However, when several other drugs were used as cueing agents, including ethanol, 3,4-methylenedioxyamphetamine, or THBC, TFMPP did generalize to these agents (Schecter, 1988; Signs and Schechter, 1988). TFMPP, *m*-CPP, MK-212, quipazine, diazepam, and other agents did not generalize to 8-OH-DPAT and other 5-HT_{1A} agents used as cue drugs in similar drug discrimination paradigms (Cunningham et al., 1987; Fozard et al., 1986; Glennon, 1986; Lucki, 1988; Tricklebank et al., 1987).

Of related interest, in another paradigm in which ethanol and benzodiazapines have antiaversive effects (aversion responses in rats elicited by stimulation of the periaqueductal gray brain region), *m*-CPP, TFMPP, and DOI all had similar antiaversive effects also (Jencke et al., 1990). On the basis of results with a series of agonists and antagonists in this model, it was suggested that the effects of *m*-CPP were most likely mediated by 5-HT_{1C} receptors (Jencke et al., 1990).

In some other behavioral models of anxiety, *m*-CPP, TFMPP, quipazine, and 8-OH-DPAT all decreased reactivity to acoustic or tactile stimuli but did not increase the rate of habituation to these stimuli, as did ritanserin and other 5-HT antagonists, or decrease habituation, as did fluoxetine (Davis et al., 1986; Geyer and Tapson, 1988). In the more complex potentiated startle procedure for which intense acoustic stimuli are paired with a light that was initially presented with an electric shock (a paradigm in which benzodiazepines and, to a varying extent, 8-OH-DPAT and the azapirones are active), *m*-CPP only reduced the amplitude of the startle response but did not exhibit any blocking effect on the potentiated startle (Davis et al., 1988; Mansbach and Geyer, 1988).

In the forced swim test model for depression, in which most antidepressant drugs are active, neither *m*-CPP nor DOB were active; in contrast, 8-OH-DPAT, buspirone, and other azapirones were all effective when given subchronically in producing dose-related decreases in immobility in the water (Cervo et al., 1989; Cervo and Saminin, 1987; Press et al., 1989; Wieland and Lucki, 1990). In another study, TFMPP was also found to be inactive in the forced swim test; however, small single doses of TFMPP reversed the positive effects of a 7-day treatment with the antidepressant, desipramine (Cervo et al., 1989). Further studies revealed that very small amounts of TFMPP injected into the ventral tegmental area, but not other brain areas, blocked desipramine's effect; metergoline pretreatment prevented this TFMPP effect (Cervo et al., 1989). A 5-HT-mediated action on mesolimbic neurons innervating the nucleus accumbens was postulated as the basis for this action of TFMPP (Cervo et al., 1989).

TFMPP was also not active in several other depression models in rodents; it neither affected reserpine-induced hypothermia nor increased yohimbine-induced toxicity (Frances, 1988). However, TFMPP and *m*-CPP had tricyclic antidepressant-like activity in normalizing a social behavioral deficit state produced by isolation and in antagonizing oxotremorine-induced hypothermia (Frances, 1988; Frances et al., 1990a,b). The effects of TFMPP and *m*-CPP on the social behavioral deficit state were blocked by penbuterol but not by ritanserin, mianserin, cyproheptidine, or ICS 205–930 (Frances et al., 1990b). Opposite effects—an increase in isolation-induced social behavioral deficit—were produced by 8-OH-DPAT, buspirone, and ipsapirone (Frances et al., 1990a).

In another pharmacological model, the marked aggressive behavior produced by apomorphine in clonidine-pretreated grouped rats was dose dependently suppressed by *m*-CPP (Hahn et al., 1982). Stereotyped movements induced by repeated treatment with morphine or methadone were prevented by *m*-CPP or fenfluramine; a 5-HT-deficit state in animals chronically treated with narcotics was previously postulated (Cervo et al., 1981).

g. SEXUAL FUNCTION, NOCICEPTION, SLEEP, AND BRAIN ENERGY METABOLISM. *m*-CPP given intravenously or subcutaneously in doses from 0.1 to 3 mg/kg produced penile erections with ejaculations in rats and rhesus monkeys but not humans (Aloi et al., 1984; Berendsen and Broekkamp, 1987; Berendsen et al., 1990a; Murphy et al., 1989a; Szele et al., 1988). TFMPP and MK-212 also produced penile erections in rats; the *m*-CPP precursor, trazodone, has the side effect of leading to prolonged penile erections (priapism) and increased libido in humans (Abber et al., 1987). DOI produces penile erections in rodents only when coadministered with 5-HT_2 antagonists (Berendsen et al., 1990a).

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The rank order of agonist efficacy (MK 212 > *m*-CPP > TFMPP > quipazine > DOI) in producing penile erections in rats and the profile of antagonist efficacy in blocking *m*-CPP-induced penile erections in rats and rhesus monkeys both corresponded closely to the ratio of affinity of these agonists and antagonists for 5-HT_{1C} versus 5-HT_2 or 5-HT_{1B} sites, suggesting that this effect of *m*-CPP is mediated by central 5-HT_{1C} receptors (Berendsen et al., 1990a; Szele et al., 1988). The actions of *m*-CPP on penile erections in rats were also antagonized by some 5-HT agonists: 8-OH-DPAT > 5-MEODMT > DOI (Berendsen et al., 1990a).

m-CPP given intravenously increased the firing rates of cavernous nerves supplying the penis but not the bladder; cavernous nerve firing was accompanied by an increase in intracavernous pressure in rats (Steers and De Groat, 1989). These effects were observed both in intact, anesthetized rats and in rats studied after acute or chronic spinal transection; as in the other studies in rats and monkeys, *m*-CPP's effects were blocked by pretreatment with metergoline and were interpreted as representing a 5-HT receptor-mediated activation of preganglionic cholinergic pathways in the pelvic nerve (Steers and De Groat, 1989). Earlier studies in squirrel monkeys had revealed that intravenously administered 5-HT, but not stimulation of the raphe nuclei, elicited penile erections, with a similar conclusion that this effect was mediated by peripheral rather than central mechanisms (Aloi et al., 1984; Bachman and Katz, 1977; Berendsen and Broekkamp, 1987; MacLean et al., 1963; Szele et al., 1988).

m-CPP, TFMPP, and MK-212 all had antinociceptive effects in squirrel monkeys, increasing the tolerated electrical shock intensity in a paradigm in which shock intensity is regulated by the animals; methysergide, but not ketanserin or piramperone, antagonized this action of the substituted piperazines (McKearney, 1989b). In rodents, *m*-CPP had antinociceptive effects on the hot plate test which were blocked by metergoline pretreatment; however, *m*-CPP was inactive in the tail immersion test (Rochat et al., 1982). Shock-induced analgesia, a model that is sensitive to fenfluramine, 5-MEODMT, and MK-212, was unaffected by TFMPP or quipazine (Tricklebank et al., 1982). Sleep in rats was affected by TFMPP in a dose-dependent manner; rapid eye movement sleep was markedly suppressed, whereas non-rapid eye movement sleep was relatively unaffected, although δ sleep waves were increased (Pastel and Fennstrom, 1987).

Local cerebral glucose utilization was generally decreased by *m*-CPP, quipazine, and some other piperazine-containing 5-HT agonists (Freo et al., 1990; Grome and Harper, 1986). *m*-CPP decreased glucose utilization in 28 of 71 (40%) of the rat brain regions studied, with reductions in all cortex areas, the hippocampus, some parts of the amygdala, and the caudate nucleus but not other basal ganglia structures; there were no changes in the raphe nuclei (Freo et al., 1990). MK-212 and quipazine decreased glucose utilization in many brain regions; MK-212 also reduced glucose utilization in the raphe nuclei (Grome and Harper, 1986). These results are in contrast to those observed with agents such as 5-MEODMT and 8-OH-DPAT, which increased brain glucose utilization, apparently related to the induction of the 5-HT behavioral syndrome (Kelly et al., 1988).

C. Other Substituted Phenylpiperazines Studied in Humans

1. 6-Chloro-2-(l-piperazinyl)pyrazine. MK-212, 10 to 40 mg orally, given to healthy male volunteers led to dose-related increases in serum cortisol concentrations after 20 or 40 mg and increases in serum prolactin concentrations after 40 mg; serum growth hormone was not altered (Lowy and Meltzer, 1988). Systolic and diastolic blood pressure were increased without a change in heart rate. Side effects included nausea, mild nonmigrainous headaches, and difficulty thinking. Significant increases in self-ratings of "anxious" and decreases in "feel good overall" were found (Lowy and Meltzer, 1988).

Patients with OCD given 20 mg of MK-212 had significantly smaller increases in plasma cortisol and prolactin concentrations compared with healthy controls (Bastani et al., 1990). Compared to placebo, MK-212 produced small but statistically significant increases in self-ratings of "feeling strange," "restless," "active," "anxious," "high," "calm," "depressed," "dizzy," and "nauseated" which were of equal magnitude in the patients with OCD and the controls. MK-212 did not affect OCD symptoms. Anecdotally, alcoholic subjects, but not healthy controls, reported LSD-like effects after MK-212 treatment (Lowy and Meltzer, 1988).

MK-212 had highest affinity for 5-HT_3 sites labeled with [^{3}H]quipazine, with an IC_{50} of 29 nM, comparable to that of *m*-CPP (20 nM) (Glennon et al., 1989). Its affinity at 5-HT_{1C} sites was 15-fold less than that of *m*-CPP (K_D 6.16) and its rank order of affinities at other sites was 5-HT_{1A} (5.32) > 5-HT_{1B} (5.03) > 5-HT_2 (4.76) (Hoyer, 1988a, 1989). MK-212 was active at 5-HT sites that increase phosphatidylinositol turnover (Conn and Sanders-Bush, 1987); it was a partial agonist in rat cortex and a full agonist at 5-HT_{1C} sites in choroid plexus (Conn and Sanders-Bush, 1987). MK-212 was a potent anorectic in rats, increased body temperature in rats and rabbits, but had only small effects on locomotor activity in mice and rats; it also produced head twitches and the 5-HT syndrome in rats (Clineschmidt, 1979). These latter three effects constituted MK-212's greatest differences from *m*-CPP, which, as described above, markedly slowed locomotor activity, did not produce the 5-HT syndrome, and antagonized 5-HT_2-mediated head twitches.

The behavioral effects of MK-212 in rodents were blocked by a number of 5-HT antagonists, including metergoline, cinanserin, and cyproheptidine, and its neu-

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roendocrine effects (increased plasma corticosterone and β-endorphin concentrations) were preferentially blocked by agents with higher 5-HT_2 (or 5-HT_{1C}) selectivity, i.e., ketanserin, ritanserin, and altanserin, and not by the 5-$HT_{1A/1B}$ antagonist, (−)-pindolol (Clineschmidt, 1979; Koenig et al., 1987). However, in drug discrimination studies using MK-212 as the cue drug, ketanserin did not block the discriminative stimulus properties of MK-212; LSD partially substituted for MK-212 in this paradigm (Cunningham et al., 1986). In an electrophysiological study using iontophoretic drug administration, MK-212 was only weakly active compared to 5-HT in inhibiting the firing of neurons in the rat cortex, but it equaled 5-HT's inhibitory effects on neurons in the dorsal raphe (Yarbrough et al., 1984).

2. Quipazine. Quipazine [2-(1-piperazinyl)quinoline] given in a 50-mg oral dose to eight normal subjects and 15 patients with neurological disorders led to modest elevations in plasma cortisol concentrations, inconsistent changes in other plasma hormone levels (prolactin, growth hormone, and gonadotropins), and frequent gastrointestinal and other side effects, including nausea, increased intestinal peristalsis, epigastric pain, vomiting, rashes, itching, and a migraine headache in a patient with a history of migraine (Parati et al., 1980).

Quipazine had moderate affinity for 5-HT_1 sites (pK_D 5.5 to 6.7), with highest affinity at the 5-HT_{1C} site among the 5-HT_1 sites; this was, however, 10 times lower than *m*-CPP's affinity for the 5-HT_{1C} site; it had a similar affinity for 5-HT_2 sites (6.2) but had highest affinity for 5-HT_3 sites (8.7) (Hoyer, 1988a, 1989; Hoyer et al., 1989). It also bound to the 5-HT transporter site (Van Wijngaarden et al., 1990).

In rodents, quipazine increased plasma prolactin and reduced plasma luteinizing hormone concentrations (Lynch et al., 1984). Its prominent anorectic effects were blocked by ritanserin, pirenperone, and metergoline, implicating a 5-HT_2 or perhaps 5-HT_{1C} mediation of this effect (Shukla et al., 1990). However, pimozide also blocked quipazine-induced anorexia, and quipazine has been shown to have dopaminergic and β-adrenergic effects (Frances et al., 1980; Lynch et al., 1984; Rokosz-Pelc et al., 1980; Shukla et al., 1990). Quipazine produced head twitches in rodents and elicited complex behavioral changes in cats which resembled those produced by hallucinogens (Trulson et al., 1982). In drug discrimination studies, quipazine generalized to the LSD cue (White et al., 1981). Its behavioral effects were enhanced by 5-HT synthesis inhibition by *p*-chlorophenylalanine and were blocked by pretreatment with methysergide and other 5-HT antagonists, as well as by monoamine oxidase inhibitor pretreatment (Trulson et al., 1982).

3. 1-(2-Methoxyphenyl)piperazine. 2-MPP given to humans in doses up to 1.3 mg/kg intravenously lowered blood pressure; it also produced drowsiness and, in some patients, nausea and vomiting (Page et al., 1959). In larger oral doses (100 to 1000 mg/day) administered for up to 12 weeks, the hypertensive effect gradually dissipated. Side effects included prominent drowsiness and lethargy, with mental confusion; in some patients muscular jerking, nervous agitation, and regularly recurring dreams of impending disaster and death developed (Page et al., 1959).

2-MPP is a metabolite of the antipsychotic drug, millipertine (Caccia et al., 1985). 2-MPP had high affinity for rat brain 5-HT_1 ([^{3}H]5-HT) sites (K_i 35 nM), and considerably lower affinity for 5-HT_2 ([^{3}H]ketanserin) sites (K_i 3500 nM) (Lyon et al., 1986). At high doses, 2-MPP antagonized apomorphine-induced stereotypic and rotational behavior (Minard et al., 1979; Pawlowski et al., 1983). In drug discrimination studies using TFMPP as the cuing drug, 2-MPP showed complete generalization to the TFMPP stimulus (Lyon et al., 1986). It also had a marked hypotensive effect in rodents and produced dose-dependent hyperthemia and a number of other effects attributed to agonist activity at 5-HT receptors; the latter conclusion was reached on the basis of an effective antagonism of these effects by metergoline and cyproheptidine (Morphis et al., 1959; Page et al., 1959; Pawlowski et al., 1983).

D. Conclusions

These substituted phenylpiperazines and a related piperazine, MK-212, are noteworthy among 5-HT-selective agents because of the panoply of behavioral, neuroendocrine, temperature, and other effects they elicit in humans after single-dose oral or intravenous administration. The behavioral and physiological responses to *m*-CPP have been most completely characterized, and *m*-CPP's anxiogenic and other behavioral effects have been found to differ considerably in comparisons of patient groups with different neuropsychiatric disorders with healthy controls. Some *m*-CPP response differences related to age, gender, and pretreatment with 5-HT antagonists (metergoline, methysergide) and 5-HT uptake inhibitors (clomipramine, fluoxetine) have also been described.

Many of the effects of *m*-CPP and the related compounds in humans might have been predicted on the basis of the similar neuroendocrine responses (increased plasma cortisol and prolactin concentrations), hyperthermia, pressor effects, and behavioral responses (including anxiogenic changes) observed in animals and generally attributed to serotonergic mechanisms. However, assignment of these responses to actions at one or another or a combination of the still-evolving number of multiple 5-HT receptor subtypes continues to prove challenging.

In receptor-binding experiments in animals, *m*-CPP exhibits highest affinities for the 5-HT_{1C} and 5-HT_3 subtypes. A current, dominant hypothesis based primarily on correlations between relative antagonist efficacies in opposing certain of *m*-CPP's effects in rats and the

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binding site affinities of these antagonists in vitro attributes *m*-CPP's anxiogenic and a number of its other effects to 5-HT_{1C}-mediated agonist actions (Berendsen et al., 1990a; Fozard et al., 1986; Jencke et al., 1990; Kennett and Curzon, 1988a,b; Kennett et al., 1989). If this proves to be the case when more selective 5-HT_{1C} antagonists and agonists are discovered, this hypothesis would be in keeping with the recent description of a widespread distribution of neurons expressing 5-HT_{1C} receptor messenger RNA in the brain and spinal cord, particularly in the hippocampal areas of the limbic system, the basal ganglia, and such monoaminergic cell groups as the locus coeruleus, substantia nigra, and raphe and reticular nuclei (Hoyer, 1988b; Hoyer et al., 1986b; Molineaux et al., 1989).

Alternative hypotheses exist, and the newly discovered high affinity of *m*-CPP and related compounds for 5-HT_3 sites has been little explored in relation to the behavioral and other pharmacological effects of *m*-CPP, although there were two observations of an attenuation of *m*-CPP's anxiogenic effects in rats by 5-HT_3 antagonists (Kennett and Blackburn, 1990; Kennett et al., 1989). The 5-HT_{1C} hypothesis neglects the fact that binding affinities for the antagonists were determined in multiple tissues, some from different species, and the pharmacological antagonist studies were all done in rats (Berendsen et al., 1990a; Jenck et al., 1990; Kennett and Curzon, 1988a,b; Kennett et al., 1989). Other incompletely resolved issues in the evaluation of possible mechanisms for *m*-CPP's effects in humans include the known lack of 5-HT_{1B} sites in humans, because 5-HT_{1B} receptors in rodents are functionally important terminal autoreceptors with moderate to high affinity for *m*-CPP. Thus, extrapolation from rodent studies may be misleading; although the 5-HT_{1D} receptor may subserve similar terminal autoreceptor functions in humans as does the 5-HT_{1B} receptor in rats and mice, 5-HT_{1D} receptor pharmacology has not yet been well delineated (Hoyer and Middlemiss, 1989; Waeber et al., 1989, 1990). The facts that *m*-CPP and some related piperazines are antagonists at central and peripheral 5-HT_2 sites (Britt et al., 1988; Simansky and Schechter, 1988) and partial agonists (with, therefore, antagonist potential under some circumstances) at 5-HT_{1C} sites (Conn and Sanders-Bush, 1987) and may have autoreceptor effects via 5-HT_{1C} sites found in the raphe area (Mollineaux et al., 1989) must also be taken into account when considering the possible mechanisms of action of these interesting agents.

III. Azapirones

Buspirone, ipsapirone, and several other azapirones share potent, selective effects at the 5-HT_{1A} receptor. They have anxiolytic and probable antidepressant effects after longer-term administration (Glaser, 1988; Goa and Ward, 1986; Kennett et al., 1987b; Robinson et al., 1989; Taylor, 1988, 1989; Traber and Glaser, 1987; Yocca, 1990). Buspirone, ipsapirone, gepirone, and tandospirone have also been investigated in single-dose challenge paradigms in attempts to assess what physiological functions are subserved by 5-HT_{1A} receptors in humans and to evaluate whether the functional responsivity of the 5-HT_{1A} receptor complex might be altered in patients with neuropsychiatric disorders and following treatment of these disorders.

A. Single-Dose Studies in Humans

1. Ipsapirone, buspirone, and other azapirones in healthy normal subjects. Buspirone was the first azapirone given to humans in a neuroendocrine challenge paradigm. Doses of 30, 60, and 90 mg orally produced marked increases in plasma prolactin concentration, which appeared to be dose related; plasma growth hormone concentrations were also markedly increased in comparison to placebo administration (Meltzer et al., 1983). Buspirone in a dose of 10 mg orally had no effect on plasma prolactin, cortisol, or growth hormone concentrations (Cohn et al., 1986; Tollefson et al., 1989). Subsequent studies in which oral buspirone doses of 15 to 60 mg (Cowen et al., 1990; Dinan et al., 1990; Gregory et al., 1990; Seppala et al., 1987) and 0.5 mg/kg (Coccaro et al., 1990) were used all revealed substantial, dose-related increases in plasma prolactin concentrations. All of these studies were carried out in men; one study included a subgroup of female subjects who had somewhat greater prolactin increases than did the male subjects; a statistically significant greater prolactin level increase was found in the premenstrual period compared to early and mid-menstrual cycle challenges (Dinan et al., 1990). Dose-related increases in cortisol and growth hormone concentrations were elicited by buspirone in one small study (Cowen et al., 1990). However, another small study found inconsistent growth hormone, cortisol, and ACTH increases (Coccaro et al., 1990). No side effects except mild sedation were reported in any of these studies, although apparently no formal behavioral assessments were carried out.

Ipsapirone, given in doses of 0.1, 0.2, and 0.3 mg/kg to male volunteers, produced dose-dependent, statistically significant increases in plasma cortisol and ACTH levels at the two higher ipsapirone doses (Lesch et al., 1989, 1990e). Although plasma prolactin was not affected by ipsapirone, plasma growth hormone increases were modest but statistically significant at the highest dose of ipsapirone (Lesch et al., 1989; unpublished data). Ipsapirone also produced dose-dependent reductions in body temperature, without any effects on blood pressure, heart rate, or respiratory rate (Lesch et al., 1989, 1990d,e). Some subjects experienced mild nausea, vertigo, difficulty thinking, and fatigue; although these responses were not quantitated, there did not appear to be a strong dose-response relationship (Lesch et al., 1989, 1990d,e). In subsequent studies, healthy controls rated themselves on visual analog scales as feeling significantly more

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drowsy and less energetic after ipsapirone treatment than after placebo (Lesch et al., 1991a,c).

Gepirone, given in doses of 10 and 20 mg orally to male volunteers, produced significant increases in plasma prolactin, cortisol, ACTH, and β-endorphin levels after the 20-mg dose and increases in growth hormone concentration after both the 10- and 20-mg doses; prolactin levels decreased significantly after the 10-mg dose (Anderson et al., 1990). Body temperature was also significantly decreased after the 20-mg, but not the 10-mg, dose of gepirone. Self-ratings on a visual analog scale revealed increased feelings of being "light-headed" after both doses and mild nausea and greater drowsiness after 20 mg of gepirone. A number of these responses were intercorrelated (Anderson et al., 1990).

Tandospirone given in oral doses of 30, 40, and 50 mg led to statistically significant increases in plasma growth hormone concentration which were approximately equivalent after all three doses; plasma cortisol increases were highly variable, and no change in plasma prolactin concentrations was observed (Fischette et al., 1990).

Antagonist studies of the neuroendocrine and temperature responses to the azapirones revealed that the 5-HT_1/5-HT_2 antagonist metergoline completely blocked the prolactin response to buspirone (Coccaro et al., 1990; Gregory et al., 1990) and the ACTH response to ipsapirone; the cortisol increase and temperature decrease produced by ipsapirone were attenuated approximately 50% by metergoline pretreatment (Lesch et al., 1990d,e). Metergoline had negligible effects on the cortisol, ACTH, and growth hormone increases produced by buspirone (Coccaro et al., 1990; Cowen et al., 1990). Pindolol, which is a nonselective β-adrenergic antagonist and a 5-$HT_{1A/1B}$-selective antagonist, completely blocked the cortisol, ACTH, growth hormone, and temperature responses to ipsapirone (Lesch et al., 1990d,e), blocked the growth hormone response to buspirone (Cowen et al., 1990), and also tended to block the prolactin response to buspirone (Coccaro et al., 1990). The selective β_1-adrenergic antagonist betaxolol did not affect the temperature or most of the neuroendocrine responses to ipsapirone but potentiated the growth hormone increases (Lesch et al., 1990d,e).

2. Studies of the azapirones in patients with neuropsychiatric disorders. a. ANXIETY DISORDERS. Patients with panic disorder given 0.3 mg/kg of ipsapirone had significantly smaller temperature and plasma ACTH and cortisol responses compared with healthy volunteers (Lesch et al., 1991c). The patients rated themselves on visual analog scales as significantly more nervous after ipsapirone treatment compared to placebo; in contrast, the controls did not respond to ipsapirone with significant changes in anxiety but, rather, rated themselves as significantly more drowsy after ipsapirone treatment than after placebo. During the administration of ipsapirone but not placebo, three of 12 patients reported panic attack-like symptoms. Both the patients with panic disorder and the controls had significantly higher ratings on an acute panic disorder inventory after ipsapirone treatment; however, this inventory primarily detects somatic symptoms, and the state-trait anxiety inventory did not reveal statistically significant increases in the patients after ipsapirone compared to placebo. Plasma concentrations of ipsapirone were no different in the patients compared with the controls (Lesch et al., 1991a,c).

Patients with OCD given 0.3 mg/kg of ipsapirone or placebo had decreases in temperature and increases in plasma ACTH and cortisol concentrations that were no different from normal controls (Lesch et al., 1991a). On self-rated visual analog scales, the controls but not the patients rated themselves as more drowsy and less energetic after ipsapirone treatment than placebo. No alterations in rated OCD symptoms followed ipsapirone or placebo administration in the patients (Lesch et al., 1991a).

When the patients with OCD were rechallenged with ipsapirone after treatment for 3 months with fluoxetine at a mean dose of 52 mg/day, the temperature, ACTH, and cortisol responses to ipsapirone were all significantly reduced (Lesch et al., 1991b). On self-rated visual analog scales, the fluoxetine-treated patients responded to ipsapirone with statistically lower ratings of "drowsy" compared with their pre-fluoxetine responses to ipsapirone. Fluoxetine treatment was not associated with any change in peak ipsapirone plasma concentrations (Lesch et al., 1991b).

b. DEPRESSION. Patients with unipolar depression given 0.3 mg/kg of ipsapirone had significantly smaller reductions in temperature and smaller increases in plasma ACTH and cortisol concentrations than did normal controls (Lesch et al., 1990b,c). Baseline plasma cortisol levels were higher in the patients than the controls, but baseline ACTH and temperature were no different, and plasma concentrations of ipsapirone were no different in the patients compared with the controls. Successful treatment of the depressed patients with amitriptyline at a mean dose of 163 mg/day for at least 6 weeks led to a further impairment of the temperature, but not neuroendocrine, responses to ipsapirone compared either with the patients' responses before amitriptyline treatment or with normal controls (Lesch et al., 1990a, unpublished data).

In a study in which controls were not included, depressed patients manifested significant increases in plasma cortisol and growth hormone, but not prolactin, concentrations after 10 mg of gepirone compared to placebo (Rausch et al., 1990). After treatment with gepirone for 3 to 6 weeks at a dosage of 30 to 70 mg/day, single 10-mg doses of gepirone no longer led to increases in plasma cortisol or growth hormone levels that were different from placebo.

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c. PERSONALITY DISORDER. In a preliminary study of patients with personality disorder, the magnitude of increase in plasma prolactin after 0.5 mg/kg of buspirone was inversely correlated with a baseline measure of "impulsive aggression," which had previously been shown to be similarly correlated with prolactin responses to two other serotonergic agents, *m*-CPP and fenfluramine (Coccaro et al., 1990).

B. Relevant Studies of the Azapirones in Vitro and in Animals

1. Receptor affinity profile, second messenger system, and electrophysiological effects. In rodent brain, the azapirones have a highly preferential affinity for 5-HT_{1A} sites relative to other 5-HT sites; for example, the pK_D for ipsapirone at 5-HT_{1A} sites estimated in two studies was 7.73 and 8.26, which is >100-fold greater than its affinity for 5-HT_{1B} (3.87, 5.45), 5-HT_{1C} (4.53, <5), 5-HT_{1D} (4.88, <5), 5-HT_2 (5.07, 5.58), and 5-HT_3 (<5) sites (Hoyer, 1988a, 1989; Neijt et al., 1988; Van Wijngaarden et al., 1990). Ipsapirone's affinities for catecholamine and histamine receptors are in the micromolar range, again 100-fold lower than its affinity for 5-HT_{1A} sites (Van Wijngaarden et al., 1990). Similar data have been reported for buspirone, gepirone, and the other azapirones, as well as 8-OH-DPAT, with the one exception that buspirone has a higher affinity (7.38) than the other azapirones for the D_2 dopamine receptor (Van Wijngaarden et al., 1990).

The azapirones and other 5-HT_{1A} agonists inhibited forskolin-stimulated adenylyl cyclase in rat, guinea pig, and calf hippocampus (Bockaert et al., 1987; De Vivo and Maayani, 1985, 1986; Schoeftler and Hoyer, 1988), an effect mediated by a pertussis toxin-sensitive G protein, probably G_i (Harrington et al., 1988). The azapirones exhibited partial agonist activities in these assays, with intrinsic activities of 0.5 for buspirone and 0.75 for gepirone (De Vivo and Maayanni, 1986). Similar inhibitory effects on adenylyl cyclase were demonstrated using cloned 5-HT_{1A} receptors which were transfected and expressed in mammalian cell lines (Albert et al., 1990; Fargin et al., 1989). Ipsapirone and 8-OH-DPAT have also been shown to inhibit carbachol-stimulated phosphatidyl inositol hydrolysis in rat hippocampus (Claustre et al., 1988).

In electrophysiological studies, the azapirones and 8-OH-DPAT acted as partial agonists at 5-HT_{1A} receptors on hippocampal pyramidal cells, slowing their firing rate (Andrade et al., 1986; Andrade and Nicoll, 1987; Basse-Tomusk and Rebec, 1986; Blier and de Montigny, 1987; VanderMaelen et al., 1986). The 5-HT_{1A} agonists were full agonists at somatodendritic sites on the dorsal raphe nucleus, markedly inhibiting firing rates of these serotonergic neurons (Sprouse and Aghajanian, 1987, 1988), an effect that was antagonized by spiperone and propranolol (Adrien et al., 1989; Sprouse and Agahjanian, 1987). Both the presynaptic (raphe) and postsynaptic (hippocampal pyramidal cells) effects were interpreted as resulting from the opening of potassium channels coupled to 5-HT_{1A} receptors via a pertussis toxin-sensitive G protein (Andrade et al., 1986; Innis and Aghajanian, 1987; Innis et al., 1988).

2. Neurochemical effects. Buspirone, 8-OH-DPAT, and other 5-HT_{1A} agonists decreased 5-hydroxyindoleacetic acid and 5-HT turnover in rat brain (Fuller and Perry, 1989; Fuller et al., 1986; Hamon et al., 1988; Hjorth and Carlsson, 1982), results generally interpreted as reflecting autoreceptor effects at raphe somatodendritic receptors (Hjorth and Magnusson, 1988). A similar conclusion was derived from observations during in vivo microdialysis studies, which revealed reduced 5-HT release in rat hippocampus following systemically administered gepirone, buspirone, and ipsapirone but not their common metabolite, 1-(2-pyrimidyl)piperazine (Sharp et al., 1989). Buspirone and 8-OH-DPAT also produced increased brain norepinephrine turnover; in the case of buspirone, this appeared partially attributable to the α_2-adrenergic antagonist properties of 1-(2-pyrimidyl)piperazine, although indirect, 5-HT-mediated changes also appeared involved (Fuller and Perry, 1989; Maj et al., 1987). Proposals that 1-(2-pyrimidyl)piperazine may be responsible for, or contribute to, the antianxiety and antidepressant effects of the azapirones continue to generate some interest (Bianchi and Garattini, 1988; Caccia et al., 1986; Gower and Tricklebank, 1987; Rimele et al., 1987).

3. Physiological effects at different serotonin receptors. a. TEMPERATURE. The azapirones, 8-OH-DPAT and another 5-HT_{1A} agonist, LY165163, produced dose-dependent hypothermia in rats and mice; the temperature-decreasing effect of 8-OH-DPAT in rats was attenuated by methiothepin, pindolol, haloperidol, and quipazine (Goodwin et al., 1985a,b, 1987; Goodwin and Green, 1985; Green and Goodwin, 1987; Gudelsky et al., 1986; Hjorth, 1985; Hutson et al., 1987; Koenig et al., 1988; Nash et al., 1989; Wozniak et al., 1988). Some (Goodwin et al., 1987; Hillegaart, 1990; Wozniak et al., 1988), but not all (Hjorth, 1985; Hutson et al., 1987), investigators found that inhibition of 5-HT synthesis by *p*-chlorophenylalanine or serotonergic lesions produced by 5,7-DHT prevented 8-OH-DPAT-induced hypothermia, suggesting possible mediation of this response by presynaptic 5-HT_{1A} receptors. Hypothermic responses to 8-OH-DPAT were greater in female than male rats (Carlsson and Eriksson, 1987). Chronic (22 day), but not acute, treatment with the monoamine oxidase-inhibiting antidepressant, clorgyline, attenuated 8-OH-DPAT-induced hypothermia; in contrast, neither acute nor chronic treatment with the tricyclic antidepressants, imipramine or clomipramine, affected this response (Wozniak et al., 1988). Species differences exist, because the temperature response in mice was not blocked by propranolol or pindolol (Goodwin et al., 1985b; Goodwin and Green, 1985). A number of 5-HT antagonists enhanced the hypothermic responses to 8-OH-DPAT, including metergoline and ri-

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tanserin, whereas the 5-HT_2/5-HT_{1C} agonist, DOI, attenuated it (Bill et al., 1990; Goodwin et al., 1985a; Green and Goodwin, 1987).

b. FOOD INTAKE. Food, milk, and hypertonic saline intake, but not water intake, was increased by 8-OH-DPAT and the azapirones (Cooper and Desa, 1987; Cooper et al., 1988; Dourish et al., 1985, 1986b; Gilbert and Dourish, 1987; Hutson et al., 1988b; Neill and Cooper, 1988). These effects were blocked by pindolol, ipsapirone, and metergoline but not by ketanserin or ICS 205–930 (Hutson et al., 1988a). They were also blocked by *p*-chlorophenylalanine or 5,7-DHT and showed rapid tolerance as well as cross-tolerance to repeated administration of 8-OH-DPAT, ipsapirone, or buspirone (Bendotti and Saminin, 1986; Dourish et al., 1986a; Hutson et al., 1988b; Kennett et al., 1987a), results leading to the general hypothesis that they are presynaptic autoreceptor effects mediated by 5-HT_{1A} receptors.

c. NEUROENDOCRINE MEASURES. 8-OH-DPAT, ipsapirone, buspirone, and gepirone all increased corticosterone and ACTH concentrations in rats (Aulakh et al., 1988a,b,c; Gilbert et al., 1988b; Koenig et al., 1987, 1988; Lorens and Van de Kar, 1987; Matheson et al., 1989; Urban et al., 1986). Direct injections of 8-OH-DPAT into the paraventricular nucleus produced dose-dependent increases in corticosterone, and 8-OH-DPAT administered to explanted hypothalami elicited CRH release (Calogero et al., 1989; Haleem et al., 1989). 1–(2-pyrimidyl)piperazine was 10% as active as gepirone in eliciting corticosterone release (Matheson et al., 1989). 8-OH-DPAT's effects on ACTH were somewhat attenuated by hyperimmune CRH rabbit serum; ACTH responses were also partially preserved in pituitary stalk-sectioned animals, suggesting actions of 8-OH-DPAT at both the hypothalamic and pituitary levels (Calogero et al., 1989, 1990). Studies with antagonists revealed that the ACTH responses to 8-OH-DPAT, ipsapirone, and buspirone were blocked by spiperone; pindolol also attenuated these responses to 8-OH-DPAT and ipsapirone but not buspirone (Gilbert et al., 1988a; Koenig et al., 1987, 1988).

Plasma β-endorphin, but not vasopressin or renin, was increased by 8-OH-DPAT (Brownfield et al., 1988; Koenig et al., 1987; Lorens and Van de Kar, 1987). The β-endorphin increases were blocked by spiperone and pindolol but not by metergoline or cyanopindolol (Koenig et al., 1987).

Plasma prolactin in rodents has generally been found to be unaffected by gepirone or ipsapirone and variably altered by 8-OH-DPAT (Aulakh et al., 1988a; Di Renzo et al., 1989; Nash and Meltzer, 1989; Simonovic et al., 1984; Van de Kar et al., 1989). Buspirone increased plasma prolactin in rats, as did gepirone in rhesus monkeys (Heninger et al., 1987; Meltzer et al., 1982). Growth hormone was decreased by intravenous 8-OH-DPAT in rats (Aulakh et al., 1988a).

d. CARDIOVASCULAR RESPONSES. The azapirones and 8-OH-DPAT have centrally mediated blood pressure-lowering effects and, in some paradigms, decreased heart rate and sympathetic nerve discharge in normal and hypertensive rats, cats, and dogs (Fozarr et al., 1987; McCall and Harris, 1988; Ramage and Fozard, 1987). In addition, 8-OH-DPAT produced dose-dependent increases in plasma epinephrine and norepinephrine in rodents, as did some other 5-HT agonists; because these responses correlated highly with ACTH increases, a parallel activation of the sympathoadrenomedullary system and the hypothalamic-pituitary-adrenocortical axis was suggested (Bagdy et al., 1989a).

e. LOCOMOTOR ACTIVITY. Several azapirones, including buspirone and gepirone, as well as 8-OH-DPAT, induced some components of the "5-HT behavioral syndrome," specifically forepaw treading and flat body posture (Eison et al., 1986; Glaser et al., 1987; Hjorth and Carlsson, 1982; Moser et al., 1990; Smith and Peroutka, 1986). 8-OH-DPAT, in addition, elicited other elements of the syndrome including hyperlocomotion and head weaving; however, these elements were susceptible to blockade by non-5-HT_{1A}-selective agents including ketanserin, haloperidol, and reserpine, whereas 5-HT_1-selective antagonists such as pindolol and propranolol were effective in blocking reciprocal forepaw treading and flat body posture in reserpine-treated rats treated with 8-OH-DPAT (Tricklebank et al., 1987). Ipsapirone did not elicit the syndrome and, in fact, antagonized the syndrome elicited by 8-OH-DPAT (Smith and Peroutka, 1986). Also, in contrast to 8-OH-DPAT's ability to produce hyperlocomotion, the three azapirones induced a dose-dependent decrease in locomotion which was antagonized by propranolol (Hillegaart et al., 1989; Mittmann and Geyer, 1989). Attempts to localize the site of this action by direct injection of 8-OH-DPAT resulted in some evidence that the median, rather than the dorsal raphe, nucleus mediated this hyperlocomotion (Hillegaart and Hjorth, 1989).

f. OTHER BEHAVIORAL MEASURES: ANIMAL MODELS OF ANXIETY AND DEPRESSION AND DRUG DISCRIMINATION PARADIGMS. The azapirones and 8-OH-DPAT have been found in one experimental model of anxiety to increase punished responding maintained by food or water reinforcers in some, but not all, studies in rats and monkeys; however, these effects were weaker and more variable when compared with similar studies in which benzodiazepines were used (Carli and Samanin, 1988; Dourish, 1987; Eison et al., 1986; Geller and Hartmann, 1982; Glaser, 1988; Schuurman et al., 1991; Traber and Glaser, 1987; Weissman et al., 1984). Direct injection of 8-OH-DPAT into the median or dorsal raphe nuclei, but not the amygdala (where benzodiazepines are active), produced antipunishment effects (Carli and Samanin, 1988; Higgins et al., 1988; Hodges et al., 1987). A comparison of the administration of buspirone for 12 days versus 1 day did not yield any evidence that chronic treatment produced any greater effect on rates of suppressed responding in squirrel monkeys (Wettstein, 1988). Similarly, variable results have been found with the azapirones in social interaction tests and in the elevated X

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maze in rodents, with reports of anxiolytic, anxiogenic, or no effects (Critchley and Handley, 1987; Dunn et al., 1989; Moser et al., 1990; Moser, 1989; Pellow et al., 1987; Soderpalm et al., 1989; Traber et al., 1985).

Other animal models of anxiety appear to be more sensitive to possible anxiolytic effects of the 5-HT_{1A} agents. Aggression induced by foot shock in mice or by introducing intruder rats into home cages of resident rats was reliably reduced by ipsapirone (Schuurman et al., 1991; Traber et al., 1984). Isolation-induced ultrasonic calling in mice and rat pups was also reduced by 8-OH-DPAT or ipsapirone (Benton and Nastiti, 1988; Hard and Engle, 1988). The potentiated startle response in rats was reduced by buspirone, ipsapirone, and gepirone (Kehne et al., 1988; Mansbach and Geyer, 1988). Ipsapirone also enhanced social exploration under both light and dark conditions in one study; diazepam lacked this effect (Schuurman et al., 1991). Buspirone similarly increased exploration in a light/dark box in both rats and mice; this effect was prevented by lesioning 5-HT neurons using 5,7-DHT (Carli et al., 1989; Costall et al., 1988; Merlo Pich and Samanin, 1986).

In the forced swim test model for depression, in which most antidepressant drugs are active, buspirone, gepirone, ipsapirone, and tandospirone, together with 8-OH-DPAT, were all active in doses similar to desipramine in rats (Cervo et al., 1988; Cervo and Samanin, 1987; Kennett et al., 1987b; Wieland and Lucki, 1990); 8-OH-DPAT was also active in mice (Luscombe et al., 1988) and when injected directly into the dorsal raphe nucleus in rats (Cervo et al., 1988). These effects were blocked by propranolol, pindolol, methiothepin, and 5,7-DHT lesions (Cervo et al., 1988; Cervo and Samanin, 1987). The azapirones and 8-OH-DPAT, like typical antidepressants, also reversed the "learned helplessness" state produced by inescapable shock in rats (Giral et al., 1988; Martin, 1990).

In drug discrimination paradigms, 8-OH-DPAT, among the 5-HT_{1A} agonists, has been the most extensively studied agent. The azapirones as well as lisuride generalize to the 8-OH-DPAT discrimination cue, whereas RU 24969, 5-dimethoxy-4-methylphenylisopropylamine, TFMPP, MK-212, fenfluramine, sertraline, and LSD do not (Cunningham et al., 1987; Fozard et al., 1986; Glennon, 1986; Lucki, 1988; Mir et al., 1988; Tricklebank et al., 1987). Pindolol, but not ketanserin or MDL-72222, blocked the 8-OH-DPAT cue (Tricklebank et al., 1987). Buspirone and ipsapirone have also successfully been used as cueing drugs; in these cases, their effects generalize to 8-OH-DPAT but not to benzodiazepines (Hendry et al., 1983; Mansbach and Barrett, 1987; Spencer and Traber, 1987).

C. Conclusions: Azapirones

Studies in humans and other species reveal many similarities in the pharmacological effects of the azapirones. However, the prototypical 5-HT_{1A} agonist for which there is the most data in animals, 8-OH-DPAT, has not been studied in humans.

On the physiological level, dose-dependent reductions in temperature which are antagonized by pindolol in both humans and animals are compatible with a 5-HT_{1A}-mediated response in the different species. Similarly, the blockade of the ACTH and cortisol responses to ipsapirone by pindolol indicates a 5-HT_{1A} site of action of this drug in humans and animals. The more variable ACTH, cortisol, prolactin, and growth hormone responses to buspirone and to different doses of gepirone and tandospirone, and the incomplete or conflicting data concerning the partial blockade of these responses by metergoline or pindolol, apparently require more detailed study.

The explication of the mechanisms involved in the dampened temperature and neuroendocrine responses to ipsapirone in patients with panic disorder and depression (but not in patients with OCD), and the reduction of these temperature and neuroendocrine responses after patients were treated with fluoxetine, but not with amitriptyline (although here a baseline difference may be involved), might be investigated in animal models.

With regard to the behavioral effects of the azapirones, several observations seem pertinent. First, almost all of the behavioral studies in animals have been carried out after administration of single doses of these drugs. Although some "anxiolytic" and "antidepressant" effects in rodents have been documented using some paradigms (often ones that are not those found to be the most sensitive indices of benzodiazepine-type anxiolytic effects), it is striking that, in the single-dose studies in humans reviewed here, no antianxiety effects were observed. Drowsiness was noted more in controls than in patient groups, and some patients, specifically those with panic disorder, rated themselves as more anxious after ipsapirone than placebo. As clinical antianxiety and, more recently, antidepressant effects of the azapirones have become increasingly substantiated, it is noteworthy that there have been few biological or behavioral studies of the effects of the longer-term administration of these agents to animals. Likewise, it is apparent that more biological studies are needed of patients treated with these agents chronically, comparing those who improve with those who may not improve.

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