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Selective Cross-Tolerance to 5-HT_{1A} and 5-HT_2 Receptor-Mediated Temperature and Corticosterone Responses

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NASH, J. F., JR., H. Y. MELTZER AND G. A. GUDELSKY. *Selective cross-tolerance to 5-HT_{1A} and 5-HT_2 receptor-mediated temperature and corticosterone responses.* PHARMACOL BIOCHEM BEHAV **33**(4) 781–785, 1989.—The repeated administration of 5-methoxy-N,N-dimethyltryptamine (5-MeODMT, 3 mg/kg, twice daily for 14 days) significantly diminished hypothermia and corticosterone secretion induced by an acute challenge with the 5-HT_{1A} agonist 8-OH-DPAT (0.1 mg/kg) when compared to the responses in animals treated chronically with the solvent vehicle. In contrast, the chronic administration of 5-MeODMT did not alter the magnitude of hyperthermia or corticosterone secretion induced by the acute administration of MK-212 (1.0 mg/kg). The repeated administration of the 5-HT_2 agonist DOI (1.0 mg/kg, daily for 7 days) significantly reduced the increase in corticosterone, but not body temperature, produced by MK-212. Chronic treatment with DOI did not alter the hypothermia or increase in corticosterone secretion elicited by 8-OH-DPAT. These data are consistent with other evidence that these physiological effects of 8-OH-DPAT and MK-212 are mediated by 5-HT_{1A} and 5-HT_2 receptors, respectively. Thus, data presented in these studies are suggestive that the chronic administration of 5-MeODMT diminishes the responsiveness of 5-HT_{1A} receptor-mediated changes in body temperature and corticosterone secretion without altering the responses mediated by 5-HT_2 receptors. In contrast, the chronic administration of DOI selectively diminishes the magnitude of 5-HT_2 receptor-mediated changes in corticosterone secretion without affecting the responsiveness of those receptors involved in thermoregulatory responses. These selective changes in receptor responsiveness following the chronic administration of these 5-HT agonists further establishes the independence of 5-HT_{1A} and 5-HT_2 receptor-mediated pharmacological effects.

Body temperature Corticosterone Cross-tolerance MK-212 5-MeODMT 8-OH-DPAT Tolerance

IDENTIFICATION of multiple serotonin (5-HT) receptors in radioligand binding studies has resulted in the classification of three major subtypes, 5-HT_1, 5-HT_2 and 5-HT_3 (20,29). For the most part, agonists such as [^{3}H]-8-hydroxy-2-(di-n-propylamino)-tetralin ([^{3}H]-8-OH-DPAT) and [^{3}H]-5-HT have been used to label 5-HT_1 sites (27). On the other hand, 5-HT_2 binding sites have been characterized by the binding of antagonists such as [^{3}H]-ketanserin or [^{3}H]-spiperone (28). Thus, based on radioligand studies, a relatively strong correlation exists between the affinity of 5-HT agonists for 5-HT_1 sites and in vivo effects of these agonists. The relationship between the binding affinity of reputed 5-HT_2 agonists and their in vivo effects is not as strong. However, several phenylisopropylamines including 1-(2,4-dimethoxy-4-iodo-phenyl)-2-aminopropane (DOI) have been identified as 5-HT_2 agonists (14,34). These agents appear to bind with high affinity to 5-HT_2 sites, which have been referred to as 5-HT_{2H} (H: high affinity) sites in binding assays using agonist radioligands (e.g., ^{3}H-DOB) to label 5-HT_2 receptors (35).

There is evidence that some physiological processes are subserved by multiple 5-HT receptor subtypes. In some instances, these receptor subtypes are functionally opposed to one another. In other cases, multiple receptor subtypes function in a complementary fashion. For example, food consumption in nonfood-deprived rats is enhanced by the 5-HT_{1A} agonist, 8-OH-DPAT (10,11). Conversely, it is well established that the administration of direct 5-HT agonists such as 1-(m-chlorophenyl)-piperazine (mCPP) (19), 6-chloro-2-(1-piperazinyl)-pyrazine (MK-212) (4) and DOI (31) or 5-HT releasers similar to fenfluramine (30) produce anorexia. These agents are thought to stimulate postsynaptic 5-HT receptors, which may be 5-HT_{1B} or 5-HT_2 receptors, since 5-HT_{1B} or 5-HT_2 antagonists, such as (−)iodopindolol or ketanserin, have been reported to block the anorectic effect of these agonists (16,19).

Opposing effects of 5-HT_1 and 5-HT_2 agonists on body temperature also have been documented. For example, Gudelsky *et al.* (15) found that the administration of 8-OH-DPAT produced a dose-dependent hypothermia which was blocked by the 5-HT_{1A} antagonist, (−) pindolol. Conversely, in the same study the

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administration of the 5-HT agonist, MK-212, resulted in a dose-dependent hyperthermia in heat-adapted rats which was blocked by several selective 5-HT_2 antagonists such as pirenperone and ketanserin.

Finally, 5-HT_2 and 5-HT_{1A} receptors may act in concert in the regulation of the hypothalamic-pituitary-adrenal axis. Koenig *et al.* (21,22) have reported that activation of either 5-HT_2 or 5-HT_{1A} receptors results in increased serum corticosterone concentrations. Similarly, the behavioral effects of 5-HT agonists are comprised of 5-HT_1- and 5-HT_2-mediated components. For example, the classical 5-HT behavioral syndrome characterized by forepaw treading, flat body posture, straub tail and head shakes has been reported to be mediated by both 5-HT_1 and 5-HT_2 receptor mechanisms based on antagonist studies (33,37).

The indolealkylamine, 5-MeODMT, has been found to have a high affinity for 5-HT_{1A} binding sites (33). The repeated administration of 5-MeODMT has previously been reported to selectively attenuate the behavioral syndrome elicited by 5-MeODMT without affecting the decrease in locomotor activity produced by mCPP (32). These data are supportive of the view that 5-HT receptor subtypes may be differentially regulated by the chronic administration of agonists. Likewise, radioligand binding studies are also supportive of this viewpoint. For example, the chronic administration of DOI has been found to significantly reduce the number of 5-HT_2 binding sites in the frontal cortex of rats (3).

The purpose of this study was to determine whether the selective 5-HT_2 agonist, DOI, stimulates the secretion of corticosterone and elevates body temperature and if the chronic administration of either 5-MeODMT or DOI produces selective desensitization of 5-HT_2 or 5-HT_{1A} receptor-mediated changes in body temperature and corticosterone secretion.

METHOD

Male Sprague-Dawley rats, weighing 175–200 g upon delivery, were purchased from Zivic-Miller Laboratory (Hillson, PA) and used in all experiments. The animals were housed six per cage in a temperature-controlled room (22–24°C) with a light/dark cycle of 12/12 hours (lights on at 0600). Food (Wayne Lab Blox) and tap water were available ad lib.

The drugs used in these studies were obtained from the following sources: DOI hydrochloride and 8-OH-DPAT hydrobromide were purchased from Research Biochemical, Inc. (Natick, MA) and 5-MeODMT hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO). MK-212 was generously supplied by Merck, Sharpe and Dohme Co. (West Point, PA). MK-212 was dissolved in 0.1 N HCl and administered intraperitoneally (IP). 5-MeODMT and DOI were dissolved in saline and administered IP, and 8-OH-DPAT was dissolved in 0.1% sodium meta-bisulfite and administered subcutaneously (SC). The respective vehicles for each drug were administered to control animals. All experiments were performed between 0800–1100 hr.

Initially, the effect of DOI (0.1, 0.3 and 1.0 mg/kg, IP) on corticosterone secretion was determined in serum of rats killed 30 min following the administration of DOI or its vehicle. To determine the effect of DOI on body temperature, rats were acclimated for 2 hours at 29°C. Body temperature measurements were performed 30 and 15 min prior to the administration of DOI (0.1, 0.3 and 1.0 mg/kg). A final body temperature was obtained 30 min following DOI administration.

In the next study, groups of rats were treated chronically with 5-MeODMT (3.0 mg/kg, IP twice daily for fourteen days) or its vehicle. In another study, groups of rats were treated chronically with DOI (1.0 mg/kg daily for the seven days) or its vehicle. In both studies, 24 hr following the last drug injection, the animals were injected with either 8-OH-DPAT (0.1 mg/kg) or MK-212 (1.0 mg/kg) and body temperature or serum corticosterone were measured according to the procedures detailed below.

TABLE 1

EFFECT OF DOI ON CORTICOSTERONE SECRETION AND CHANGE IN BODY TEMPERATURE (°C) IN RATS

Treatment	Dose (mg/kg)	Corticosterone (μg/dl)	Δ Body Temperature (°C)
Vehicle	—	9.1 ± 3.0	—
DOI	0.1	5.3 ± 1.7	0.4 ± 0.1*
DOI	0.3	18.0 ± 3.3*	1.3 ± 0.2*
DOI	1.0	28.0 ± 2.3*	1.8 ± 0.3*

*$p<0.05$ as compared to vehicle-treated groups.
Each value represents the mean ± S.E.M. of 6 rats.

For the studies in which serum corticosterone concentrations were determined, the animals chronically-treated with either 5-MeODMT, DOI or their corresponding vehicle were acutely challenged with either vehicle, 8-OH-DPAT (0.1 mg/kg, SC) or MK-212 (1.0 mg/kg, IP), and sacrificed 30 minutes later. The doses of MK-212 and 8-OH-DPAT used in these experiments were obtained from previously reported dose-response studies (21). Following decapitation, trunk blood was collected and allowed to clot. Serum was obtained following centrifugation and stored at −20°C until the time of assay.

On the day of an experiment in which body temperatures were to be determined, the animals were transferred to a temperature-controlled room. The rats were acclimated for 1–2 hours at either 29°C for the study of MK-212-induced hyperthermia or at 23°C for the study of 8-OH-DPAT-induced hypothermia. Body temperatures were recorded 30 min, 15 min and immediately prior to the administration of either MK-212 (1.0 mg/kg, IP) or 8-OH-DPAT (0.1 mg/kg, SC). The doses of MK-212 and 8-OH-DPAT used in these temperature experiments were chosen on the basis of previously reported dose-response studies (15). A final measurement of body temperature was performed 30 min after the injection of MK-212 or 8-OH-DPAT. Rectal temperature measurements were made using a telethermometer (Model 44TA, Yellow Spring Instr. Co.) and a thermistor probe. Each rat was lightly restrained in a large sheet following which the thermistor probe, lubricated with a small amount of petroleum jelly, was inserted 5 cm into the rectum until a stable temperature was obtained.

Serum corticosterone concentrations were determined by radioimmunoassay. [^{3}H]Corticosterone was purchased from Dupont New England Nuclear (Boston, MA), and the antiserum was purchased from Radioassay Systems Laboratories, Inc. (Carson, CA). The unlabeled corticosterone used in preparing the RIA standard was purchased from Steraloids, Inc. (Wittam, NH). The assay sensitivity was 25 pg/ml.

The data was analyzed with one-way and two-way analysis of variance. Differences between treatment groups were evaluated using student Newman-Keuls test. In each statistical test, significance was set at a level of $p<0.05$.

RESULTS

The effects of DOI on serum corticosterone concentrations and on body temperature are presented in Table 1. DOI produced a dose-dependent elevation of serum corticosterone concentrations. The lowest dose at which a significant ($p<0.05$) elevation occurred was 0.3 mg/kg. Similarly, DOI produced a dose-dependent

TABLE 2

EFFECT OF CHRONIC 5-MeODMT OR DOI ADMINISTRATION ON THE CHANGE IN BODY TEMPERATURE FOLLOWING ACUTE 8-OH-DPAT OR MK-212 CHALLENGE

Acute Treatment	Dose (mg/kg)	Δ Body Temperature (°C) Chronic Treatment Vehicle	5-MeODMT	DOI
8-OH-DPAT	0.1	−1.1 ±0.1	−0.6* ±0.1	−1.0 ±0.1
MK-212	1.0	1.2 ±0.1	1.4 ±0.2	1.1 ±0.1

Each value is the mean ± S.E.M. for 6 animals. Body temperature was recorded 30 min following the acute treatment of 8-OH-DPAT and MK-212. The asterisk (*) indicates significant ($p<0.05$) difference from chronic vehicle-treated rats.

increase in body temperature. All three doses of DOI (0.1, 0.3 and 1.0 mg/kg) significantly ($p<0.05$) elevated body temperature.

Table 2 presents the effect on body temperature of either 8-OH-DPAT (0.1 mg/kg) or MK-212 (1.0 mg/kg) in animals treated chronically with 5-MeODMT or DOI. In animals treated chronically with the solvent vehicle, the administration of 8-OH-DPAT produced a hypothermic response, whereas the administration of MK-212 produced hyperthermia. In the group of animals treated chronically with 5-MeODMT (3 mg/kg), there was a significant ($p<0.05$) attenuation of the 8-OH-DPAT-induced hypothermia. However, the chronic administration of 5-MeODMT had no significant effect on MK-212-induced hyperthermia. The chronic administration of DOI had no effect on 8-OH-DPAT-induced hypothermia or MK-212-induced hyperthermia.

The effect of chronic 5-MeODMT administration on the corticosterone response to either 8-OH-DPAT (0.1 mg/kg) or MK-212 (1.0 mg/kg) is illustrated in Fig. 1. No differences were observed in the basal serum corticosterone concentrations of rats treated

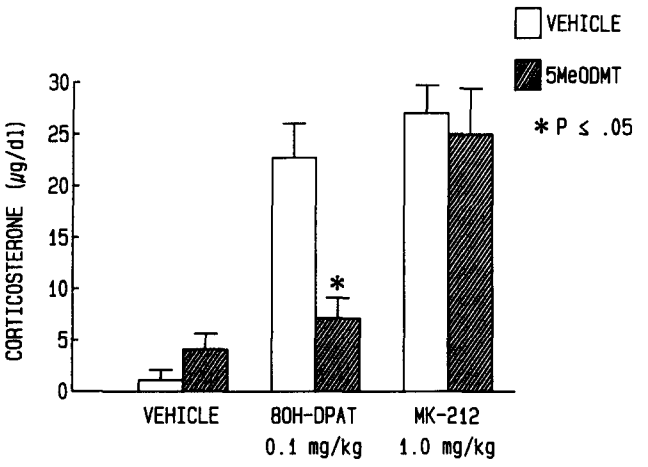

FIG. 1. Effect of chronic 5-MeODMT administration on 8-OH-DPAT- and MK-212-induced corticosterone secretion. 5-MeODMT (3.0 mg/kg) was administered for 14 days; 24 hr following the last injection, rats were challenged with either vehicle, 8-OH-DPAT (0.1 mg/kg, SC) or MK-212 (1.0 mg/kg, IP) and sacrificed 30 min later. Each value represents the mean ± S.E. of 6 rats. The asterisk (*) indicates significantly ($p<0.05$) less than corresponding vehicle + drug treatment.

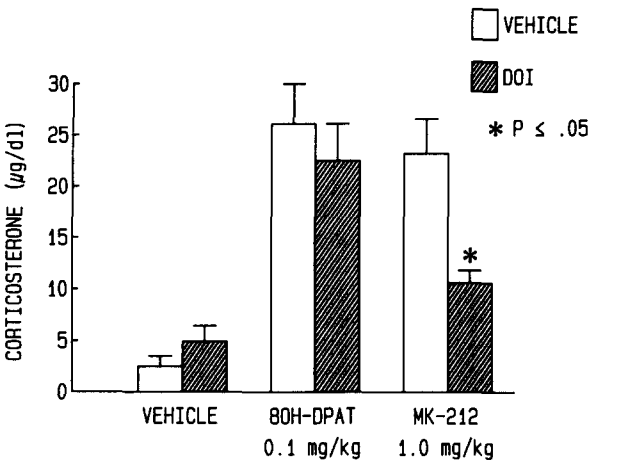

FIG. 2. Effect of chronic DOI administration of 8-OH-DPAT- and MK-212-induced corticosterone secretion. DOI (1.0 mg/kg) was administered for 7 days; 24 hr following the last injection, rats were challenged with either vehicle, 8-OH-DPAT (0.1 mg/kg, SC) or MK-212 (1.0 mg/kg, IP) and sacrificed 30 min later. Each value is the mean ± S.E. of 6 rats. The asterisk (*) indicates significantly ($p<0.05$) less than corresponding vehicle + drug treatment.

chronically with vehicle or 5-MeODMT. Administration of 8-OH-DPAT increased serum corticosterone concentrations in vehicle pretreated rats, but this response was significantly ($p<0.05$) diminished in rats treated chronically with 5-MeODMT. In contrast, no significant difference in the corticosterone response to the acute administration of MK-212 was observed in rats treated chronically with 5-MeODMT or its vehicle. Figure 2 illustrates the corticosterone responses to 8-OH-DPAT and MK-212 in rats treated chronically with DOI or its vehicle. No differences were observed in the basal serum concentration of corticosterone in rats treated chronically with DOI or its vehicle. However, the MK-212-induced increase in serum corticosterone was significantly ($p<0.05$) attenuated in rats treated chronically with DOI. There was no difference in the corticosterone response to 8-OH-DPAT in the two chronically-treated groups.

DISCUSSION

The results obtained in these studies demonstrate that a selective cross-tolerance can be produced in 5-HT agonist-induced changes in body temperature and corticosterone secretion following the chronic administration of 5-HT agonists. Thus, the repeated administration of 5-MeODMT resulted in a suppression of the thermoregulatory and neuroendocrine responses to 8-OH-DPAT but not to MK-212, and the chronic administration of DOI resulted in a suppression of the neuroendocrine response to MK-212 but not to 8-OH-DPAT.

It also is noteworthy that these results demonstrate the possibility of altering the sensitivity of only one 5-HT receptor-subtype involved in a response subserved by multiple receptor subtypes. Thus, although both 5-HT_2 and 5-HT_{1A} receptors are involved in the regulation of corticosterone secretion and body temperature, it was possible to selectively alter the responsiveness of only one of the receptor subtypes by the chronic administration of a selective 5-HT agonist.

Since 8-OH-DPAT-induced hypothermia and corticosterone secretion appear to be mediated by 5-HT_{1A} receptors (15,21), it seems reasonable to conclude that the repeated administration of

5-MeODMT selectively diminished the responsiveness of these 5-HT_{1A} receptors. These data are in accord with the report of Sills *et al.* (32), in which the repeated administration of 5-MeODMT was shown to result in an attenuation of the behavioral syndrome elicited by 5-MeODMT, which has been proposed to be mediated by 5-HT_{1A} receptors (24,37).

The phenylisopropylamine DOI possesses a high affinity for the 5-HT_2 binding site (36). In the present study, repeated DOI administration significantly reduced MK-212-induced corticosterone secretion suggesting that DOI and MK-212 share a common mechanism with respect to corticosterone secretion, viz. activation of 5-HT_2 receptors. In contrast, the repeated administration of DOI had no effect on 8-OH-DPAT-induced hypothermia and corticosterone secretion. The diminished 5-HT_2 receptor-mediated stimulation of corticosterone secretion induced by MK-212 in rats chronically treated with DOI is consistent with the work of Buckholtz *et al.* (3) in which repeated administration of DOI (1.0 mg/kg daily for 7 days) decreased the number (B_{max}) of 5-HT_2 binding sites in cortex of rats.

Although cross-tolerance was observed between the selective 5-HT_2 agonist DOI and MK-212, the latter does not appear to be as selective a 5-HT_2 agonist as DOI. Radioligand binding studies suggest that MK-212 has little affinity for either 5-HT_1 or 5-HT_2 recognition sites (13,25). The effect of MK-212 on in vitro tissue preparations has done little to clarify the specificity of this agent. Baumann and Waldmeier (1) compared the ability of several 5-HT agonists and antagonists to affect the outflow of 5-HT from electrically stimulated frontal cortex slices. These authors found that MK-212 and quipazine augmented electrically-stimulated 5-HT outflow, suggesting that these agents block presynaptic 5-HT receptors. In a study using a similar preparation, Engel *et al.* (12) also found that MK-212 produced a parallel shift-to-the-right in 5-HT inhibition of electrically-stimulated 5-HT outflow. These data support the study by Bauman and Waldmeier (1) suggesting that MK-212 acts as a 5-HT autoreceptor antagonist, i.e., 5-HT_{1B} antagonist. Conversely, Clineschmidt *et al.* (5) reported that although MK-212 had little affinity for the rat fundic receptor which may correspond to brain 5-HT_1 binding sites, it was the most effective of several arylpiperazines at inducing contraction, inferentially suggesting that this agent possesses 5-HT_1 properties. Again, in contrast to these studies, Conn and Sanders-Bush (6) reported that MK-212 was a partial agonist at 5-HT_2 receptors in the cerebral cortex on the basis of its ability to stimulate phosphoinositide hydrolysis. Collectively, these studies provide only limited information regarding the 5-HT receptor subtype with which MK-212 interacts. Alternatively, it would appear that MK-212 is, in fact, a nonselective 5-HT agonist.

Studies investigating the in vivo properties of MK-212 have been somewhat more consistent. Cunningham *et al.* (8) reported that the 5-HT_{1A} agonists 8-OH-DPAT and 5-MeODMT and the 5-HT_{1B} agonists, RU-24969 and TFMPP failed to completely substitute for MK-212 in discriminative stimulus studies. Conversely, mCPP and fenfluramine mimicked MK-212 in a dose-dependent manner. Although the 5-HT_2 antagonists, ketanserin and pirenperone, failed to block the MK-212 discriminative cue, these data do suggest that MK-212 does not elicit responses similar to prototypic 5-HT_{1A} or 5-HT_{1B} agonists. Lorens and Van de Kar (23) found that MK-212 and fenfluramine stimulated the secretion of renin which was blocked by the 5-HT_2 antagonist, LY-53857. Similarly, Brownfield *et al.* (2) reported that MK-212 administration stimulated vasopressin secretion which also was blocked by LY-53857. Moreover, MK-212-induced corticosterone and β-endorphin secretion were blocked in a dose-dependent manner by several 5-HT_2 antagonists (21). Thus, in the present study, chronic DOI administration did not affect 8-OH-DPAT-induced corticosterone secretion but did attenuate the acute effects of MK-212 on corticosterone secretion, establishing the presumed receptor independence of these agents and supporting the hypothesis that MK-212 activates the hypothalamic-pituitary-adrenocortical axis via 5-HT_2 receptors.

The possibility that 24 hr following the chronic administration of either 5-MeODMT or DOI some residual drug still occupies 5-HT_{1A} or 5-HT_2 receptors, respectively, resulting in an attenuated response to the challenge drugs cannot be ruled out at this time. However, the metabolism and elimination of both 5-MeODMT and compounds structurally-related to DOI are fairly rapid and probably complete within a 24 hr time period (17, 18, 34). Similarly, the possibility exists that the repeated administration of DOI or 5-MeODMT selectively induces the metabolism of either MK-212 or 8-OH-DPAT and that this results in diminished responses to these agents. A pharmacokinetic tolerance would seem unlikely considering that all four compounds used are structurally different. Thus, as we previously discussed, these data are suggestive of a desensitization of receptor-mediated responses, possibly related to selective receptor downregulation.

The failure of chronic DOI to attenuate acute MK-212-induced hyperthermia may be due to a conditioning phenomena. For example, tolerance to the hypothermic effect of ethanol is observed only when the drug is administered in a similar environment which previously accompanied drug administration (7). This Pavlovian conditioning has been described for other drugs (i.e., morphine) and is a well characterized event (9). Therefore, in the present study, chronic DOI administration was done at room temperature, whereas the acute challenge with MK-212 in the chronic DOI-treated group was done in a novel environment (i.e., elevated ambient temperature) in which disruption of the conditioned effects may have resulted in a loss of drug tolerance. However, this hypothesis was tested by administering DOI (1.0 mg/kg) daily for 7 days to rats maintained in an elevated ambient temperature (29°C) 1–2 hr prior to drug treatment. Repeated DOI administration under these conditions failed to attenuate MK-212-induced hyperthermia. Moreover, chronic MK-212 (1.0 mg/kg) administration for 14 days failed to produce tolerance to its hyperthermic response even though tolerance was observed to the secretion of corticosterone produced by an acute challenge with this agent (Nash *et al.*, unpublished observation). That tolerance developed to MK-212-induced corticosterone secretion but not to MK-212-induced hyperthermia is evidence that the responsiveness of a particular 5-HT receptor subtype may be differentially regulated in various brain regions.

Tolerance has been reported to develop to other pharmacological agents which produce hyperthermia. For example, morphine-induced hyperthermia is attenuated in rats chronically administered morphine (26). Mucha *et al.* (26) raise a number of issues regarding the failure of previous studies to detect tolerance to morphine-induced hyperthermia. These possibilities include the dose of drug chronically administered and the length of time the animals were treated. In addition, the dose of the challenge drug and the time point(s) at which body temperature was determined contribute to the outcome of these studies. Collectively, these factors could account for our failure to observe tolerance to the hyperthermic response to MK-212 in animals chronically-treated with DOI. Further studies are necessary to rule out these independent variables.

The results presented in this manuscript suggest that 5-HT receptor subtypes may be differentially affected by the chronic administration of selective agonists. Moreover, these data further establish the independence of 5-HT receptor subtypes even with respect to an identical response (i.e., corticosterone secretion). The diminished responses to MK-212 and 8-OH-DPAT are believed to be the result of receptor desensitization produced by the repeated activation of 5-HT_2 and 5-HT_{1A} receptors, respectively.

Finally, the establishment or cross-tolerance between DOI and MK-212 supports previous studies that at least the neuroendocrine effects of MK-212 are mediated by 5-HT_2 receptor mechanism in rodents.

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