Pharmacology Biochemistry & Behavior, Vol. 15, pp. 895–901, 1981. Printed in the U.S.A.

The Effects of Quipazine, Fenfluramine and Apomorphine on the Morphine Potentiation of Tonic Immobility

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Received 7 August 1981

WALLNAU, L. B. *The effects of quipazine, fenfluramine and apomorphine on the morphine potentiation of tonic immobility*. PHARMAC. BIOCHEM BEHAV. **15**(6) 895–901, 1981.—Acute administration of morphine (2 mg/kg, IM) enhanced tonic immobility (TI) durations in three-week old chickens. This effect could be reversed with the 5-HT receptor agonist quipazine. Similarly, promoting 5-HT release by fenfluramine antagonized the morphine potentiation of the response. Both 5-HT agonists reduced TI durations. Finally, the DA receptor agonist apomorphine produced decrements in TI duration and blocked the effect of morphine. The results suggest the involvement of serotonergic and dopaminergic mechanisms in the morphine potentiation of the response. The findings are also discussed in terms of a revised serotonergic model of tonic immobility.

Tonic immobility Morphine Quipazine Fenfluramine Apomorphine Serotonergic model Dopaminergic mechanisms Chickens

A BRIEF period of physical restraint will often produce a catatonic-like reaction known as tonic immobility (TI). In the laboratory, it is typically elicited by manually restraining an animal on its side for a few seconds. Once the initial struggling subsides, the animal assumes a motionless and rigid posture which is maintained for minutes and sometimes hours without additional restraint. Although the response has been observed in many species domestic fowl are frequently used because of the ease with which the response is elicited and quantified in these species. The most obvious characteristics of TI include loss of the righting response, rigidity, waxy flexibility of the limbs, tremors, decreases in vocalization, and no loss of consciousness [24]. Similarities have been noted between TI and other forms of catalepsy, and it has been proposed as a laboratory animal analog of catatonia [24].

The participation of serotonergic (5-HT) mechanisms in TI has been demonstrated in a number of studies that have examined the effects of precursor loading, 5-HT depletion, monoamine oxidase (MAO) inhibition, receptor agonists and antagonists, and drugs that produce effects on raphe activity [9, 10, 11, 25, 34, 40, 55, 56]. Originally, a model was proposed to provide predictions of drug effects on TI based on their effects on the activity of central serotonergic neurons of the midbrain raphe nuclei [59]. It was suggested that TI duration was inversely related to the rate of raphe firing. However, recent work has resulted in a revision of this model, with a shift in emphasis to the postsynaptic consequences of 5-HT manipulations [23].

In particular, manipulations that increase postsynaptic 5-HT action produce decrements in TI duration. For example, enhancement of 5-HT release by fenfluramine or p-chloroamphetamine [14,53] produces an abbreviated immobility reaction [9,56]. Quipazine, a 5-HT receptor agonist [36,50], also attenuates TI and this effect can be prevented by pretreatment with the 5-HT receptor antagonist cinanserin [56]. Although tryptophan and the MAO inhibitor pargyline will separately inhibit raphe firing [2,22] and increase TI duration [11, 25, 40], when administered together they produce very short durations [11]. It is believed that combined administration of these agents produces excess 5-HT that spills into the synapse if concentrations surpass the intraneuronal storage capacity [30]. Thus, like drugs which promote 5-HT release, MAO inhibition followed by tryptophan attenuates the immobility reaction. In addition, p-chlorophenylalanine (PCPA), which depletes 5-HT primarily in raphe terminals [4], prevents the reduction of TI produced by the combination of pargyline and tryptophan [11]. Amphetamine, which accelerates raphe firing rates [19] and presumably 5-HT synaptic transmission, produces decrements in TI duration [10]. This reduction can be reversed by PCPA pretreatment [10].

On the other hand, the revised model proposes that decrements in postsynaptic 5-HT function are associated with enhanced TI durations. Tryptophan enhances TI duration [25,56], and may do so because it decreases 5-HT transmission. That is, iontophoretically applied tryptophan produces inhibition of activity in raphe cells due to local increases in 5-HT in or near the raphe perikarya [22]. As a result of this presynaptic inhibition, a decrease in synaptic transmission of 5-HT should result, which would account for the increase in TI duration. This interpretation is supported by the finding

that 5-HT receptor stimulation by quipazine reverses the tryptophan enhancement of TI [56]. Furthermore, LSD has a preferential effect on the presynaptic 5-HT membrane, producing direct inhibition of raphe activity and subsequent disinhibition of areas that receive dense 5-HT input [32]. LSD produces very large increments in TI duration [40]. Similarly, low doses of 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) have a preferential effect on presynaptic 5-HT receptors, and causes a rapid inhibition of raphe cells [17]. However, larger doses are less specific and produce postsynaptic stimulation as well [17]. Consistent with the revised model of TI, a biphasic effect of 5-MeODMT has been observed, with low doses potentiating and high doses abbreviating response duration [9]. The same pattern exists for the dose-response relationship between 5-HT and TI [34], possibly reflecting a dissociation of pre- and postsynaptic effects. That is, low doses of 5-HT may produce an inhibition of raphe and a subsequent decrease in synaptic transmission of 5-HT due to its direct presynaptic action (e.g., [3]). Larger doses of 5-HT may also have postsynaptic effects, or like systemic injections, even augment raphe activity [45].

Dopaminergic (DA) receptor mechanisms also participate in tonic immobility. Subcataleptic doses of haloperidol, a dopamine receptor blocker [5], enhances immobility, while the DA receptor agonist apomorphine [6], attenuates the response [58]. There is ample evidence to suggest the existence of parallel 5-HT and DA projections to striatal regions in the mammalian brain [15,54]. Studies which examine the regional distribution of these transmitters point to a similar pattern in avians as well [38, 39, 48]. Because these areas participate in psychomotor function, it is not surprising that 5-HT and DA mechanisms interact for tonic immobility. Dopamine receptor stimulation by apomorphine reverses the tryptophan potentiation of TI [57]. Alternately, the 5-HT receptor agonists quipazine and fenfluramine can reverse the haloperidol enhancement of immobility [55,57]. A similar observation has been made for the effects of quipazine on haloperidol-induced catalepsy in rats [28]. Thus it appears that increased postsynaptic stimulation in one neurotransmitter system can counteract the effect of reduced postsynaptic action in the other system.

Among the most reliable and potent effects on TI is the morphine enhancement of response duration [16, 35, 47, 60]. This drug effect, along with the striking similarities between TI and endorphin-induced catalepsy [8,37], led to speculation that an endogenous opiate system might play a role in TI [13]. In addition, there have been claims that TI is accompanied by analgesia [12,49]. Recent data, however, cast doubt on the participation of endogenous opiate mechanisms in tonic immobility.

The opiate receptor blocker naloxone fails to alter TI duration in doses up to 10 mg/kg [60]. This largest dose is more than 300 times the effective dose for opiate antagonism in avians [42]. Similar findings have been reported for TI in rabbits [21]. In other work, the opiate-acting peptide (D-Ala^2, F$_5$Ph^4)-Met-enkephalin-NH$_2$ potentiates TI, however an analog with negligible opiate action, (D-Phe^4)-Met-enkephalin, has the same effect on response durations [46].

The mechanism for the morphine effect on TI has been questioned as well. Only exceptionally large doses of naloxone block the morphine enhancement of TI [47,60]. These findings contrast with the ability of low doses of naloxone to reverse the hypnotic effects of large injections of morphine in chickens [60]. A similar distinction has been made between opiate and non-opiate action for the morphine effect on raphe activity. Microiontophoretic application of morphine has inhibitory action on dorsal raphe cells [31]. This effect appears to be independent of opiate mechanisms because it is not reliably reversed by naloxone [31]. Furthermore, dextrorphan, an isomer of the opiate agonist levorphanol, has negligible opiate activity yet produces a suppression of raphe firing similar to that of morphine and levorphanol [31].

Additional evidence which dismisses opiate involvement is the recent finding that TI in lizards is accompanied by hyperalgesia, rather than analgesia, as measured by a standard tail-flick procedure [41]. It was also observed that TI-treated animals subsequently showed diminished analgesic response to morphine [41]. Since the integrity of the 5-HT system is crucial for morphine analgesia [1, 26, 52] and possibly for the morphine potentiation of TI [60], it was concluded that decreased postsynaptic 5-HT function may accompany TI [41]. This interpretation is consistent with the current serotonergic model of TI [23]. Specifically, increases in TI duration follow administration of drugs which decrease postsynaptic action of 5-HT by, for example, direct presynaptic inhibition of raphe firing. Because morphine has direct inhibitory action on raphe neurons [31], it is possible that it enhances TI due to a subsequent decrease in postsynaptic 5-HT function. Thus, 5-HT receptor agonists should prevent the morphine enhancement of tonic immobility. The first two experiments explored this possibility. A third experiment examined the effect of apomorphine on the morphine potentiation because DA receptor stimulation can reverse the effect of impaired postsynaptic 5-HT function on TI [57], and because DA mechanisms may contribute to morphine effects as well [18,44].

GENERAL METHOD

Animals

Straight-run Production Red chickens were obtained from a commercial hatchery (Welp, Inc.) at 1 day of age. Animals were housed in groups in heated brooders (Brower Mfg. Co., model 6401) and provided with Purina chick starter and water at all times. Artificial illumination from overhead fluorescent fixtures was presented from 8 a.m. to 10 p.m. daily. In order to reduce the effects of taming on TI baseline [24], human exposure was limited to daily feeding and maintenance.

Apparatus

TI duration was timed automatically by electronic programming equipment. Photoelectric sensors (BRS/LVE PH-901/221-10) were used to detect the righting response. To elicit TI, each animal was restrained on its right side atop a wood platform. The back of the animal was placed against a positioning block in the center of the platform to ensure reliable and accurate recording of the righting response. The platform (H×W×D=10×42×30 cm) was situated in a sound-attenuated test chamber (58×105×41 cm). A light source was located on the ceiling of the chamber and a photoelectric sensor was situated in the platform so that it would be underneath an immobilized animal. If the animal displayed TI following restraint, the experimenter would activate an electronic clock by a remote switch and then close a sound-dampened door. Restoration of contact between the light source and photosensor would stop the clock when the animal righted itself to its feet. A latching relay prevented

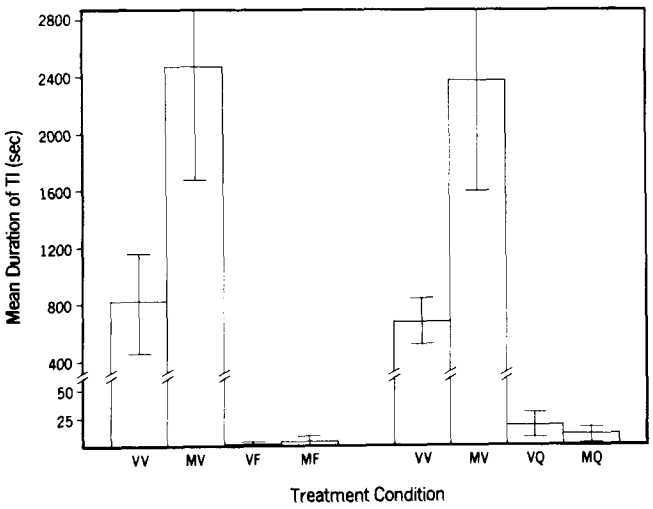

FIG. 1. Effect of drug treatments on tonic immobility duration (mean sec±SE). Treatments for Experiment 1 are on the right side and consist of vehicle-vehicle (VV), morphine-vehicle (MV), vehicle-quipazine (VQ), and morphine-quipazine (MQ). On the left, the groups for Experiment 2 are vehicle-vehicle (VV), morphine-vehicle (MV), vehicle-fenfluramine (VF), and morphine-fenfluramine (MF).

additional time recording in the event that locomotion broke the span of light following termination of TI. Small windows allowed occasional observations to be made and were positioned on the test chamber so that the observer was out of view of the immobile animal.

Testing Procedure

Following injections, animals were individually placed in cardboard holding boxes for the duration of the injection-test interval. Animals were then individually tested for TI by applying 15 seconds of manual restraint in the apparatus described above. If the initial restraint failed to produce TI, the animal was returned to its holding box for 60 seconds, followed by another elicitation attempt. This test procedure was repeated until a bird displayed TI or five unsuccessful elicitation attempts were made. Animals that still failed to display TI after five inductions were given a duration of zero seconds. Testing occurred between 10 a.m. and 5 p.m. and birds from each group were equally distributed across time of testing. The individuals who restrained animals were uninformed of group identities. This was accomplished by labeling each holding box with the identification number of the animal.

EXPERIMENT 1

METHOD

Quipazine, a 5-HT receptor agonist [36,50], attenuates TI duration [55,56]. Although quipazine may alter the functioning of other neurotransmitter systems [43], its effect on TI appears to be serotonergic in nature because cinanserin, a 5-HT receptor antagonist [20], prevents the quipazine reduction of TI [56]. In addition, quipazine produces postural effects in chickens [56] that typically accompany enhanced postsynaptic 5-HT function [11]. Tryptophan enhances TI duration, possibly due to a decrease in synaptic transmission of 5-HT following direct inhibition of raphe cells. This interpretation is supported by the finding that quipazine reverses the tryptophan potentiation of TI duration [56]. Morphine is reported to suppress raphe activity following microiontophoretic application [31]. Thus morphine, like other drugs that produce direct inhibition of raphe neurons, may increase TI duration due to a decrease in postsynaptic 5-HT action. If this account is accurate, then quipazine should reverse the morphine potentiation of TI, much like it does with tryptophan.

Procedure

At 22 days of age, thirty-six chickens were assigned to one of four treatment conditions consisting of the following pairs of injections; morphine-quipazine (MQ), morphine-vehicle (MV), vehicle-quipazine (VQ), or the two vehicle injections (VV). The first injection consisted of 2 mg/kg IM of morphine sulfate (Lilly) or an equivalent volume (2 ml/kg) of distilled water. Immediately after the first injection, animals received 25 mg/kg IP of quipazine maleate (Miles) or 2 ml/kg of distilled water. Fifteen minutes following the second injection, animals were tested for TI as previously described.

RESULTS

The findings are presented in Fig. 1. A square root transformation of TI duration was performed prior to analysis to reduce heterogeneity of variance. Analysis of variance revealed a main effect of quipazine, $F(1,32)=40.55$, $p<0.001$, reflecting suppressed durations for both groups that received quipazine. The main effect for morphine, $F(1,32)=2.69$, and the interaction of the two drug conditions, $F(1,32)=3.37$, failed to achieve statistical significance. *Post hoc* analysis by Newman-Keuls test examined the specific hypotheses that morphine by itself (MV) would enhance TI, and the MQ group would show short durations like animals receiving only quipazine. This pattern was observed, as differences were found for all comparisons ($p<0.05$), except between the VQ and MQ conditions. Thus, although morphine prolonged the response, quipazine reversed this effect. Analysis of variance of the number of inductions requred to elicit TI (Table 1) revealed that birds treated with quipazine required a greater number of elicitation attempts, $F(1,32)=39.52$, $p<0.001$. The main effects for morphine ($F<1$) and the interaction of drug treatments ($F<1$) were not significant.

EXPERIMENT 2

METHOD

Although fenfluramine inhibits raphe activity [51], it is believed to initially produce a rapid release of 5-HT [14,53]. Thus, it was crucial to examine the effect of this drug on tonic immobility. The original raphe model [59] proposed an inverse relationship between TI duration and raphe activity, and therefore would predict an enhancement of TI following fenfluramine administration. The revised serotonergic model [23], which emphasizes the postsynaptic consequences of drug manipulations, associates decreases in synaptic transmission of 5-HT with enhanced immobility, and increases in the postsynaptic 5-HT action with decreases in TI duration. It would therefore predict a fenfluramine attenuation of immobility due to 5-HT release. Fenfluramine, like quipazine,

TABLE 1
NUMBER OF INDUCTIONS REQUIRED TO ELICIT TONIC IMMOBILITY

Experiment 1	Vehicle-Vehicle	Morphine-Vehicle	Vehicle-Quipazine	Morphine-Quipazine
Mean	1.22	1.0	3.78	3.89
SE	0.22	0	0.62	0.56
Experiment 2	**Vehicle-Vehicle**	**Morphine-Vehicle**	**Vehicle-Fenfluramine**	**Morphine-Fenfluramine**
Mean	2.40	1.90	4.70	4.70
SE	0.59	0.53	0.30	0.30
Experiment 3	**Vehicle-Vehicle**	**Morphine-Vehicle**	**Vehicle-Apomorphine**	**Morphine-Apomorphine**
Mean	2.67	1.89	2.00	2.67
SE	0.62	0.58	0.50	0.55

was found to produce a dose-dependent decrease in TI duration [56], providing support for the revised serotonergic model. Thus, fenfluramine should reverse the morphine potentiation of tonic immobility like quipazine.

Procedure

At 23 days of age, forty animals were assigned to treatment groups consisting of morphine-fenfluramine (MF), morphine-vehicle (MV), vehicle-fenfluramine (VF), or two vehicle (VV) injections. The doses were 2 mg/kg IM for morphine and 40 mg/kg IP for fenfluramine HCl (A.H. Robbins). All injection volumes were 2 ml/kg. The first injection (morphine or vehicle) was followed immediately by fenfluramine or vehicle. Testing was conducted 20 minutes following the second injection as previously detailed.

RESULTS

The outcome is shown in Fig. 1. Analysis of variance following a square root transformation of durations yielded a main effect for fenfluramine, $F(1,36)=35.40$, $p<0.001$. Like quipazine, fenfluramine attenuated TI duration, a result that is consistent with previous findings [56]. The main effect for the morphine condition, $F(1,36)=2.94$, and the interaction of drug conditions, $F(1,36)=2.68$, were not statistically reliable. Multiple comparisons by Newman-Keuls test examined the specific hypotheses that morphine by itself would enhance TI, and the MF group would show short reactions like the VF group. The predictions were confirmed, with differences found for all comparisons ($p<0.05$) except between the two fenfluramine groups. Thus fenfluramine reduced TI duration and reversed the morphine enhancement of the response. Analysis of the number of elicitation attempts (Table 1) revealed that fenfluramine-treated animals were less likely to display TI on initial restraint, $F(1,36)=31.85$, $p<0.001$. The main effect for morphine ($F<1$) and the interaction ($F<1$) were not significant.

EXPERIMENT 3

METHOD

It has been suggested that dopaminergic mechanisms participate in morphine-induced catalepsy [18,44]. Since DA receptor mechanisms contribute to TI, the effect of apomorphine on the morphine potentiation was examined in the present experiment. There are several specific reasons why apomorphine was used. First, apomorphine produces reliable effects on TI duration [57,58]. Also, apomorphine antagonizes morphine-induced catalepsy in rats [18,44]. Finally, it has been observed that DA receptor stimulation by apomorphine can reverse the effects of impaired 5-HT transmission on TI [57]. This finding is in agreement with the observation that apomorphine increases 5-HT turnover in rats [27,29]. Since the previous two experiments suggest that morphine augments immobility durations due to reduced postsynaptic 5-HT function, apomorphine should block the morphine potentiation of tonic immobility.

Procedure

At 23 days of age, thirty-six animals were assigned to groups that received morphine and apomorphine (MA), morphine and vehicle (MV), vehicle and apomorphine (VA), or two vehicle (VV) injections. The first injection was 2 mg/kg IM of morphine or an equivalent volume (2 ml/kg) of distilled water. Eighteen minutes later, animals received injections of 2 mg/kg IP of apomorphine HCl (Lilly) or 2 ml/kg of distilled water. Testing was conducted as outlined before, 2 minutes following the second injection.

RESULTS

The findings for TI duration are shown in Fig. 2. Analysis of variance following a square root transformation revealed a main effect for apomorphine, $F(1,32)=16.89$, $p<0.001$, replicating the apomorphine reduction of TI duration [57,58]. The main effect for morphine was significant, $F(1,32)=8.29$, $p<0.01$, as was the interaction between drug treatments,

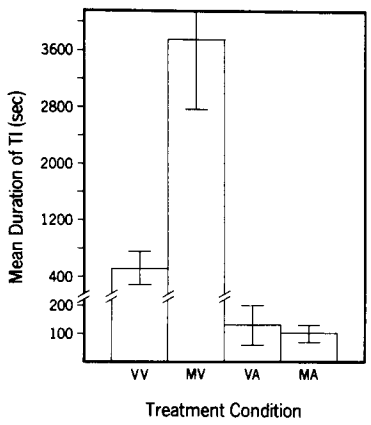

FIG. 2. Effect of drug treatments on tonic immobility duration (mean sec±SE). The groups consist of vehicle-vehicle (VV), morphine-vehicle (MV), vehicle-apomorphine (VA), and morphine-apomorphine (MA) injections.

$F(1,32)=8.75$, $p<0.01$. Planned simple effect analyses were performed to clarify the nature of this interaction. As expected, the MV group showed longer durations than VV controls, $F(1,32)=17.04$, $p<0.001$, but there was no difference between the two apomorphine groups ($F<1$). Thus apomorphine reduced TI duration and reversed the morphine enhancement of tonic immobility. Analysis of variance of the induction data (Table 1) failed to find effects for the morphine ($F<1$) and apomorphine ($F<1$) conditions, as well as the interaction, $F(1,32)=1.62$.

GENERAL DISCUSSION

The revised serotonergic model of TI emphasizes postsynaptic consequences of 5-HT manipulations [23]. Drugs which activate postsynaptic 5-HT function (e.g., quipazine, large doses of 5-MeODMT, fenfluramine, p-choloroamphetamine, combined injections of pargyline and tryptophan) produce reductions in TI duration [9, 11, 55, 56]. Alternatively, manipulations that impair postsynaptic 5-HT action by, for example, direct presynaptic inhibition of raphe cells (tryptophan, LSD, low doses of 5-MeODMT) or postsynaptic receptor blockade (cinanserin) elevate response duration [9, 11, 25, 40, 56]. In addition, the quipazine reduction of TI can be prevented by 5-HT receptor blockade [56]. Receptor stimulation by quipazine or 5-HT release by p-chloroamphetamine reverses the enhancement of TI caused by manipulations designed to impair synaptic transmission of 5-HT [56].

Consistent with this model, morphine has an inhibitory effect on midbrain raphe activity [31] and potentiates TI duration [16, 35, 47, 60]. This effect appears to be due to impaired postsynaptic 5-HT function following presynaptic inhibition of raphe, because quipazine and fenfluramine reversed the morphine potentiation of tonic immobility. It is interesting that naloxone does not reliably prevent the morphine suppression of dorsal raphe neurons, and, except for very large doses, has negligible effects on the morphine potentiation of TI [31, 47, 60]. Thus it appears that opiate receptor mechanisms are not crucial for these effects. In a recent study, tonic immobility was found to be accompanied by hyperalgesia,which casts additional doubt on opiate involvement in TI [41]. Since reduced availability of 5-HT can produce hyperalgesia [33], it was suggested that TI is accompanied by decreased postsynaptic availability of 5-HT [41]. Studies employing raphe lesions [1], 5-HT neurotoxins [26] and PCPA [52] suggest that the integrity of central serotonergic neurons is important for morphine analgesia. Since TI may be accompanied by reduced 5-HT function, it is significant that TI-induced animals subsequently show reduced morphine analgesia [41]. These data parallel the findings that 5,6-dihydroxytryptamine, a 5-HT neurotoxin [7], and PCPA prevent the morphine potentiation of TI [60].

Dopaminergic mechanisms contribute to tonic immobility and morphine-induced catalepsy. For example DA receptor blockade by haloperidol enhances TI and receptor stimulation by apomorphine abbreviates the reaction [58]. Apomorphine also blocks morphine-induced catalepsy in rats [18,44], possibly reflecting dopaminergic involvement in the action of morphine. It is possible that a similar mechanism participates in the morphine potentiation of TI, and its reversal by apomorphine (Experiment 3).

On the other hand, the action of apomorphine may be indirect and involve the interaction of 5-HT and DA mechanisms. Specifically, apomorphine reverses the tryptophan enhancement of TI [57]. Presumably tryptophan increases TI duration by impaired postsynaptic 5-HT function. This is supported by the findings that microiontophoretic application of tryptophan inhibits neurons in the midbrain raphe [22], and quipazine prevents the tryptophan enhancement of TI [56]. It is therefore interesting to note that apomorphine increases 5-HT turnover [27,29], and thus may in turn counteract the impairment of 5-HT transmission produced by tryptophan. The former effect is due to DA receptor involvement, rather than 5-HT action, because spiroperidol and transections of DA projections prevent the apomorphine enhancement in 5-HT turnover [27,29].

As is the case with tryptophan, morphine may decrease postsynaptic 5-HT function due to its presynaptic inhibitory effects on raphe activity [31]. This possibility is supported by the results of Experiments 1 and 2, in which quipazine and fenfluramine antagonized the morphine potentiation of tonic immobility. Additionally, apomorphine reversed the morphine-induced increment of TI in the last experiment, just as it does for the tryptophan enhancement. It is possible that this effect reflects the apomorphine-induced changes in 5-HT function. In summary, the present findings provide additional support for the revised serotonergic model of tonic immobility. Also, in the absence of strong evidence for opiate receptor involvement (e.g., [21, 41, 46, 60], the results shed light on the possible alternative mechanisms that might contribute to the morphine potentiation of this response.

ACKNOWLEDGEMENTS

The author appreciates the assistance of Kathie McCleary, Gerard Bordash, and Philip Corso.

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