Pharmacology Biochemistry & Behavior, Vol 14, pp 469–473, 1981 Printed in the U S A

Tonic Immobility in Domestic Fowl: Possible Interaction of Serotonergic and Dopaminergic Mechanisms[1]

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Received 20 August 1980

WALLNAU, L B., G. D. BORDASH AND P. CORSO, JR. *Tonic immobility in domestic fowl Possible interaction of serotonergic and dopaminergic mechanisms.* PHARMAC. BIOCHEM. BEHAV. **14**(4) 469–473, 1981 —Treatment with the dopamine (DA) receptor blocker, haloperidol, enhanced tonic immobility (TI) duration. Fenfluramine, a receptor agonist for serotonin (5-HT), reversed this effect. Tryptophan produced long TI reactions, and is believed to do so due to impaired synaptic transmission of 5-HT following its direct inhibitory effects on 5-HT neurons. DA receptor stimulation by apomorphine prevented the tryptophan potentiation of tonic immobility The results suggest that serotonergic and dopaminergic systems may interact with respect to tonic immobility.

Serotonergic system Dopaminergic system Tonic immobility Catalepsy Tryptophan
Fenfluramine Haloperidol Apomorphine Chickens

TONIC immobility (TI) is a catatonic-like reaction that is produced by a brief period of physical restraint. In addition to loss of the righting response, immobilized animals demonstrate waxy flexibility, rigidity, and tremors [22]. Although TI is accompanied by occasional eye closure and decreased vocalization [22], there is no loss of consciousness and animals remain able to actively monitor the environment [22]. Termination of the response is abrupt, often with no apparent aftereffects. Domestic fowl, which are frequently studied for TI, typically display the reaction for a few minutes after initial restraint, but may display response durations for over an hour under certain treatment conditions. Because of similarities in response characteristics, TI has been proposed as a laboratory model of catatonic and cataleptic states [22].

Serotonergic (5-HT) and dopaminergic (DA) systems are known to interact in catalepsy [12, 28, 33], and thus it is of interest that evidence suggests both of these neurotransmitters play a role in tonic immobility [43,44]. These findings are paralleled by anatomical and neuropharmacological evidence for DA and 5-HT innervation of striatal structures in rats that are known to be involved in psychomotor function [5, 14, 34, 40]. In avians, homologous striatal regions (e.g., nucleus basalis, paleostriatum augmentatum) contain high concentrations of 5-HT and DA [31, 32, 36, 39].

The role of 5-HT mechanisms in TI has been demonstrated by studies which implement 5-HT receptor agonists, precursor loading, monoamine oxidase (MAO) inhibition, and manipulations that directly alter firing rates of central serotonergic neurons [8, 9, 23, 35, 41, 42]. A predictive framework has been proposed for drug effects on TI, based on their effects on activity of serotonergic neurons of the midbrain raphe nuclei [44]. However, recent findings suggest that the postsynaptic effects of serotonergic manipulations provide better predictions for 5-HT effects on TI [9, 41, 42]. Specifically, manipulations designed to activate postsynaptic 5-HT function result in decreases in TI duration. For example, promoting 5-HT release by fenfluramine or p-chloroamphetamine, and the administration of the 5-HT receptor agonist quipazine result in marked decrements in TI duration [41,42]. Cinanserin, a 5-HT receptor antagonist [20,38], blocks the quipazine reduction in TI [42], suggesting that the effects of quipazine are mediated by 5-HT receptors. In addition, amphetamine, which enhances raphe electrical activity [19] and presumably 5-HT transmission, produces short immobility durations [8]. Depletion of 5-HT by p-chlorophenylalanine (PCPA) prevents this effect [8].

On the other hand, impairment of postsynaptic function of 5-HT enhances tonic immobility. For example, LSD produces a direct inhibition of raphe activity [2,29], presumably via presynaptic 5-HT autoreceptors [4], as evidenced by microiontophoretic application of LSD onto raphe neurons [2,29]. In addition to, or as a consequence of direct inhibition of raphe, LSD releases postsynaptic neurons from inhibition in areas receiving heavy 5-HT input [29]. Peripheral injections of LSD greatly enhance TI duration [35] possibly reflecting the decrease in synaptic transmission of 5-HT. Microiontophoretically applied tryptophan inhibits

[1]The authors thank Kathie McCleary and Richard Vito for assistance Our appreciation is extended to Margaret F. Ralston of McNeil Laboratories for supplying haloperidol.

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raphe activity, due to increases in 5-HT within the raphe or to direct cellular effects of a local accumulation of tryptophan [21]. This effect is not mediated at 5-HT terminals because PCPA, which inhibits 5-HT synthesis primarily in raphe terminals [3], does not block the inhibitory effects of systemically administered tryptophan [1,21]. Systemic injections of tryptophan potentiate TI duration [9, 23, 42], perhaps reflecting a decrease in synaptic transmission of 5-HT following direct inhibition of raphe. This interpretation receives support from the finding that 5-HT receptor agonists reverse the tryptophan potentiation of TI [42].

Catalepsy is often associated with DA receptor blockade. Consistent with the similarities between TI and drug-induced forms of catalepsy, subcataleptic doses of haloperidol, a DA receptor blocker [6], produce increments in TI duration [41,43]. The involvement of a DA mechanism in TI receives support from the finding that apomorphine, a DA receptor agonist [7], greatly abbreviates immobility durations [43]. It is interesting that the enhancement of postsynaptic effects of either DA or 5-HT produces the same effect on TI, namely short immobility durations. Since high concentrations of 5-HT and DA are localized in avian striatal structures [31, 32, 36, 38], and since striatal regions participate in psychomotor function, it is possible that parallel 5-HT and DA systems interact with respect to tonic immobility In rats, quipazine blocks haloperidol induced catalepsy [13,26]. Similarly, quipazine completely reverses the haloperidol enhancement of TI duration [41], suggesting that the effects of DA receptor blockade can be overcome by activation of postsynaptic 5-HT function. The present study examines the nature of this putative 5-HT-DA interaction by testing the effects of 5-HT and DA receptor manipulations on TI duration.

EXPERIMENT 1

Quipazine, a 5-HT agonist [30,37], reduces TI duration and reverses the haloperidol enhancement of tonic immobility [41]. The quipazine effect on TI appears to be mediated by 5-HT receptors because cinanserin, a 5-HT receptor blocker [20,38], prevents the quipazine reduction in immobility duration [42]. Fenfluramine, which promotes 5-HT release [11,16], decreases TI duration much like quipazine [42]. Thus, the effects of fenfluramine and haloperidol were examined to corroborate the finding that 5-HT receptor stimulation blocks the haloperidol potentiation of TI [41].

METHOD

Animals. Twenty-eight straight run Production Red chickens were received from a commercial supplier (Welp, Inc.) one day after hatch. They were housed in brooders (Brower Mfg. Co , Model 6401) and provided with continuous access to food (Purina chick starter) and water. Exposure to humans was limited to brief periods for daily maintenance and care. Artificial illumination was provided from 8 a.m. to 10 p.m. daily.

Apparatus. Tonic immobility was elicited by physical restraint, then timed by electronic apparatus. Animals were immobilized on their sides against a positioning block which protruded from a wood platform. The platform was housed in a sound-attenuated chamber. A photoelectric cell was situated under the platform and a light source was fastened to the ceiling of the chamber. When in an immobilized position, the animal broke the beam of the photoelectric sensor. A switch on the chamber activated an electronic clock. Upon righting itself, the animal would restore contact between the sensors and the clock would stop. A locking relay prevented additional time recording if the bird moved following termination and broke the beam. A small window on the chamber allowed animals to be checked occasionally, and was positioned so that the observer was out of the animal's view.

Procedure. At 18 days of age, animals were assigned to one of four groups that received two injections consisting of fenfluramine-haloperidol, fenfluramine-vehicle, vehicle-haloperidol, or vehicle-vehicle. The first injection consisted of 35 mg/kg IP of fenfluramine HCl (A. H. Robins) or an equivalent volume (2 ml/kg) of the distilled water vehicle. Immediately following the first injection, animals received 4 mg/kg IP of haloperidol (McNeil) or the lactic acid vehicle in a volume of 4 ml/kg. It was determined prior to the experiment that this dose of haloperidol did not produce catalepsy spontaneously. Animals were placed in cardboard holding boxes for 20 minutes and then individually tested for TI by restraining them for 15 seconds in the apparatus described in the previous section. If an animal did not display TI after the initial elicitation attempt, the animal was restrained again after a 60 second interval. This testing procedure was repeated until an animal displayed TI or 5 induction attempts were made Animals that received five inductions and did not display TI were given a score of zero seconds. Individuals that tested chickens for TI were unaware of group designations of the subjects they restrained.

RESULTS

Table 1 depicts the findings. A square root transformation was performed on durations to reduce heterogeneity of variance and minimize skew. Analysis of variance yielded a main effect for haloperidol, $F(1,24)=4.36$, $p<0.05$, reflecting a potentiation of the response. Fenfluramine attenuated TI duration, $F(1,24)=25.61$, $p<0.001$, but an interaction was not obtained, $F(1,24)=3.43$. Planned simple effects analyses were performed to test the specific hypotheses, that haloperidol by itself would enhance TI relative to controls and that haloperidol-fenfluramine animals would show short durations like those treated with just fenfluramine. These hypotheses follow from the finding that 5-HT receptor stimulation by quipazine reverses the haloperidol potentiation of TI [41] As predicted, the vehicle-haloperidol group showed longer durations than the vehicle-vehicle control group, $F(1,24)=7.76$, $p<0.025$, which replicates previous findings [41,43], but there was no difference between the fenfluramine-vehicle and fenfluramine-haloperidol conditions ($F<1$). Thus, although haloperidol enhanced TI duration when administered by itself, animals receiving both fenfluramine and haloperidol showed short durations like those treated only with fenfluramine. There was a main effect for fenfluramine on the number of inductions required to elicit TI, $F(1,24)=19.32$, $p<0.001$. This effect reflects an increase in the number of inductions for both fenfluramine conditions relative to the remaining groups. There was no effect of haloperidol ($F<1$) or an interaction ($F<1$) for induction data. In summary, fenfluramine decreased TI duration and increased the number of elicitation attempts, in agreement with previous findings [42]. Furthermore, fenfluramine produced these effects whether or not animals additionally received haloperidol. This finding parallels the quipazine reversal of the haloperidol potentiation of tonic immobility [41]

TABLE 1

THE EFFECTS OF FENFLURAMINE (35 mg/kg) AND HALOPERIDOL (4 mg/kg) ON TONIC IMMOBILITY

		Vehicle-Vehicle	Fenfluramine-Vehicle	Vehicle-Haloperidol	Fenfluramine-Haloperidol
Duration (sec)	Mean	664.86	23 86	2114.29	31.0
	Standard Error	402.54	19 20	884 01	12 33
Number of Inductions	Mean	1 71	3 43	1.14	3 86
	Standard Error	0.47	0.68	0.14	0 55

TABLE 2

THE EFFECTS OF TRYPTOPHAN (400 mg/kg) AND APOMORPHINE (2 mg/kg) ON TONIC IMMOBILITY

		Vehicle-Vehicle	Tryptophan-Vehicle	Vehicle-Apomorphine	Tryptophan-Apomorphine
Duration (sec)	Mean	952.63	2003.74	88.95	82 11
	Standard Error	185 99	336.29	25.58	20.69
Number of Inductions	Mean	1.68	1.0	2.42	2 37
	Standard Error	0.33	0	0.36	0.39

EXPERIMENT 2

Serotonergic receptor stimulation by fenfluramine or quipazine prevents the increase in TI caused by DA receptor blockade ([41], Experiment 1). Since evidence supports parallel 5-HT and DA input to striatal structures for mammals [5, 14, 34, 40] and avians [31, 32, 36, 39], it is possible that increased receptor stimulation of one system can compensate for or overcome the effects of decreased postsynaptic function in the other system. Microiontophoretic application of tryptophan indicates that the 5-HT precursor might have direct inhibitory effects on raphe activity [21]. A reduction in postsynaptic function due to direct inhibitory effects appears to be important for the tryptophan potentiation of TI, since 5-HT receptor agonists (e.g., quipazine) block the tryptophan enhancement of TI [42]. The present experiment attempted to prevent the tryptophan potentiation of immobility duration by DA receptor stimulation with apomorphine.

METHOD

Animals. Seventy-six Production Red chickens were acquired and maintained at outlined in the first experiment.

Procedure. At 24 days of age, animals were assigned to one of four groups that received tryptophan and apomorphine, tryptophan and vehicle, vehicle and apomorphine, or two vehicle injections. The first injection consisted of 400 mg/kg IP of L-tryptophan methyl ester HCL (U.S. Biochemical) or the distilled water vehicle. Twenty-eight minutes later, animals received 2 mg/kg IP of apomorphine HCL (Lilly) or distilled water. All injection volumes were 3.33 ml/kg. Testing was conducted 2 minutes following the second injection using the same apparatus and procedures outlined in the previous experiment. The dose and time parameters for apomorphine are comparable to those that are effective for behavioral changes (e.g., [10, 15, 43]) and for DA receptor stimulation in avians (e.g., [10,15]).

RESULTS

The findings are summarized in Table 2. Analysis of variance following a square root transformation of durations indicated main effects for the tryptophan, $F(1,72)=5.82$, $p<0.025$, and apomorphine treatments, $F(1,72)=94.53$, $p<0.001$. The interaction of these treatments was also significant, $F(1,72)=7.22$, $p<0.01$. Simple effects analyses were performed to test the predictions that tryptophan-vehicle birds would display enhanced durations and tryptophan-apomorphine animals would resemble those that received only apomorphine. As predicted, the comparisons revealed that the tryptophan-vehicle and vehicle-vehicle groups differed, $F(1,72)=13.01$, $p<0.001$, indicating that tryptophan by itself increased TI duration. However, there was no reliable difference between the tryptophan-apomorphine and vehicle-apomorphine groups ($F<1$). There was also a main effect for apomorphine on the number of inductions required to produce TI, $F(1,72)=11.43$, $p<0.005$. The main effect for tryptophan ($F=1.37$) and the interaction ($F=1.02$) were not significant. Thus, apomorphine reduced TI duration and made animals less likely to display the response on the initial induction attempts, findings that are consistent with previous work [43]. Apomorphine reversed the tryptophan potentiation of tonic immobility. Specifically, tryptophan-

apomorphine animals displayed a decrement in response duration similar to animals that received only apomorphine

DISCUSSION

Anatomical and neurochemical data support the existence of parallel 5-HT and DA afferents to striatal structures in mammals [5, 14, 34, 40] and avians [31, 32, 36, 39]. These structures and neurotransmitter systems participate in catalepsy [12, 28, 33], and the present findings suggest the involvement of 5-HT and DA systems in TI as well. Fenfluramine, which promotes 5-HT release, decreased TI duration and prevented the haloperidol enhancement of TI duration. This observation parallels those for quipazine effects [41]. The quipazine reduction of TI, and its reversal of the haloperidol potentiation [41], appear to be dependent on 5-HT receptor stimulation since cinanserin, a 5-HT antagonist, blocks the quipazine attenuation of immobility duration [42]. Thus, it appears that 5-HT receptor stimulation can reverse the effect of DA receptor blockade on tonic immobility. Similar observations have been noted for haloperidol-induced catalepsy in rats [13,26].

Tryptophan increases TI duration [9, 23, 42], possibly due to a decrease in synaptic transmission of 5-HT caused by its direct inhibitory action on raphe neurons [21]. This interpretation is supported by the finding that 5-HT receptor agonists (e.g., quipazine) prevent the tryptophan potentiation of TI duration [42]. In the second experiment, the DA receptor agonist apomorphine reduced TI duration and reversed the tryptophan potentiation. It has been argued that tryptophan impairs catecholamine synthesis [18,45], which raises questions about 5-HT and DA interactions for the second experiment. That is, perhaps the tryptophan effect on TI is dopaminergic in nature, rather than involving 5-HT mechanisms. However, impairment of catecholamine synthesis was assessed by DOPA accumulation following decarboxylase inhibition [45], which would preclude the role that end-product inhibition might normally play in the rate of synthesis. Furthermore, recent evidence suggests that tryptophan instead produces a compensatory increase in DA synthesis and release [17]

The serotonergic system participates in apomorphine effects in both mammals and avians [10,25]. For example, 5-HT receptor blockade by methysergide attenuates apomorphine-induced pecking in pigeons [10]. Apomorphine also increases 5-HT turnover in rats [24,27], which may account for its reversal of the tryptophan potentiation of TI duration. This interpretation follows from the finding that direct and indirect 5-HT receptor agonists prevent the tryptophan enhancement of TI [42]. The apomorphine effect on 5-HT function is indirect and depends on DA receptor stimulation, since spiroperidol and transections of DA afferents prevent the apomorphine-induced increase in 5-HT turnover [24,27]. Thus, it is possible that DA receptor stimulation produced a secondary increase in postsynaptic 5-HT function. Presumably this effect would in turn compensate for a decrease in 5-HT transmission caused by the direct inhibitory action of tryptophan on raphe activity [21], and prevent the tryptophan potentiation of TI duration.

Taken together, the findings of the present study and of quipazine and haloperidol effects on TI [41], suggest a possible interaction between 5-HT and DA systems for tonic immobility. Increased postsynaptic function of DA [43] or 5-HT [9, 41, 42] is associated with decreases in TI duration, while decreased postsynaptic function of these neurotransmitters appears to produce an enhancement of TI [9, 42, 43]. In terms of a functional interaction between these systems, receptor stimulation for one neurotransmitter system can offset the effects of impairment of postsynaptic function in the other ([41], present study). Additional work is needed to identify the postsynaptic structures and systems that might be involved in tonic immobility

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