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Pharmacology, Biochemistry and Behavior 77 (2004) 623–629
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
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Role of central 5-HT_2 receptors in mediating head bobs and body shakes in the rabbit

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Received 9 September 2003; received in revised form 16 December 2003; accepted 23 December 2003

Abstract

Systemic administration of the 5-$HT_{2A/2C}$ agonist DOI [(1(2,5-dimethoxy-4-iodophenyl)-2-aminopropane)hydrochloride] in rabbits elicits head bobs and body shakes, which are mediated by 5-HT_{2A} and 5-HT_{2C} receptors, respectively. This study was designed to determine whether the receptors mediating these behaviors are primarily located in the brain or in the periphery. Systemic administration of the peripheral 5-$HT_{2A/2C}$ antagonist xylamidine 30 min before systemic DOI challenge attenuated DOI-elicited body shakes by 50% without an effect on head bobs, suggesting a central origin for head bobs and a partial peripheral and a partial central origin for body shakes. Central administration of DOI into the lateral ventricle (ICV) elicited head bobs but not body shakes, demonstrating that the receptors mediating head bobs are centrally located. Pretreatment with ICV xylamidine blocked head bobs elicited by ICV DOI, indicating that the lack of inhibition, when systemically administered, is due to xylamidine's failure to reach central receptors. ICV pretreatment with the 5-HT_{2A} receptor antagonist ketanserin inhibited ICV DOI-elicited head bobs establishing that 5-HT_{2A} receptors activation elicits head bobs. In conclusion, 5-HT_{2A} receptors mediating head movements are located in the brain whereas 5-HT_{2C} receptors mediating the body movements appear to be located at different central sites as well as in the periphery.

Keywords: 5-HT_{2A} receptors; 5-HT_{2C} receptors; Head bobs; Body shakes; DOI; Rabbit; Intracerebroventricular; Xylamidine; Ketanserin

1. Introduction

Motor movement, a fundamental component of behavior, is the principle extrinsic action of the brain (Rekling et al., 2000). Numerous neurotransmitters and their receptors are involved in facilitating and modulating motor movements. The role of the serotonergic neurotransmitter system in modulating neuronal excitability and in turn modulating motor behavior has been extensively studied (for reviews, see Jacobs et al., 2002; Jacobs and Fornal, 1997). Evidence for the role of central serotonin (5-HT) in motor behavior was first demonstrated in rodents where administration of drugs that increase synaptic 5-HT, including 5-HT releasers, precursors, and direct-acting agonists, produced a motor syndrome similar to that seen in a large number of vertebrates including humans (Jacobs, 1976; Sternbach, 1991). This motor syndrome consists of hyperactivity, tremor, rigidity, hindlimb abduction, lateral head weaving, straub tail, forepaw treading, hyperreactivity, and shaking behaviors (head shakes, head twitches, and body shakes). These behavioral features have been studied as models for activation of the endogenous 5-HT system and selective ligands have been used to relate subsets of these behaviors with activation of different 5-HT receptors in the central nervous system (CNS) (Bedard and Pycock, 1977; Grahame-Smith, 1971; Jacobs, 1976). For example, in the rodent, systemic administrations of 5-$HT_{2A/2C}$ receptor agonists such as (1(2,5-dimethoxy-4-iodophenyl)-2-aminopropane)hydrochloride (DOI) elicits head and body movements (head shakes, head twitches, and body shakes), which have been established as behavioral correlates of 5-HT_{2A} receptors activation (Dursun and Handley, 1996; Pranzatelli, 1990; Schreiber et al., 1995; Wettstein et al., 1999). In the rat, head and body shakes have been shown to be mediated by 5-HT_{2A} receptors in the brain (Ciccocioppo et al., 1995; Hawkins et al., 2002; Nagayama and Lu, 1996). In the rabbit, systemic administration of DOI also dose-dependently elicits head movements (vertical down–up head bobs)

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doi:10.1016/j.pbb.2003.12.017

and body shakes (Dave et al., 2002). Similar to the rodent, the head bobs in the rabbit are mediated by 5-HT_{2A} receptors. However, unlike the rodent, the body shakes in the rabbit are mediated by 5-HT_{2C} receptors, indicating species differences in the receptors mediating 5-HT-elicited motor movements.

The present study was designed to determine whether, in the rabbit, the 5-HT_{2A} and 5-HT_{2C} receptors mediating the separate DOI-elicited behaviors are located in the brain or the periphery. First, systemic injections of the peripherally acting 5-$HT_{2A/2C}$ receptor antagonist xylamidine were employed to study its effects on head bobs and body shakes produced by systemic injections of DOI. Second, DOI was infused into the lateral ventricle to determine whether head bobs and body shakes could be elicited by direct central administrations of DOI and whether central administrations of ketanserin and xylamidine would block these behavioral effects.

2. Material and methods

2.1. Animals

Adult male New Zealand rabbits (Covance, Denver, PA) weighing 1.6–1.8 kg were housed individually upon arrival. They were housed under a 12/12-h light/dark cycle with access to 125 g of chow per day and free access to water in an AAALAC-approved animal facility maintained at 22 °C. Rabbits were adapted to their home-cages for 5 days and were handled for at least 2 days before the initiation of experiments. All animal experiments were carried out in accordance with the National Institute of Health guide *Principles of Laboratory Animal Care* (NIH publication no. 85-23, revised 1985) and university IACUC guidelines.

2.2. Cannulae and surgery

The 22-gauge guide cannulae, 28-gauge obdurators, and 28-gauge injector cannulae were prepared as previously described (Welsh and Harvey, 1991). The obdurator was prepared to fit flush with the tip of the guide cannula, and the injector cannula was calibrated to extend the tip of the injector 1 mm beyond the tip of guide cannula. The guide cannula/obdurator assemblies were implanted into the left lateral ventricle under pentobarbital anesthesia using a Kopf stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). The head holder was adjusted so that the surface of the skull at bregma was 1.5 mm above the surface of the skull at lambda. Implantation coordinates were 2.0 mm lateral to bregma and 5.5 mm below the surface as measured at bregma. The cannulae were cemented with dental acrylic to two screws drilled into the skull. Rabbits were given at least 4 days to recover from surgery before initiating the behavioral experiments. At the end of the behavioral experiments, all cannulae-implanted animals in this study were injected with 10 μl of 1% methylene blue delivered over 1 min and then were sacrificed by decapitation, and the brains were removed, dissected, and visually inspected for the presence of dye within the ventricle. Delivery of dye into the ventricle was confirmed for all animals in this study.

2.3. Drugs

DOI and ketanserin tartrate were purchased from Sigma-RBI (St. Louis, MO). Xylamidine tosylate was obtained from the Wellcome Foundation (Beckenham, Kent, UK). Artificial cerebrospinal fluid (aCSF) consisted of 147 mM NaCl, 2.3 mM $CaCl_2$, 0.9 mM $MgCl_2$, and 4.0 mM KCl (adjusted to pH 7.3–7.4) (Du et al., 1999).

All drugs were prepared fresh on the day of the experiment. For systemic injections, drugs were dissolved in sterile saline and injected subcutaneously between the scapula in a volume of 1 ml/kg. For central infusions, drugs were dissolved in sterile aCSF and infused into the left lateral ventricle in a total volume of 10 μl delivered over 1 min by a CMA/100 microinjection pump (Carnegie Medicin, Stockholm, Sweden). The injector cannula was left in place for an additional minute before being removed.

For systemic injections, a submaximal dose of DOI (0.3 μmol/kg or 0.1 mg/kg) was selected based upon the dose–response experiments previously published in Dave et al. (2002). Doses of xylamidine [0.2 μmol/kg (0.1 mg/kg) and 2.0 μmol/kg (1.0 mg/kg)] were chosen based upon studies concerning DOI's effect on renin secretion and arterial pressure in rodents (Alper, 1990; Pergola and Alper, 1991; Rittenhouse et al., 1991). ICV doses of DOI [10 nmol (3.5 μg) and 30 nmol (10 μg)] were selected based upon experiments in the rat where DOI was shown to produce behavioral effects including an increase in the number of head shakes (Ciccocioppo et al., 1995; Raghavendra and Kulkarni, 2000). Similarly, the ICV dose of ketanserin [30 nmol (16 μg)] selected reflects a behaviorally effective dose that inhibited the head twitch response in mice (Chairungsrilerd et al., 1998).

2.4. Behavioral observations

A detailed methodology for behavioral observations has been previously described in Dave et al. (2002). For systemic injections, rabbits were injected with antagonist or vehicle and returned to their home-cages. After 30 min, rabbits were injected with DOI and returned to their home-cages for behavioral observations. For central infusions, rabbits were placed in Plexiglas restrainers and antagonist or vehicle was infused after which they were returned to their home-cages. After 15 min, rabbits were replaced in the Plexiglas restrainers and DOI was infused. They were then returned to their home-cages for behavioral observations. The number of head bobs (rapid sequential "down–

up" movements of the head) and body shakes (a paroxysmal shudder of the head, neck and trunk combined, similar to wet dog shakes in rodents) were recorded in blocks of 10 min for a total observation period of 90 min immediately after DOI administration. Food and water were available during the antagonist or vehicle pretreatment interval but were removed immediately before DOI administration. All observations took place in the animal's home-cage between 09:00 and 15:00 h. Some of the animals were videotaped and an independent rater blind to the drug treatment recorded the video to score head bobs and body shakes. This method gave the interrater reliability of .95.

2.5. Experimental design

For systemic injections, animals were pretreated with either saline ($n=8$) or xylamidine (0.2 or 2 μmol/kg, $n=4$/dose) 30 min before administration of DOI (0.3 μmol/kg). For dose–response analyses of ICV DOI, rabbits were infused with either aCSF ($n=4$) or DOI (10 or 30 nmol, $n=4$/dose). For antagonist experiments, rabbits were infused with aCSF ($n=8$), ketanserin (30 nmol, $n=4$), or xylamidine (50 nmol, $n=4$) 15 min before administration of DOI (30 nmol).

2.6. Data analysis

The cumulative time-course data were analyzed with a repeated measures analysis of variance, and total numbers of behaviors were subjected to one-way analyses of variance. Post hoc analyses were done by Dunnett's t test with the limit of significance set at $P<.05$.

3. Results

3.1. Systemic DOI administration: effects of systemic xylamidine on DOI-elicited behaviors

DOI (0.3 μmol/kg) administration elicited 40.9 ± 3.2 head bobs in the vehicle-pretreated group (Fig. 1, upper panel). Pretreatment with the peripheral 5-$HT_{2A/2C}$ receptor antagonist xylamidine had no significant effect on head bobs elicited by DOI (0.3 μmol/kg) [$F(2,13)=0.9$]. For example, in rabbits pretreated with xylamidine (0.2 μmol/kg), DOI elicited 43.0 ± 2.3 head bobs. Even a 10 times higher dose of xylamidine (2.0 μmol/kg) had no significant effect on DOI-elicited head bobs (36.2 ± 1.3) compared to the vehicle-pretreated group. In contrast to the head bobs, xylamidine pretreatment significantly attenuated DOI-elicited body shakes (Fig. 1, lower panel) [$F(2,13)=20.4$, $P<.001$]. For example, DOI (0.3 μmol/kg) administration elicited 12.6 ± 0.9 body shakes in the vehicle-pretreated group. Xylamidine (0.2 μmol/kg) decreased the number of body shakes compared to the vehicle-pretreated group to 5.5 ± 0.6, a 56% reduction. The higher dose of xylamidine (2.0 μmol/kg) attenuated body shakes to 7.25 ± 0.5, a 43% reduction. Hence, both doses of xylamidine appear to have produced a maximal antagonism of approximately 50% of DOI-elicited body shakes.

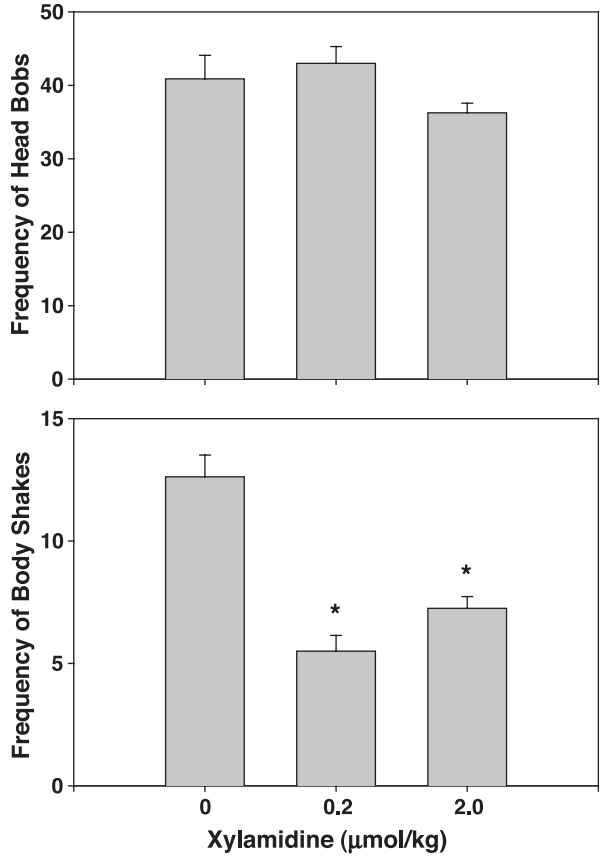

Fig. 1. Effects of peripheral 5-$HT_{2A/2C}$ receptor antagonist xylamidine on DOI-elicited head bobs (upper panel) and body shakes (lower panel). Animals were pretreated with either vehicle ($n=8$) or xylamidine (0.2 or 2.0 μmol/kg, $n=4$/dose) 30 min before administration of DOI (0.3 μmol/kg). Head bobs and body shakes were counted immediately after DOI injection for 90 min. Results are shown as mean ± S.E.M. * Significantly different from the vehicle-pretreated group; Dunnett's test, $P<.05$ (no asterisk indicates no significant differences).

3.2. Central DOI administration

Unilateral ICV infusion of aCSF elicited an average of 9.2 ± 1.3 head bobs and 1.5 ± 0.3 body shakes (Fig. 2, upper panel). Unilateral administrations of DOI into the lateral ventricle significantly and dose-dependently increased the number of head bobs [$F(2,9)=119.28$, $P<.01$]. DOI (10 and 30 nmol) increased the number of head bobs to an average of 20.0 ± 2.9 and 63.7 ± 3.2, respectively. In contrast, DOI (10 and 30 nmol) did not significantly increase the number of body shakes (1.25 ± 0.3 and 3.25 ± 0.8) compared to the vehicle controls [$F(2,9)=5.03$]. The cumulative time course for the increase in head bobs produced by ICV DOI (10 and 30

nmol) and aCSF is presented in the lower panel of Fig. 2. There was a significant main effect of time across the nine 10-min intervals [$F(8,72) = 185.85$, $P < .01$]. More importantly, there was a significant interaction between time, and drug treatment [$F(16,72) = 76.91$, $P < .01$] due to the significantly large increase in the number of head bobs produced by DOI. The time course illustrated a rapid onset in the number of head bobs and the effect lasted for about 60 min after DOI infusion. It should be noted that approximately 35% of the total head bobs (63.7 ± 3.2) occurred within the first 10 min (24.5 ± 1.8) following ICV infusion of DOI (30 nmol).

3.3. Central DOI administration: effects of ICV ketanserin and ICV xylamidine on DOI-elicited behaviors

ICV DOI (30 nmol) elicited 61.1 ± 3.6 head bobs and 2.7 ± 0.6 body shakes in the vehicle-pretreated group (Fig. 3). ICV administration of ketanserin (30 nmol) and xylamidine (50 nmol) significantly attenuated head bobs elicited by ICV DOI (30 nmol) [$F(2,13) = 38.13$, $P < .01$]. Ketanserin pretreatment significantly decreased head bobs to an average of 17.5 ± 2.5 (71% decrease). Similarly, xylamidine pretreatment also significantly decreased head bobs to an average of 21.5 ± 5.5 (65% decrease). Both ketanserin and xylamidine produced a complete antagonism of DOI-elicited head bobs since there were no significant differences in head bobs between ketanserin- and xylamidine-pretreated groups and aCSF alone controls [$F(2,9) = 3.0$, $P = .1$]. There was no effect of ICV ketanserin and xylamidine pretreatment on body shakes [$F(2,13) = 0.51$, $P = .61$].

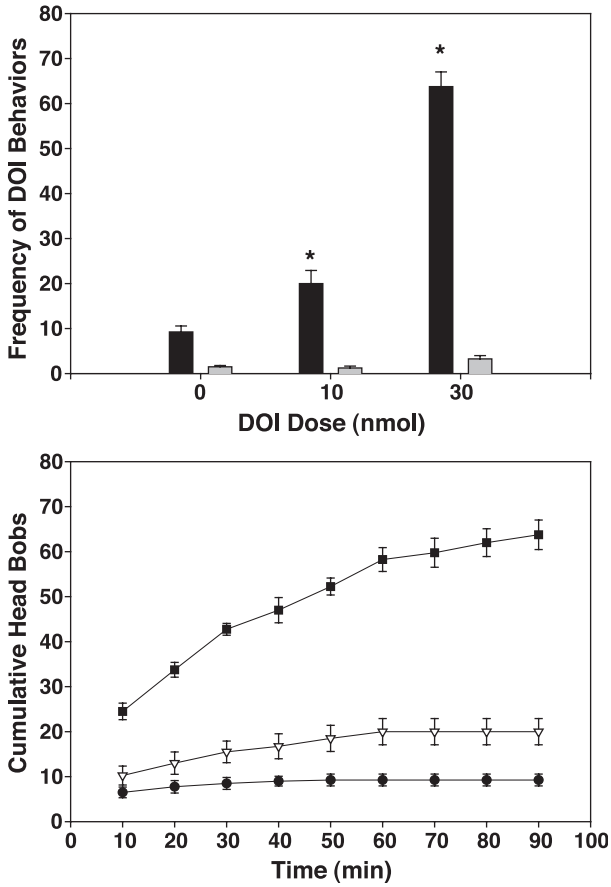

Fig. 2. DOI dose–response. Upper panel: Total number of head bobs (black bar) and body shakes (gray bar) were counted for the 90 min immediately following unilateral ICV administration of aCSF ($n = 4$) or DOI (10 or 30 nmol, $n = 4$/dose). Results are shown as mean ± S.E.M. * Significantly different from the aCSF control group; Dunnett's test, $P < .05$. Lower panel: Cumulative time course of head bobs for both aCSF (●) and DOI [10 nmol (▽) or 30 nmol (■)] is shown in 10-min intervals. Results are shown as mean ± S.E.M.

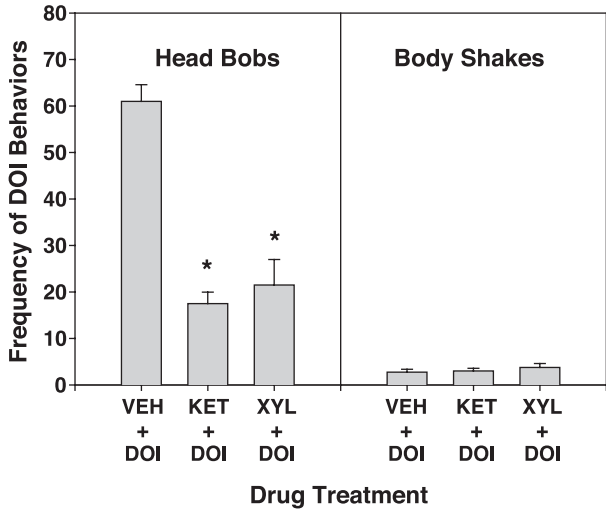

Fig. 3. Effects of centrally administered 5-HT_{2A} antagonist ketanserin and 5-$HT_{2A/2C}$ antagonist xylamidine on behaviors elicited by ICV DOI. Animals were pretreated ICV with either aCSF ($n = 4$), ketanserin (30 nmol, $n = 4$), or xylamidine (50 nmol, $n = 4$) 15 min before ICV administration of DOI (30 nmol). The total number of head bobs and body shakes were counted for 90 min immediately after DOI infusion. Results are shown as mean ± S.E.M. * Significantly different from the vehicle-pretreated group; Dunnett's test, $P < .05$. KET = ketanserin, VEH = vehicle, XYL = xylamidine.

4. Discussion

The major finding of this study is that 5-HT_{2A} and 5-HT_{2C} receptors mediating separate motor movements have divergent underlying neuronal circuitry localized to different brain regions. 5-HT_{2A} receptors mediating head movements are located centrally in areas accessible to lateral ventricle infusions. In contrast, 5-HT_{2C} receptors mediating the body movements appear to be located in the brain and the periphery. In contrast to the 5-HT_{2A} receptors mediating the head bobs, 5-HT_{2C} receptor mediating body shakes are not located in brain areas accessible to lateral ventricle infusions of DOI.

4.1. DOI-elicited head bobs are mediated by central 5-HT_{2A} receptors

Previously, we demonstrated that systemic administration of DOI elicited a dose-dependent increase in head bobs, which were mediated by 5-HT_{2A} receptors (Dave et al., 2002). 5-HT_{2A} receptors are present both in the CNS and in peripheral tissues, such as vascular smooth muscle (for a review, see Roth et al., 1998). Xylamidine was employed to determine whether the 5-HT_{2A} receptors mediating head bobs were located in the brain or the periphery. This selective high affinity 5-$HT_{2A/2C}$ receptor antagonist has been shown to poorly penetrate the blood–brain barrier (Copp et al., 1967; Fuller et al., 1986; Leysen, 1992; Mawson and Whittington, 1970), and therefore following peripheral administration, this antagonist would be expected to only block peripheral 5-HT_{2A} receptors. Pretreatment with xylamidine (0.2 μmol/kg) had no effect on head bobs elicited by systemically administered DOI. This finding is in agreement with earlier reports where xylamidine failed to inhibit 5-$HT_{2A/2C}$ receptor agonist MK-212-elicited head twitches in mice (Clineschmidt et al., 1977) and 5-HT precursor 5-hydroxytryptophan (5-HTP)-elicited head shakes in rats (Matthews and Smith, 1980). In contrast to these data regarding DOI's behavioral effects, the same dose of xylamidine has been shown to attenuate DOI-elicited (5-HT_{2A} receptor-mediated) physiological effects including increases in renin secretion and arterial pressure demonstrating that the receptors mediating the physiological effects are peripheral (Alper, 1990; Pergola and Alper, 1991; Rittenhouse et al., 1991). To further verify the lack of effect of xylamidine on head bobs, a 10 times higher dose of xylamidine (2.0 μmol/kg) was also employed again without significant effect on DOI-elicited head bobs. These data support the conclusion that DOI-elicited head bobs are mediated by central and not by peripheral 5-HT_{2A} receptors.

To further test the hypothesis that 5-HT_{2A} receptors in the CNS are responsible for DOI-elicited head bobs, DOI was directly infused into the left lateral ventricle of the rabbit. ICV DOI significantly and dose-dependently increased the number of head bobs confirming that DOI-elicited head bobs are mediated by receptors in the CNS. This is in agreement with results obtained with the rat where a similar dose of ICV DOI (10 nmol) elicited head shakes (Ciccocioppo et al., 1995). To determine whether central 5-HT_{2A} receptors mediate DOI-elicited head bobs, pharmacological analyses were performed with ICV administrations of the selective 5-HT_{2A} receptor antagonist ketanserin and 5-$HT_{2A/2C}$ receptor antagonist xylamidine. In the rodent, ICV infusion of ketanserin has been shown to inhibit 5-HT_{2A} receptor-mediated head twitches (Chairungsrilerd et al., 1998). Ketanserin has a high affinity for the rabbit 5-HT_{2A} receptor (K_i = 0.54 nM) and is 30-fold more selective for 5-HT_{2A} compared to 5-HT_{2C} receptors (Aloyo and Harvey, 2000). Moreover, systemic administration of ketanserin attenuated head bobs elicited by systemically administered DOI (Dave et al., 2002). In this study, ICV pretreatment with ketanserin significantly antagonized ICV DOI-elicited head bobs, indicating that DOI elicited head bobs via activation of 5-HT_{2A} receptors in the brain. Furthermore, ICV pretreatment with xylamidine significantly antagonized ICV DOI-elicited head bobs, indicating that the lack of inhibition of head bobs following systemic administration of xylamidine was not due to the lack of efficacy but due to the failure of systemic xylamidine to reach and block 5-HT_{2A} receptors at the critical sites in the brain responsible for the behavior. Hence, these data establish that behavioral correlates of 5-HT_{2A} receptor activation in the rabbit, head bobs, are mediated by 5-HT_{2A} receptors located in the CNS.

Interestingly, the number of head bobs elicited by 30 nmol of ICV DOI (63.7 ± 3.2; Fig. 2, upper panel) was considerably greater than the maximal number of head bobs elicited by systemically administered DOI (38.7 ± 9.1; Dave et al., 2002). The observation showing rapid onset in head bobs after central infusion of DOI with maximal number occurring in the first 10 min (Fig. 2, lower panel) suggests that ICV DOI directly and easily reaches critical brain loci responsible for head bobs in the rabbit. Previous investigations in the rodent regarding brain loci mediating 5-HT_{2A} receptor-mediated behavior have focused on the frontal cortex as an area of interest. For example, direct administrations into the medial prefrontal cortex of 5-HT_{2A} receptor agonists, such as DOI and DOB (1(2,5-dimethoxy-4-bromophenyl)-2-aminopropane), dose-dependently elicited head shakes (Granhoff et al., 1992) and wet dog shakes in rats (Ciccocioppo et al., 1999) and head twitches in mice (Willins and Meltzer, 1997), suggesting that the prefrontal cortex is a site of action for 5-HT_{2A} receptor agonists to induce behavioral responses. However, total ablation of the frontal cortex did not impair the head shake response elicited either by systemic administrations of the 5-HT precursor 5-HTP or the direct acting 5-$HT_{2A/2C}$ receptor agonist quipazine (Lucki and Minugh-Purvis, 1987). Moreover, Bedard and Pycock (1977) reported that denervation produced by specific knife cuts in the frontal cortex region had no effect on 5-HTP-elicited head twitches. These data indicate that the ability of 5-HT_{2A} agonists to elicit motor movements does not depend on the frontal cortex and that the frontal cortex may be a sufficient but not a necessary brain locus in mediating 5-HT_{2A} receptor-mediated behaviors. 5-HT_{2A} receptors have been shown to have a widespread heterogeneous distribution, including forebrain areas such as the hippocampus and the caudate putamen (Aloyo et al., 2001; Appel et al., 1990; Burnet et al., 1995; Pompeiano et al., 1994; Wright et al., 1995). Indeed, infusion of 5-HT bilaterally into the hippocampus and the caudate nucleus has been shown to increase locomotor activity (Takahashi et al., 2000). Thus, the rapid onset in head bobs after central infusion of DOI suggests that brain areas close to the lateral ventricle may also mediate 5-HT_{2A} receptor-elicited motor movements. Hence,

investigation of other forebrain loci (besides the frontal cortex) critical for 5-HT_{2A} receptor-mediated motor movements is warranted.

4.2. DOI-elicited body shakes are mediated by both central and peripheral 5-HT_{2C} receptors

Previously, we demonstrated that in the rabbit DOI-elicited body shakes in the rabbit were attenuated by selective 5-HT_{2C} receptor antagonists SB 206553 and SDZ SER 082 but not by the 5-HT_{2A} receptor antagonist ketanserin, demonstrating that 5-HT_{2C} receptors mediate this behavior (Dave et al., 2002). Xylamidine was employed to determine whether the 5-HT_{2C} receptors mediating body shakes were located in the brain or the periphery. As described above, xylamidine is a peripherally acting 5-$HT_{2A/2C}$ receptor antagonist that exhibits equal affinities for both the 5-HT_{2A} and the 5-HT_{2C} receptors (Leysen, 1992). Xylamidine pretreatment attenuated body shakes elicited by systemically administered DOI suggesting a possible role for peripheral receptors. The dose of xylamidine (0.2 μmol/kg), which had no effect on head bobs, attenuated body shakes, providing further evidence that separate receptors mediate head bobs and body shakes elicited by DOI. Furthermore, even a 10-fold higher dose of xylamidine (2.0 μmol/kg) did not produce any greater attenuation of body shakes, indicating that body shakes elicited by peripheral administration of DOI may be partially produced by 5-HT_{2C} receptors in the periphery and partially in the brain. The ability of the peripherally acting xylamidine to block body shakes might be due to actions at the circumventricular organs in the brainstem and/or midbrain (such as the area postrema and the subfornical region), which lie outside the blood–brain barrier, are highly vascularized (McKinley et al., 1990; Pergola and Alper, 1991) and express 5-HT_{2C} receptor mRNA (Pompeiano et al., 1994).

Although it appears that some of the 5-HT_{2C} receptors mediating body shakes are located in the brain, ICV DOI (which elicited increases in 5-HT_{2A} receptor-mediated head bobs) failed to increase the number of 5-HT_{2C} receptor-mediated body shakes. These data indicate that, although 5-$HT_{2A/2C}$ receptors coexist in many areas of the brain (Aloyo et al., 2001; Pompeiano et al., 1994; Wright et al., 1995), the 5-HT_{2A} receptors mediating head bobs and the 5-HT_{2C} receptors mediating body shakes are located in different brain regions.

4.3. Conclusions

This study establishes that activation of 5-HT_{2A} receptors in brain areas accessible to lateral ventricle administration elicits head bobs in the rabbit. These brain areas also contain 5-HT_{2C} receptors; however, these receptors are not involved in mediating DOI-elicited body shakes. 5-HT_{2C} receptors mediating the body shakes may be located in the midbrain/brainstem areas as well as in the periphery. This study establishes the differential location of 5-HT_2 receptors mediating head and body movements in the rabbit. In general, this study also advances our understanding of the role of the serotonergic system in modulating motor activity. The facilitation of motor output by 5-HT is both receptor and circuit specific.

Acknowledgements

This research was supported by USPHS Grant No. MH16841 from the National Institute for Mental Health. The authors also thank Dr. Anthony G. Romano and Dr. Kenny J. Simansky for their thoughtful suggestions and advice during the course of these experiments.

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