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Phencyclidine-Induced Wet-Dog Shakes Observed in Rats After Withdrawal From Reserpine Treatment

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NABESHIMA, T., K. YAMAGUCHI, S. YOSHIDA, H. FURUKAWA AND T. KAMEYAMA. *Phencyclidine-induced wet-dog shakes observed in rats after withdrawal from reserpine treatment.* PHARMACOL BIOCHEM BEHAV **24**(5) 1275–1279, 1986.—This study was designed to assess the involvement of serotonergic neurons in phencyclidine (PCP)-induced wet-dog shakes in rats after termination of reserpine treatment. Administration of L-5-hydroxytryptophan (7.5–12.5 mg/kg) to rats 30 min following pretreatment with pargyline induced wet-dog shakes which included head shake and whole body shake. *p*-Chloroamphetamine (PCA) (5 mg/kg) alone also produced wet-dog shakes in the vehicle-pretreated rats, but PCP (2.5–7.5 mg/kg) and tryptophan (100 mg/kg) alone did not. The number of wet-dog shakes significantly increased after the injection of PCA (2.5 and 5 mg/kg) in the reserpine-pretreated rats, in which the 5-hydroxyindoleacetic acid/serotonin (5-HT) ratio was significantly higher and postsynaptic 5-HT receptors were also in a state of supersensitivity, compared to that of the vehicle-pretreated rats. PCP (2.5–7.5 mg/kg) also produced wet-dog shakes in a dose-dependent fashion in rats after pretreatment with reserpine. Furthermore, PCP-induced wet-dog shakes were potentiated by imipramine, a 5-HT-uptake blocker, and prevented by mianserin, a 5-HT receptor-blocker. Tryptophan (100 mg/kg) alone produced wet-dog shakes in the reserpine-pretreated rats and it was enhanced in combination with imipramine. These results may indicate that the PCP-induced wet-dog shakes after reserpine withdrawal are due to an increased release of 5-HT from the functional pool and supersensitivity of postsynaptic 5-HT receptors.

Phencyclidine Wet-dog shakes Reserpine Serotonin

PHENCYCLIDINE (PCP) was introduced over 20 years ago as an intravenous anesthetic [3] but has had limited use in clinical medicine due to psychotomimetic and convulsant side effects. In recent years, there has been a dramatic increase in the abuse of PCP in the form of a recreational drug "angel dust" among young people in the USA [27].

Treatment of rats with an irreversible inhibitor of monoamine oxidase followed by L-tryptophan produces a characteristic behavioral neurological syndrome such as increased locomotion, reciprocal forepaw treading, hind-limb abduction, head weaving, tremor, body shakes and Straub tail. This behavioral syndrome is apparently mediated by 5-hydroxytryptamine (5-HT) [1, 10, 13]. The newly formed 5-HT "spills over" into the synapse after its levels exceed the capacity of the presynaptic neurons to store or metabolize it [11,12]. The behavioral syndrome can also be produced by direct 5-HT receptor agonists such as 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) [22] or by drugs including *p*-chloroamphetamine (PCA) that release 5-HT from the presynaptic neurons [22]. This syndrome has been used extensively to study drugs which act on the brain 5-HT neuronal system by altering synthesis and release, or by interacting with 5-HT receptors directly. This behavioral syndrome is similar to some components of PCP-induced stereotypies [17,22]. In addition, we have suggested that PCP-induced stereotyped behaviors are mediated by serotonergic neurons since a specific serotonergic neuronal toxin (5,6-dihydroxytryptamine)-induced lesion of the striatum and the electrolytic lesion of the raphe nucleus which contains 5-HT cell bodies diminish PCP-induced stereotyped behaviors [20,21]. Furthermore, PCP-induced stereotyped behaviors are attenuated by the 5-HT depletors, reserpine, *p*-chlorophenylalanine and PCA and antagonized by the putative 5-HT antagonists, cinanserin and cyproheptadine [17,22]. Furthermore, PCP-induced stereotyped behaviors are potentiated by 5-HT-precursor (tryptophan), monoamine oxidase inhibitor (pargyline) and 5-HT-reuptake inhibitor (imipramine) [22]. We have also suggested that PCP may interact with the 5-HT_2 receptor and inhibit [^{3}H]-spiperone binding to 5-HT_2 receptors [23, 24, 25].

The chronic reserpinization is accompanied by increased catecholamine synthesis [19] and supersensitivity of catecholamine receptors [5], which might compensate for the lack of "stored" catecholamines. Amphetamine can release catecholamines from tissues derived from reserpinized animals [6,26]. In addition, chronic reserpine treatment has also been shown to increase intensity of the methamphetamine-induced stereotyped behavior and

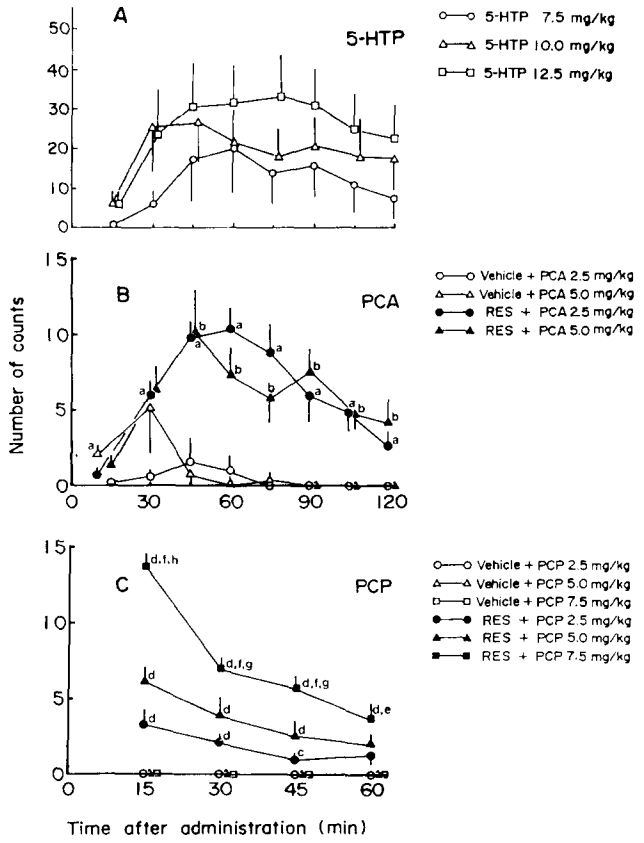

FIG. 1. Time course of 5-hydroxytryptophan (5-HTP), *p*-chloroamphetamine (PCA) and phencyclidine (PCP)-induced wet-dog shakes in vehicle- or reserpine (RES)-pretreated rats. Rats in experiment A were given pargyline (25 mg/kg, IP) 30 min prior to the 5-HTP injection. Each rat in experiments B and C was pretreated with vehicle or RES. After 5 drug-free days, the rats were challenged with PCA (experiment B) or PCP (experiment C). The total number of wet-dog shakes was counted by using the scoring system described in the Method section. Values are the mean±S.E. of 5–10 rats. $^{a}p<0.05$ vs. Vehicle + PCA 2.5 mg/kg, $^{b}p<0.05$ vs. Vehicle + PCA 5.0 mg/kg, $^{c}p<0.05$, $^{d}p<0.01$ vs. Vehicle + PCP 2.5, 5.0 or 7.5 mg/kg, $^{e}p<0.05$, $^{f}p<0.01$ vs. RES + PCP 2.5 mg/kg, $^{g}p<0.05$, $^{h}p<0.01$ vs. RES + PCP 5.0 mg/kg.

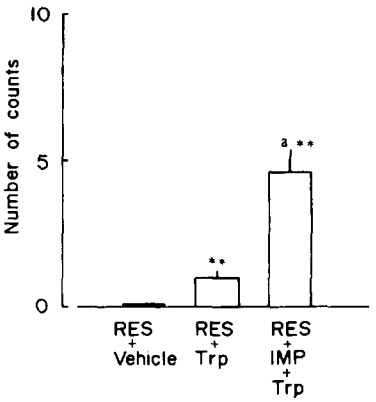

FIG. 2. L-tryptophan (Trp)- or [Trp and imipramine (IMP)]-induced wet-dog shakes in reserpine (RES)-pretreated rats. Each rat was pretreated with RES. After 5 drug-free days, the rats were pretreated with vehicle or IMP (12.5 mg/kg, IP) 2.5 hr prior to the injection of Trp (100 mg/kg, IP). The total number of wet-dog shakes was counted by using the scoring system described in the Method section. The results were evaluated for 60 min observation-period after vehicle or Trp injection. Values are the mean±S.E. of 8–9 rats. $^{**}p<0.01$ vs. RES + Vehicle, $^{a}p<0.01$ vs. RES + Trp.

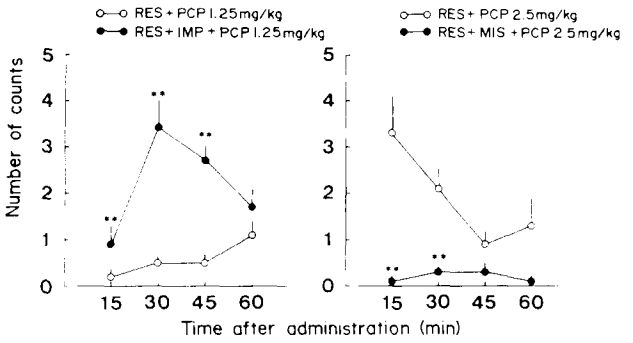

FIG. 3. Effects of imipramine (IMP) or mianserin (MIS) on the phencyclidine (PCP)-induced wet-dog shakes in vehicle- or reserpine (RES)-pretreated rats. Each rat was pretreated with vehicle or RES. After 5 drug-free days, the rats were pretreated with IMP (12.5 mg/kg, IP) 2.5 hr prior to the injection of PCP (1.25 mg/kg, IP) or pretreated with MIS (20 mg/kg, IP) 45 min prior to the injection of PCP (2.5 mg/kg, IP). The total number of wet-dog shakes was counted by using the scoring system described in the Method section. Values are the mean±S.E. of 10 rats. $^{**}p<0.01$ vs. RES + PCP.

hypermotility [30]. Inhibition of the synthesis of the catecholamines in reserpinized rats prevents amphetamine effects or methamphetamine-induced behavioral responses [28,34]. Recently, Friedman *et al.* [7] have reported that treatment with reserpine produced an increase in responsiveness to 5-MeODMT after withdrawal from reserpine treatment. Furthermore, it is also indicated that PCA releases 5-HT into the synaptic cleft from a small cytoplasmic pool which is resistant to reserpine in rats treated with reserpine 24 hr before the decapitation and this newly synthesized compartment of 5-HT represents the "functional" transmitter pool [14]. To confirm an involvement of the serotonergic neuronal system in the action of PCP, we investigated whether PCP produces wet-dog shakes, which is well known to be one of the 5-HT-dependent behaviors [1], using rats pretreated with reserpine since PCP is not able to produce it in normal rats.

METHOD

Male Fischer 344 rats (Charles River Breeding Co., Japan), weighing 150–200 g were used. The animals were maintained in a temperature- and humidity-conditioned room (22–24°C, 55±5%) with controlled lighting (light on 8:00–20:00 hr).

Phencyclidine-HCl (PCP, synthesized by us), DL-*p*-chloroamphetamine-HCl (PCA, Sigma), imipramine-HCl (Fujisawa), mianserin-HCl (Sankyo) and pargyline-HCl (Sigma) were dissolved in a 0.9% saline. Reserpine (Roche) was suspended with 0.3% carboxymethylcellulose in 0.9% saline. L-5-hydroxytryptophan (5-HTP, Sigma) and

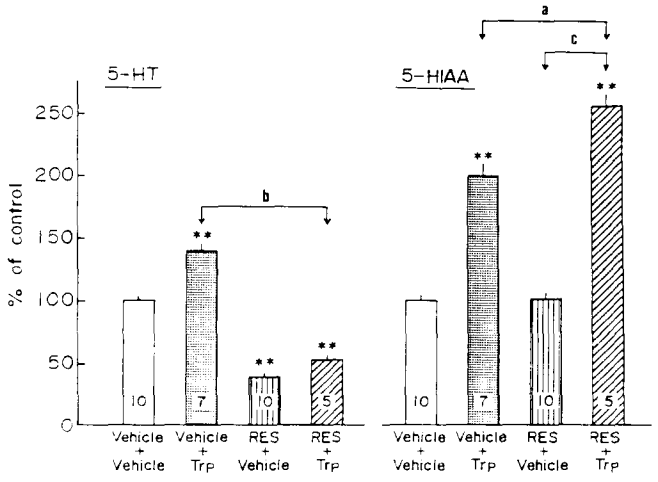

FIG. 4. Effect of reserpine (RES)-pretreatment in combination with L-tryptophan (Trp) on the serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) levels in rat brain. Each rat was pretreated with vehicle or RES. After 5 drug-free days, the rats were challenged with vehicle or Trp (50 mg/kg, IP) as described in the Method section. The number in the columns shows the number of samples. Each value is expressed as a % of the control level described in the Method section. Values are the mean±S.E. $^{**}p<0.01$ vs. Vehicle + Vehicle, $^{a}p<0.05$, $^{b}p<0.01$ vs. Vehicle + Trp, $^{c}p<0.01$ vs. RES + Vehicle.

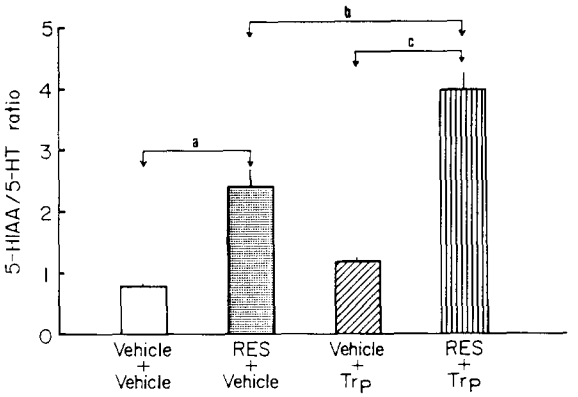

FIG. 5. Comparison of 5-hydroxyindoleacetic acid (5-HIAA)/serotonin (5-HT) ratio between vehicle- and reserpine (RES)-pretreated rats. $^{a}p<0.01$ vs. Vehicle + Vehicle, $^{b}p<0.05$, $^{c}p<0.01$ vs. RES + Trp.

L-tryptophan (Sigma) were dissolved in saline acidified with a minimum amount of hydrochloric acid. 5-Methoxy-N,N-dimethyltryptamine (5-MeODMT, Sigma) was dissolved in 0.9% saline containing 0.5% ascorbic acid.

Rats (5 rats per group) were treated with pargyline (25 mg/kg, IP) 30 min prior to the intraperitoneal injection of 5-HTP (7.5, 10 and 12.5 mg/kg). Following the injection of 5-HTP, the animals were transferred to an observation cage (19×30×13 cm) and were observed for eight periods, each observation period being 15 min. During the observation periods, the total number of wet-dog shakes, including whole body shake and head shake, was counted. A treatment with reserpine was performed following the schedule of Friedman *et al.* [7] with minor modification. Rats were given reserpine (2.5 mg/kg, IP) once a day for 2 days between 9:00 and 11:00 a.m. Control rats were given the same volume of vehicle following the same schedule as for reserpine treatment. After 5 drug-free days, the rats (5–10 rats per group) were challenged with PCP or PCA and the total number of wet-dog shakes was determined following the same protocol used after 5-HTP treatment. Drugs were administered in a randomized manner. Observation of wet-dog shakes was carried out by two of the authors who were unaware of which drug treatment had been given.

The animal was decapitated on the 5th day of withdrawal from reserpine treatment between 10:00 a.m. and 1:00 p.m. The brain was frozen rapidly and stored in a freezer at −70°C until assay. The 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) contents of brain were determined by the method of Curzon and Green [4]. Contents in the vehicle-pretreated rats were as follows: 5-HT 513.2±23.4, 5-HIAA 446.3±24.0 (ng/g wet tissue±S.E., n=10). All results were expressed as the mean±S.E. Behavioral data were evaulted using the two tailed Mann-Whitney U-test and biochemical data were compared by Scheffé's Multiple comparison test after one way analysis of variance [8].

RESULTS

5-HTP-, PCA- and PCP-Induced Wet-Dog Shakes in the Vehicle or Reserpine-Pretreated Rats

Administration of 5-HTP (7.5–12.5 mg/kg, IP) to rats 30 min after pretreatment with pargyline resulted in marked behavioral changes. The predominant behaviors observed were wet-dog shakes, head twitch and head weaving (data not shown). The wet-dog shakes began at 15 or 30 min and then reached a peak at 45 min after the injection of 5-HTP (Fig. 1A). PCA (2.5 and 5 mg/kg), a 5-HT releaser, produced a smaller number of wet-dog shakes at 15–75 min after injection in the vehicle-pretreated rats (Fig. 1B). No wet-dog shakes were observed in the vehicle-pretreated rats given PCP (2.5–7.5 mg/kg) (Fig. 1C). In contrast, the number of wet-dog shakes was significantly greater in the reserpine-pretreated rats than in the vehicle-pretreated rats after the injection of PCA (2.5 and 5 mg/kg) (Fig. 1B). At doses of 2.5–7.5 mg/kg, PCP also produced wet-dog shakes dose dependently in the reserpine-pretreated rats (Fig. 1C).

Effect of Imipramine and Mianserin on the PCP-Induced Wet-Dog Shakes in the Reserpine-Pretreated Rats

Tryptophan alone (which did not induce wet-dog shakes in the vehicle pretreated rats) produced wet-dog shakes in the reserpine pretreated rats (Fig. 2). Furthermore, tryptophan-induced wet-dog shakes were potentiated by imipramine. PCP (1.25 mg/kg)-induced wet-dog shakes in the reserpine-pretreated rats were also significantly potentiated by imipramine (12.5 mg/kg, IP) but were prevented by mianserin (20 mg/kg, IP) (Fig.3).

Effect of Reserpine-Pretreatment on 5-HT Metabolism

In the biochemical studies, the brain level of 5-HIAA in

the reserpine-pretreated rats was the same as that of the vehicle-treated rats on the 5th day of withdrawal from reserpine, although the brain level of 5-HT was significantly lower (Fig. 4). L-tryptophan, as expected, significantly increased the brain levels of 5-HT and 5-HIAA in the vehicle- or reserpine-pretreated rats. However, the brain level of 5-HT was significantly lower in the reserpine-pretreated rats when compared to the vehicle-pretreated rats, although the brain level of 5-HIAA after the injection of tryptophan was significantly higher in the reserpine-pretreated rats. On the other hand, the 5-HIAA/5-HT ratio was significantly higher in the reserpine-pretreated rats compared to that in vehicle-treated rats. The 5-HIAA/5-HT ratio in the reserpine-pretreated rats was also significantly higher than in the vehicle-pretreated rats after the administration of tryptophan (Fig. 5).

DISCUSSION

The wet-dog shakes have been reported to be seen after the injection of L-tryptophan, L-5-HTP and the proposed 5-HT agonists, lysergic acid diethylamide and quipazine [1]. This syndrome is inhibited in a rapid and dose-dependent fashion by the selective 5-HT_2 receptor antagonists, ketanserin and pirenperone [35]. In the present study, the number of wet-dog shakes induced by PCA (2.5 and 5 mg/kg) significantly increased in the reserpine-pretreated rats as compared to the vehicle-pretreated rats. Tryptophan or PCP (2.5–7.5 mg/kg) alone, which did not induce wet-dog shakes in the vehicle-pretreated rats, also produced wet-dog shakes in the reserpine-pretreated rats. Furthermore, tryptophan- and PCP-induced wet-dog shakes were potentiated by a 5-HT uptake blocker, imipramine, while PCP-induced wet-dog shakes were prevented by a 5-HT receptor blocker, mianserin [16]. In addition, 5-HT direct agonist, 5-MeODMT-induced head weaving was also potentiated in the reserpine-pretreated rats (data not shown). These findings suggested that the activation of a serotonergic system may play an important role in the PCP-induced wet-dog shakes.

From biochemical studies, it has been proposed that 5-HT is stored in the presynaptic neuron with different pools or compartments [9, 14, 18, 29, 31, 33]. In general, one pool is quite large, comprised of approximately 80–90% of total brain 5-HT, while the other pool is much smaller, containing 10–20% of total brain 5-HT. The large compartment is thought to be a storage or reserve pool for the transmitter and the small pool is often referred to as the "functional" pool, since it is generally assumed to contain the newly-synthesized 5-HT which is preferentially released. It has been reported that 5-HT synthetic capacity remains intact in rats pretreated by reserpine [15,18], although reserpine abolishes 5-HT storage and markedly reduces the brain level of 5-HT [32]. The reserpine-resistant fraction of 5-HT, is located outside of storage vesicles [14,33]. Recently, Kuhn *et al.* [14] have found that, despite the fact that the brain level of 5-HT was drastically reduced in rats treated with reserpine (5 mg/kg, IP) 24 hr before behavioral testing, the PCA-induced 5-HT behavioral syndrome is not different from that observed in normal rats given PCA. This effect of PCA is blocked by treatment with *p*-chlorophenylalanine and methergoline. In addition, it has also been reported that 5-HT synthesis remains normal [15,18] and postsynaptic 5-HT receptors as judged by [^{3}H] 5-HT binding remain normal in rats treated with reserpine 24 hr before the decapitation [2]. Therefore, it has been suggested that PCA acts primarily on the small pool of newly-synthesized 5-HT in the reserpinized rats and that the reserpine-resistant pool of 5-HT, despite its small size, is sufficient to induce 5-HT behavioral syndrome. We have also found that at a PCA dose of 7.5 mg/kg, PCA-induced wet-dog shakes were substantially greater in the reserpine-pretreated rats which were given reserpine (2.5 mg/kg, IP) once a day for 2 days and then were drug-free for 1 day (data not shown). In the present study, despite the drastic reduction in the brain level of 5-HT, tryptophan alone or tryptophan and imipramine produced wet-dog shakes in the reserpine-pretreated rats and the utilization of 5-HT was also enhanced on the 5th day of withdrawal from reserpine treatment, since the ratio of 5-HIAA/5-HT, one of the parameters of 5-HT turnover rate, was significantly higher in the reserpine-pretreated rats than in the vehicle-pretreated rats.

Taken together, the present results indicate that the PCP-induced wet-dog shakes after reserpine withdrawal are due to an increased 5-HT release from the small pool of newly-synthesized 5-HT and supersensitivity of postsynaptic 5-HT receptors.

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