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Long-term antidepressant treatments alter 5-HT_{2A} and 5-HT_{2C} receptor-mediated hyperthermia in Fawn-Hooded rats

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Abstract

We have recently demonstrated that hyperthermia induced by 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and *m*-chlorophenylpiperazine (*m*-CPP) are separately mediated by selective stimulation of 5-HT_{2A} and 5-HT_{2C} receptors, respectively in Wistar rats. Furthermore, hyperthermia induced by either DOI or *m*-CPP was found to be significantly less in Fawn-Hooded rats (a rat strain suggested to represent a genetic model of depression) relative to Wistar rats. In the present study, we studied the effects of long-term antidepressant treatments on DOI (2.5 mg/kg)-induced and *m*-CPP (2.5 mg/kg)-induced hyperthermia in male Fawn-Hooded rats. Long-term (21 days) treatment with the tricyclic antidepressants, imipramine or clomipramine (each 5 mg/kg/day), attenuated DOI-induced hyperthermia, while *m*-CPP-induced hyperthermia was accentuated. On the other hand, long-term (21 days) treatment with the monoamine oxidase type-A inhibiting antidepressant, clorgyline (1 mg/kg/day), did not modify *m*-CPP-induced hyperthermia, but significantly attenuated DOI-induced hyperthermia. These findings demonstrate that long-term antidepressant treatments alter 5-HT_{2A} and 5-HT_{2C} receptor-mediated hyperthermia in a genetic animal model of depression.

Keywords: DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane); *m*-CPP (*m*-chlorophenylpiperazine); Depression, genetic model; Clorgyline; Imipramine; Clomipramine

1. Introduction

Brain serotonin (5-hydroxytryptamine, 5-HT) changes have been implicated in the etiology of affective illness and mode of action of antidepressant and antimanic drugs (Meltzer and Lowy, 1987). Due to the therapeutic lag between the initiation of antidepressant treatment and onset of clinical effects, animal studies of molecular mechanisms pertinent to antidepressant efficacy have concentrated on the adaptive changes in the various aminergic neurotransmitter mechanisms following long-term antidepressant treatment. Adaptive changes in central serotonergic functions following long-term antidepressant treatment have been identified using behavioral, electrophysiological and neuroendocrine paradigms as well as in measurements of 5-HT receptor densities in various brain areas (Willner, 1985).

Advances in radioligand binding studies have revealed several subtypes of 5-HT receptors. Recently, these receptors have been classified as 5-HT_1 (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}), 5-HT_2(5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}), 5-HT_3 and 5-HT_4 (Humphrey et al., 1993). In radioligand binding studies, the phenylisopropylamine hallucinogen 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) has been shown to have a similar high affinity for 5-HT_{2A} and 5-HT_{2C} receptors (Titeler et al., 1988) while *m*-chlorophenylpiperazine (*m*-CPP) possesses an approximately 10-fold higher affinity for 5-HT_{2C} versus 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2A} sites (Hoyer, 1988). Systemic administration of both DOI and *m*-CPP produces hyperthermia in Wistar rats. In two recent reports from our laboratory, we have demonstrated that hyperthermia induced by DOI and *m*-CPP is mediated by selective stimulation of 5-HT_{2A} and 5-HT_{2C} receptors, respectively (Mazzola-Pomietto et al., 1993, 1995).

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In several previous reports from this laboratory, we have demonstrated altered central serotonergic function in the Fawn-Hooded rat strain relative to the Wistar and Sprague-Dawley rat strains (Aulakh et al., 1988, 1989a, 1992, 1994c; Wang et al., 1988). Recently, the Fawn-Hooded rat strain has been suggested to represent a genetic model of depression and alcoholism (Aulakh et al., 1992, 1994b; Overstreet et al., 1992). The purpose of the present study was to investigate functional adaptational changes in serotonergic neurotransmitter mechanisms regulating temperature following long-term antidepressant treatment in this genetic animal model of depression. Therefore, we studied the effects of short-term (3 days) and long-term (21 days) antidepressant treatment on DOI-induced and *m*-CPP-induced hyperthermia in Fawn-Hooded rats.

2. Materials and methods

Male Fawn-Hooded rats (Frederick Cancer Research and Development Center, Frederick, MD, USA) and Wistar rats (Charles River, Kingston, NY, USA) weighing approximately 250 g at the beginning of the study were used. The animals were housed three per cage in a temperature-controlled (22 ± °C) room with 12-h light/dark cycle (lights on 07.00 h). Animals had free access to Purina rat chow and water at all times. Separate groups of animals were used for *m*-CPP challenge and DOI challenge studies.

Animals were brought into the test environment (ambient temperature 22 ± °C) at least 1 h prior to any recording. Animals were housed six per cage in Plexiglas cages with bedding during temperature studies. Rectal temperature was measured with a rectal probe and digital thermometer (Sensorteck, Clifton, NJ, USA), all recordings being made between 10 a.m. and 1 p.m. Each animal received several habituating exposures to the rectal probe, which was inserted 2.5 cm into the colon, while each rat was held lightly by the tail.

For the strain comparison study, 12 Wistar and 12 Fawn-Hooded animals were used. Both Fawn-Hooded and Wistar animals (six from each strain) were injected intraperitoneally (i.p.) either with *m*-CPP (2.5 mg/kg) or DOI (2.5 mg/kg). Rectal temperature was recorded prior to and 30 min or 60 min after i.p. administration of *m*-CPP or DOI, respectively.

For antidepressant treatments, separate groups of animals were subcutaneously administered imipramine (5 mg/kg/day), clomipramine (5 mg/kg/day), clorgyline (1 mg/kg/day) or saline continuously by means of osmotic minipumps (Model 2002, Alza Corporation, Palo Alto, CA, USA) for 28 days. Each animal was given a test dose of either *m*-CPP (2.5 mg/kg) or DOI (2.5 mg/kg) injected i.p. after short-term (3 day) and long-term (21 day) antidepressant treatment. Rectal temperature was recorded prior to and 30 min or 60 min after i.p. administration of *m*-CPP or DOI, respectively, since the peak hyperthermic effect occurs at 30 min and 60 min following i.p. administration of *m*-CPP and DOI, respectively (Mazzola-Pomietto et al., 1993, 1995). The selection of 2.5 mg/kg challenge dose of *m*-CPP or DOI was based on our previous dose-response studies (Mazzola-Pomietto et al., 1995; Wozniak et al., 1989).

2.1. Drugs

The following drugs were used: *m*-CPP hydrochloride (Aldrich Chemical Company, Milwaukee, WI, USA), DOI hydrochloride, clorgyline hydrochloride, clomipramine hydrochloride and imipramine hydrochloride (Research Biochemicals, Natick, MA, USA). All drugs were dissolved in 0.9% saline. The volume injected was 0.1 ml/100 g of body weight. All drug doses given in the text refer to the salt.

2.2. Data analysis

The data used were changes in rectal temperature from baseline at 30 min and 60 min after *m*-CPP and DOI administration, respectively. The data were analyzed using one-way analysis of variance accompanied by contrasts (means comparisons) specified a priori comparing each antidepressant treatment to the saline control. For the strain comparisons, the data were analyzed using a two-tailed Student's *t*-test.

3. Results

The comparative hyperthermic effects of DOI (2.5 mg/kg) and *m*-CPP (2.5 mg/kg) in the Wistar and the Fawn-Hooded rat strains are shown in Fig. 1. The baseline temperature values were significantly ($P <$

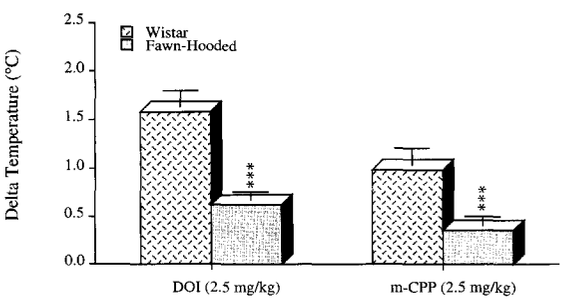

Fig. 1. Changes in rectal temperature in the Wistar and the Fawn-Hooded rat strains following acute administration of DOI (2.5 mg/kg) or *m*-CPP (2.5 mg/kg). Values are expressed as means ± S.E.M. from six animals. Values of Fawn-Hooded rats significantly different from those of Wistar rats are represented by $^{***}P < 0.001$.

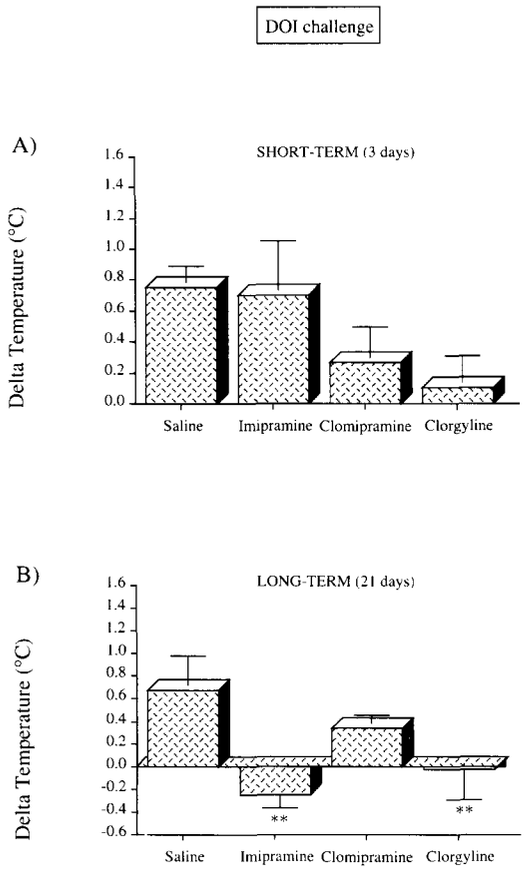

Fig. 2. Effects of short-term (A) and long-term (B) antidepressant treatment on DOI (2.5 mg/kg)-induced hyperthermia in Fawn-Hooded rats. Values are expressed as means ± S.E.M. from six animals. Values of long-term antidepressant-treated animals significantly different from saline-treated animals are represented by $^{**}P < 0.01$.

0.01) lower in the Fawn-Hooded rat strain (37.5 ± 0.14°C) relative to the Wistar rat strain (38.1 ± 0.11°C). Both DOI-induced and *m*-CPP-induced hyperthermia was significantly less in the Fawn-Hooded rat strain relative to the Wistar rat strain (Fig. 1). The effects of short-term (A) and long-term (B) antidepressant treatment on DOI-induced hyperthermia in Fawn-Hooded rats are shown in Fig. 2. Administration of DOI (2.5 mg/kg) produced significant increases in rectal temperature in both short-term ($P < 0.01$) and long-term ($P < 0.05$) saline-treated animals relative to the baseline values. For short-term antidepressant treatment, analysis of variance showed an overall nonsignificant ($F(3,17) = 1.68$, $P > 0.05$) treatment effect. However, for long-term antidepressant treatment, analysis of variance showed an overall significant ($F(3,17) = 3.72$, $P < 0.05$) treatment effect. Further analysis revealed that DOI-induced hyperthermia was significantly less in long-term imipramine and clorgyline-treated animals relative to saline-treated animals (Fig. 2B).

The effects of short-term (A) and long-term (B) antidepressant treatment on *m*-CPP-induced hyperthermia in Fawn-Hooded rats are shown in Fig. 3. Administration of *m*-CPP (2.5 mg/kg) produced significant increases in rectal temperature in both short-term ($P < 0.01$) and long-term ($P < 0.01$) saline-treated animals relative to the baseline values. For short-term antidepressant treatment, analysis of variance showed an overall nonsignificant ($F(3,18) = 0.93$, $P > 0.05$) treatment effect. However, for long-term antidepressant treatment, analysis of variance showed an overall significant ($F(3,18) = 4.72$, $P < 0.05$) treatment effect. Further analysis revealed that long-term imipramine and clomipramine treatment accentuated *m*-CPP-induced hyperthermia relative to saline treatment (Fig. 3B). There was no significant difference in the baseline temperature between the long-term saline-treated (37.3 ± 0.14°C) and long-term imipramine (37.0 ± 0.17°C) or clomipramine (37.3 ± 0.12°C) or clorgyline (37.2 ± 0.18°C) treated Fawn-Hooded rats.

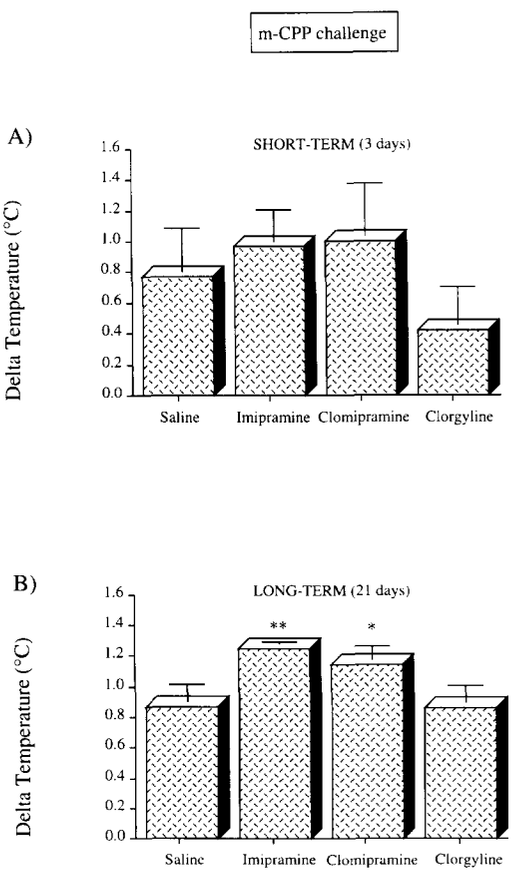

Fig. 3. Effects of short-term (A) and long-term (B) antidepressant treatment on *m*-CPP (2.5 mg/kg)-induced hyperthermia in Fawn-Hooded rats. Values are expressed as means ± S.E.M. from six animals. Values of long-term antidepressant-treated animals significantly different from saline-treated animals are represented by $^{*}P < 0.05$; $^{**}P < 0.01$.

4. Discussion

The present study demonstrates that systemic administration of both DOI and *m*-CPP induced hyperthermia in rats. This is consistent with several earlier reports from our own laboratory as well as by other investigators (Klodzinska and Chojnacka-Wojcik, 1992; Mazzola-Pomietto et al., 1995; Pranzatelli, 1990; Wozniak et al., 1989). The present study further demonstrates that both DOI-induced and *m*-CPP induced hyperthermia was significantly less in the Fawn-Hooded rat strain relative to the Wistar rat strain. In two recent reports from this laboratory, we have demonstrated that DOI and *m*-CPP produce hyperthermia in Wistar rats by selective stimulation of 5-HT_{2A} and 5-HT_{2C} receptors, respectively (Mazzola-Pomietto et al., 1993, 1995). Thus, the present findings suggest functional subsensitivity of both the 5-HT_{2C} and 5-HT_{2A} receptors that mediate hyperthermia in the Fawn-Hooded rat strain.

Our results are consistent with several earlier reports from this laboratory demonstrating decreased sensitivity to other 5-HT_{2C} receptor-mediated responses such as *m*-CPP-induced increases in plasma prolactin (Aulakh et al., 1988), decreases in food intake (Wang et al., 1988), and locomotor activity (Aulakh et al., 1989a) in the Fawn-Hooded rat strain relative to Wistar and Sprague-Dawley rat strains. On the other hand, our results are in disagreement with those of Gudelsky et al. (1985) who demonstrated increased sensitivity to responses attributed to 5-HT_{2A} receptor effects such as quipazine-induced wet dog shakes and 5-methoxy-*N*-*N*-dimethyltryptamine (5-MeODMT)-induced hyperthermia, based on antagonism by ketanserin and pirenperone, in the Fawn-Hooded rat strain relative to the Sprague-Dawley rat strain. However, ketanserin and pirenperone have been shown to possess antagonist activity at α_1-adrenoceptor (Brazenor and Angus, 1982; Kalkman et al., 1982) and dopamine (Leysen et al., 1981; Meltzer et al., 1983) receptor sites, which could be pertinent to the experimental results obtained with these 5-HT_{2A} receptor antagonists. In addition, it is of note that unlike DOI, 5-MeODMT and quipazine are not highly selective 5-HT_{2A} receptor agonists. In functional studies, 5-MeODMT has been reported to act as a full agonist like 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) in inducing all six components (forepaw-treading, head-weaving, tremor, hind limb abduction, flattened body posture and Straub tail) of the 5-HT behavioral syndrome in rats which is mediated by activation of post-synaptic 5-HT_{1A} receptors (Smith and Peroutka, 1986; Tricklebank et al., 1985). Furthermore, 5-MeODMT was shown to be a potent inhibitor of [^{3}H]8-OH-DPAT binding in the rat frontal cortex, but was only weakly active against 5-HT_2 receptor binding (Smith and Peroutka, 1986; Tricklebank et al., 1985). Similarly, quipazine has also been shown to have considerably higher affinity at 5-HT_3 receptor sites and also slightly higher affinity at 5-HT_{1B} and 5-HT_{2C} receptor sites than the 5-HT_{2A} receptor site in radioligand binding studies (Hoyer, 1988).

There are numerous reports in the literature suggesting that the hypothalamus is involved in the regulation of temperature. However, it is of note that we did not observe any differences in either [^{3}H]mesulergine-labeled 5-HT_{2C} receptor density or [^{3}H]ketanserin-labeled 5-HT_{2A} receptor density in the hypothalamus between the Wistar and Fawn-Hooded rat strains (Hulihan-Giblin et al., 1992, 1993). In a previous report from this laboratory, we have demonstrated that brain levels of *m*-CPP were not different between the Fawn-Hooded and the Wistar rat strains following i.p. administration of 1.25 mg and 2.5 mg/kg doses of *m*-CPP (Aulakh et al., 1988). Therefore, alternative possibilities include speculation that the functional subsensitive responses observed in this study in the Fawn-Hooded rat strain may be due to a more efficient temperature control system in Fawn-Hooded rats, or changes in post-receptor signal-transducing mechanisms, or possible interactions with other neurotransmitter systems that modulate temperature in rodents (Kruk, 1972).

The present study further demonstrates that long-term but not short-term treatment with the tricyclic antidepressants, imipramine and clomipramine, accentuated *m*-CPP-induced hyperthermia in Fawn-Hooded rats. This finding contrasts with our previous finding in Wistar rats in which *m*-CPP-induced hyperthermia was uniformly significantly attenuated following 22-day treatment with imipramine (−60%), clomipramine (−60%) or clorgyline (−80%) (Wozniak et al., 1989). In Fawn-Hooded rats, long-term clorgyline treatment did not modify *m*-CPP-induced hyperthermia. The demonstration of a differential effect of long-term antidepressant treatment in the Fawn-Hooded rat strain versus the Wistar rat strain is very intriguing. Recently, we have demonstrated accentuation of *m*-CPP-induced hypophagia in Fawn-Hooded rats following long-term lithium treatment (Aulakh et al., 1994a), whereas the same treatment produced attenuation of *m*-CPP-induced hypophagia in Wistar rats (Aulakh et al., 1989b). As mentioned earlier in the discussion, the Fawn-Hooded rat strain is also functionally subsensitive to the hypophagic effect of *m*-CPP relative to the Wistar rat strain (Wang et al., 1988). Furthermore, *m*-CPP-induced hypophagia is also mediated by stimulation of 5-HT_{2C} receptors (Kennett and Curzon, 1991).

One possible explanation for potentiation of *m*-CPP-induced hyperthermia may be that brain levels of *m*-CPP were higher in chronic imipramine and clomipramine-treated animals. Recently, Kennett et al. (1994) have demonstrated approximately 4 times higher

brain levels of *m*-CPP in Sprague-Dawley rats treated chronically (10 mg/kg p.o. daily × 21 days) with two other antidepressants, paroxetine or fluoxetine. These investigators also demonstrated significant attenuation of *m*-CPP's effects on locomotion and rears following chronic treatment with paroxetine, fluoxetine or clomipramine in the same study. Although we did not measure brain levels of *m*-CPP in the present study, the contribution of pharmacokinetic factors seems unlikely due to several reasons. As mentioned earlier in the discussion, we have previously demonstrated attenuation of *m*-CPP-induced hyperthermia in Wistar rats following similar long-term treatment with imipramine, clomipramine or clorgyline as used in the present study. Furthermore, long-term lithium treatment attenuated *m*-CPP-induced hypophagia in Wistar rats but accentuated it in Fawn-Hooded rats. It is of note that brain levels of *m*-CPP were not significantly different in control and long-term lithium-treated Fawn-Hooded rats following intraperitoneal *m*-CPP administration (Aulakh et al., 1994a).

Another possible explanation for potentiation of *m*-CPP-induced hyperthermia may be that 5-HT_{2C} receptors become supersensitive in Fawn-Hooded rats following long-term treatment with the tricyclic antidepressants, imipramine and clomipramine. Unfortunately, the effects of long-term tricyclic antidepressant treatment on brain 5-HT_{2C} receptor binding site density have apparently not yet been assessed in Fawn-Hooded rats. In Wistar rats, we have recently reported that similar long-term treatment (as used in the present study) with imipramine and clomipramine did not modify [^{3}H]mesulergine-labeled 5-HT_{2C} receptor density in various brain areas, whereas clorgyline treatment significantly reduced [^{3}H]mesulergine binding (B_{max} values) in both the hypothalamus and striatum compared to saline-treated animals (Hulihan-Giblin et al., 1994). Since the subsensitive functional responses in the Fawn-Hooded rat strain may be due to changes in post-receptor signal-transducing mechanisms rather than receptor density as mentioned earlier in the discussion, it is tempting to speculate that the differential effects of long-term antidepressant treatment in Fawn-Hooded versus Wistar rats may also be due to a differential effect of long-term antidepressant treatment on post-receptor signal-transducing mechanisms between these two rat strains. Only further experimentation will clarify this phenomenon.

The present study also demonstrates that in contrast to 5-HT_{2C} receptor-mediated hyperthermia, long-term antidepressant treatment attenuated 5-HT_{2A}-receptor-mediated hyperthermia in Fawn-Hooded rats. Although the effects of long-term antidepressant treatment on brain 5-HT_{2A} receptor density in Fawn-Hooded rats have not been assessed, it is well known that long-term treatment with the tricyclic antidepressants and monoamine oxidase inhibiting antidepressants causes down-regulation of 5-HT_{2A} receptor density in Sprague-Dawley and Wistar rat strains (Kendall et al., 1982; Peroutka and Snyder, 1980; Stolz et al., 1983; Willner, 1985).

In summary, the present study demonstrates that long-term antidepressant treatments alter 5-HT_{2A} and 5-HT_{2C} receptor-mediated hyperthermia in Fawn-Hooded rats. It is of interest to note that, like depressed patients, the Fawn-Hooded rat strain has higher baseline levels of corticosterone (Aulakh et al., 1988), reduced platelet 5-HT uptake (Arora et al., 1983), and also manifests functional subsensitivity to 5-HT receptor agonists (Aulakh et al., 1988, 1989a; present study). In depressed patients, long-term treatment with the tricyclic antidepressant, clomipramine, potentiated fenfluramine-induced increases in plasma prolactin (Shapira et al., 1992). In another study, long-term lithium treatment enhanced 5-HT-mediated neuroendocrine responses in tricyclic-resistant depressed patients (Cowen et al., 1989). The demonstration of enhancement of 5-HT_{2C} receptor-mediated functions following long-term treatment with the tricyclic antidepressants in the present study and with lithium (Aulakh et al., 1994a) observed in a genetic animal model of depression suggests that these effects of tricyclic antidepressants and lithium may be responsible for correcting as yet unspecified abnormalities of 5-HT function, which may be involved in the pathogenesis of depression. Alternatively, enhanced sensitivity of 5-HT_{2C} receptors following long-term treatment with the tricyclic antidepressants observed in the present study may be secondary to a primary action related to their therapeutic efficacy.

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