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The selective 5-HT_{2A} receptor antagonist, MDL 100,907, increases dopamine efflux in the prefrontal cortex of the rat

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Abstract

Diminished function within the mesocortical dopamine system has been to hypothesized to contribute directly to the negative and indirectly to the positive symptoms of schizophrenia. Based on the proposed role of 5-HT_2 receptor blockade in the antipsychotic profile of clozapine and its preferential augmentation of prefrontal dopamine release, we have examined the effects of the selective 5-HT_{2A} receptor antagonist, *R*-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol (MDL 100,907), on dopamine release in the rat medial prefrontal cortex using in vivo microdialysis. The results indicate that local 5-HT_{2A} receptors exert a tonic inhibitory influence on dopamine efflux in the medial prefrontal cortex. These observations are consistent with the hypothesis that 5-HT_{2A} receptor blockade contributes to the unique antipsychotic profile of clozapine and that MDL 100,907 may have antipsychotic activity.

Keywords: Prefrontal cortex; 5-HT_2 receptor; Microdialysis; Clozapine; Antipsychotic

1. Introduction

Excessive activity within the A10 or mesolimbic dopamine system is believed to be the underlying neurochemical abnormality responsible for the symptoms of schizophrenia. Although the dopaminergic projections to the nucleus accumbens remain the major pharmacological target of schizophrenia research, the mesocortical dopamine system has recently received increased attention as an important contributor to the pathophysiology of schizophrenia. Clinical observations suggest a role for the prefrontal cortex particularly in the negative or deficit symptoms of the disorder. The similarity between the deficit symptoms of schizophrenia and the manifestations of frontal lobe disease has frequently been discussed (Goldberg et al., 1987, 1989; Beatty et al., 1993). Moreover, there is direct evidence of reduced metabolic activity in the prefrontal cortex of schizophrenic patients (see Weinberger, 1989).

One of the paradoxes of schizophrenia is the simultaneous presence of productive (positive) and negative symptoms. The positive symptoms of schizophrenia appear to be due to excessive dopaminergic activity, whereas the deficit symptoms appear to involve reduced dopaminergic function. Thus dopamine agonists such as amphetamine or L-dihydroxyphenylalanine (L-DOPA) alleviate negative symptoms while exacerbating positive symptoms (Angrist et al., 1980).

The explanation for this pattern of symptoms may lie in recent studies suggesting that the prefrontal cortex can regulate the subcortical mesolimbic and mesostriatal dopaminergic systems (Deutch, 1992). Afferents from the prefrontal cortex have been shown to make synaptic contact with dopaminergic structures within the ventral tegmental area and to be in close proximity to tyrosine hydroxylase positive terminals in the nucleus accumbens of the rat (Sesack and Pickel, 1992). Activation of the prefrontal cortex has been shown to increase subcortical dopaminergic activity (Gariano and Groves, 1988; Murase et al., 1993; Taber and Fibiger, 1993). The effect of the dopaminergic inputs to the prefrontal cortex in turn appear to be inhibitory. Hence, increased activity within the mesocortical dopamine system is inhibitory with respect to the subcortical dopamine systems (Louilot et al., 1989; Jaskiw et al., 1991). Conversely, reductions in prefrontal dopaminergic activity result in increased activity or enhanced sensitivity of the subcortical systems

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(Pycock et al., 1980; Leccese and Lyness, 1987; Haroutunian et al., 1988; Deutch et al., 1990; Rosin et al., 1992). Thus, a dopaminergic deficit in one area of the brain (mesocortical) would be responsible for the negative symptoms while a consequential increase in activity in another region (mesolimbic) would lead to the manifestation of positive symptoms.

Given the above considerations, the recent demonstration that the atypical antipsychotic clozapine preferentially increases dopamine release in the medial prefrontal cortex (Moghaddam and Bunney, 1990) provides a potential explanation for its unique clinical profile including its reported activity against negative symptoms. Unfortunately, the mixed receptor profile of clozapine makes it difficult to assign such clinical effects to any particular receptor interaction (Leysen et al., 1993). However, Meltzer and colleagues have provided data suggesting that the atypical profile of clozapine is due to its preference for 5-HT_{2A} over dopamine D_2 receptors (Meltzer, 1989, 1992; Meltzer et al., 1989). The effects of clozapine on dopamine release in the medial prefrontal cortex may in fact be attributable to 5-HT_{2A} receptor blockade. Pehek et al. (1993a) recently reported an increase in medial prefrontal cortex dopamine efflux following local infusion of a high concentration of the mixed 5-$HT_{2A/C}$ receptor antagonist ritanserin. Consequently, there may be a link between 5-HT_{2A} receptor blockade, prefrontal dopaminergic activity and the alleviation of negative symptoms. Interestingly, ritanserin has been shown to primarily affect negative symptoms in schizophrenia (Reyntjens et al., 1986; Duinkerke et al., 1993).

The purpose of the present study was to directly investigate the effects of 5-HT_{2A} receptor blockade on dopamine efflux in the medial prefrontal cortex using the potent and highly selective antagonist, MDL 100,907 (Palfreyman et al., 1993). Previous studies with MDL 100,907 have revealed a pattern of neurochemical, electrophysiological and behavioral effects consistent with atypical antipsychotic activity (Schmidt et al., 1993; Sorensen et al., 1993).

2. Materials and methods

Male Sprague-Dawley rats (200–300 g) were maintained on a 12-h light and dark cycle and allowed free access to food and water.

2.1. In vivo release experiments

2.1.1. Probe design

Microdialysis probes were made using a concentric design. Each probe consisted of a 15 mm 25 gauge stainless steel tube connected to PE20 tubing which served as the inlet. The outlet consisted of a fused silica capillary (75 μm i.d., 150 o.d., Polymicro Technologies, Phoenix, AZ, USA) passed through the wall of the PE20, threaded down through the stainless steel tubing and into a 4 mm length of sealed dialysis tubing (AN.69-HOSPAL, CGH Medical, Lakewood, CO, USA). A piece of PE10 was attached to the silica capillary where it exits the probe. All junctions were glued using 2-ton epoxy (Devon Bearings, Brooklyn Hts, OH, USA).

2.1.2. Surgery

Probes were implanted stereotaxically in the right medial prefrontal cortex under pentobarbital anesthesia. Coordinates relative to bregma were 3.2, 0.8, −6.0 mm from the top of the skull. A small machine screw was also partially inserted into the skull to serve as an anchor for the probe. Dental acrylic was used to secure the probe to the screw and the skull.

2.1.3. Microdialysis

All experiments were performed one day after probe implantation. Each implanted rat was tethered in a circular 12-inch Plexiglas container and placed inside a lighted and sound-proof environmental chamber. The chambers were ventilated by means of a small baffled fan. A two-channel liquid swivel was used to connect both inlet and outlet lines to the probe. Probes were perfused at 2 μl/min using a Harvard 22 pump (Harvard Apparatus, South Natrick, MA, USA) and an artificial CSF composed of Dulbecco's phosphate buffered saline adjusted to 1.2 mM $CaCl_2$ and pH 7.3. The dialysate was collected into tubes containing 10 μl of 0.5 M perchloric acid using a refrigerated microfraction collector (Carnegie Medicin, Stockholm, Sweden). A collection period of 30 min was used for all experiments. All samples were frozen at −70°C until assayed for dopamine, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) by high performance liquid chromatography with electrochemical detection (Schmidt et al., 1992). The injection volume used was 60 μl. Rats were killed 1 week later and the site of probe implantation was verified visually.

2.2. Drugs

R-(+)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (MDL 100,907) was synthesized at the Marion Merrell Dow Research Institute (Cincinnati, OH, USA). Ritanserin was purchased from RBI (Natick, MA, USA). Both antagonists were administered as a suspension in Tween-80.

2.3. Data analysis

All data are expressed as a percentage of basal release after normalizing using the mean of the first

90–120 min of sample collection. Sigmastat (Jandel Scientific, San Rafael, CA, USA) was used for all statistical analyses. Parametric statistical procedures were used except in those cases where nonparametric procedures were dictated by failed tests for normality and equal variance. In several cases, the mean release over time was calculated and used for the determination of treatment effects. The specific test used for each experiment is described in the figure legends.

3. Results

Fig. 1 shows that the systemic administration of MDL 100,907 (1 mg/kg s.c.) produced a sustained increase in dopamine release in the rat medial prefrontal cortex. The increase in extracellular dopamine could be observed within 30 min of drug administration and remained elevated for the 5 h of sample collection. Although the pattern of release was quite stable over the time course, a peak release of approximately 300% occurred at 3.5 h. Table 1 shows the increase in extracellular concentrations of dopamine, DOPAC and HVA averaged over the entire duration of the experiment. At 1 mg/kg, MDL 100,907 slightly more than doubled the extracellular dopamine concentration in the medial prefrontal cortex ($P < 0.01$ versus vehicle). In contrast, the 5-HT_{2A} receptor antagonist had no effect on either prefrontal DOPAC or HVA concentrations.

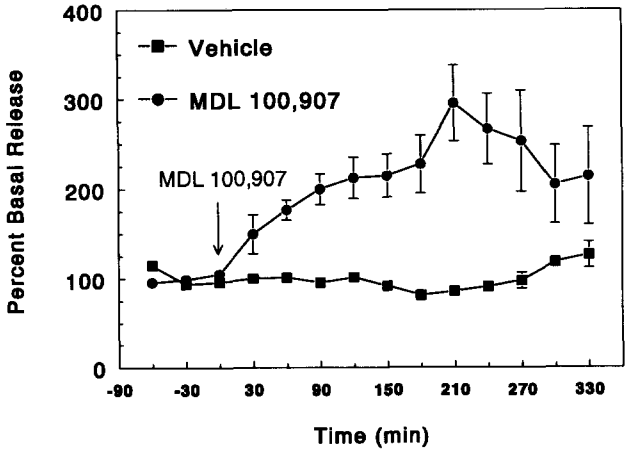

Fig. 1. Systemic administration of MDL 100,907 (1 mg/kg s.c.) increases dopamine efflux in the rat medial prefrontal cortex. MDL 100,907 or vehicle was administered at the time indicated by the arrow. Basal dialysate concentrations of dopamine per injection were 1.74 ± 0.51 pg ($n = 3$) for the vehicle group and 1.97 ± 0.43 pg ($n = 5$) for the drug treated group. Values for DOPAC and HVA were 594.2 ± 136.7 pg and 739.6 ± 72.6 pg, respectively, in the vehicle group and 337.9 ± 43.0 pg and 536.1 ± 67.3 pg, respectively, in the MDL 100,907 group. See Table 1 for statistical analysis.

Table 1
Effect of MDL 100,907 on dopamine efflux in the rat medial prefrontal cortex expressed as a percent of basal release

	Vehicle (n)	MDL 100,907 (n) (1 mg/kg s.c.)
Dopamine	95.3 ± 1.0 (3)	220.1 ± 25.6 (5) [a]
DOPAC	84.0 ± 4.4 (3)	105.9 ± 12.5 (5)
HVA	96.0 ± 9.0 (3)	106.4 ± 8.3 (5)

The average concentration of extracellular dopamine concentrations was calculated for the 5 h period immediately following drug administration. Comparisons were by the two-tailed Student's t-test. See Fig. 1 legend for additional details.
[a] $P < 0.01$.

To determine the site of action of MDL 100,907, the drug was infused via the microdialysis probe directly into the medial prefrontal cortex for 2 h followed by a 1 h washout period. The results of these experiments are shown in Fig. 2. At a perfusate concentration of 1.0 μM, MDL 100,907 produced a rapid increase in extracellular concentrations of dopamine which reached an average of 198% of basal transmitter levels during the 2 h immediately following drug perfusion ($P < 0.05$). Extracellular dopamine concentrations rapidly returned to baseline following washout of MDL 100,907. There was no effect of MDL 100,907 on DOPAC concentrations in the dialysate. HVA concentrations were not determined.

The effect of MDL 100,907 (0.1 mg/kg s.c.) on dopamine efflux in the medial prefrontal cortex was compared to that of the 5-$HT_{2A/C}$ receptor antagonist, ritanserin (2.5 mg/kg s.c.). The 25-fold difference in dose was selected based on the apparent potency difference of the two drugs in vivo (J.H. Kehne, personal

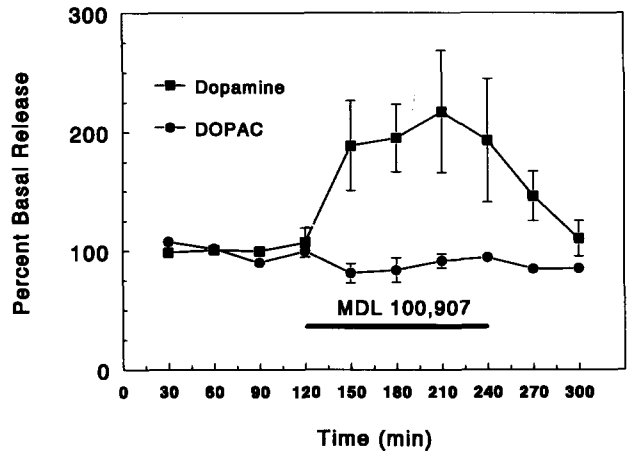

Fig. 2. Effect of direct infusion of MDL 100,907 (1.0 μM) on extracellular concentrations of dopamine and DOPAC in the rat medial prefrontal cortex ($n = 4$). The 2 h duration of the infusion is indicated by the black bar. The increase in dopamine efflux was statistically significant ($P < 0.05$) by the Mann-Whitney ranked sum test. Basal dialysate concentrations of dopamine and DOPAC were 1.25 ± 0.25 pg and 496.7 ± 146.4 pg, respectively.

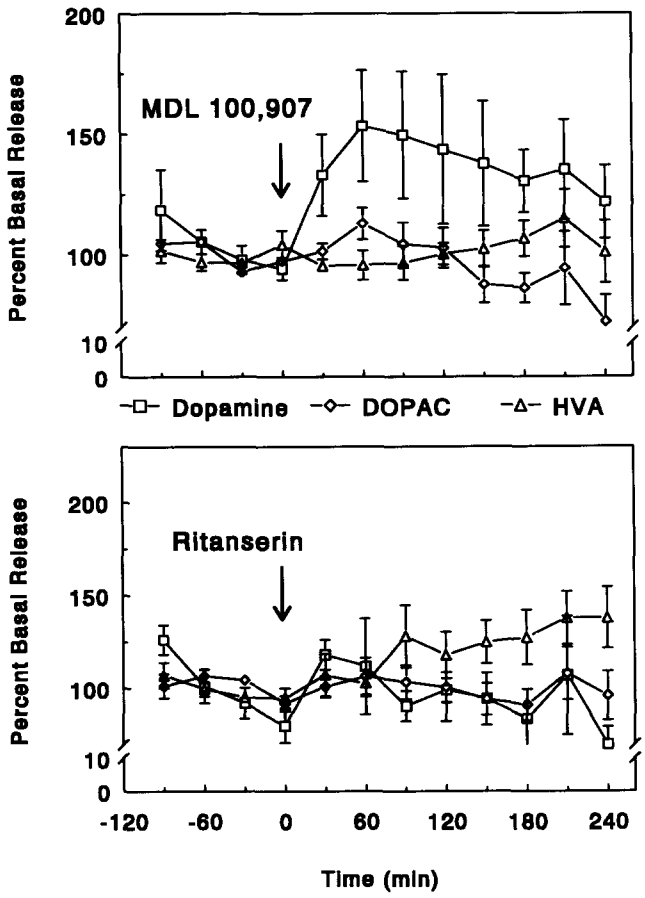

Fig. 3. Comparison of the effect of systemic administration of MDL 100,907 (0.1 mg/kg s.c.) and ritanserin (2.5 mg/kg s.c.) on extracellular dopamine and metabolite concentrations in the rat medial prefrontal cortex. The time of drug administration is indicated by the arrows. Unlike ritanserin, MDL 100,907 produced a significant increase in dopamine efflux ($P < 0.05$ by repeated measures ANOVA, $n = 6$ for both drugs). The increase in extracellular HVA concentrations produced by ritanserin was also statistically significant ($P < 0.05$ by repeated measures ANOVA). Basal dialysate concentrations of dopamine, DOPAC and HVA for the MDL 100,907 group ($n = 6$) were 1.19 ± 0.17 pg, 316.1 ± 41.8 pg and 615.5 ± 111.5 pg, respectively. The same values for the ritanserin group ($n = 6$) were 1.53 ± 28 pg, 700.4 ± 206.1 and 398.5 ± 44.7 pg, respectively.

communication). As shown in Fig. 3, this low dose of MDL 100,907 produced a small but significant increase in dopamine efflux in the medial prefrontal cortex ($P < 0.05$, repeated measures ANOVA). The mean increase over the 4 h of the experiment was 138% of the predrug dopamine concentration. No change was observed in the concentrations of either DOPAC or HVA. In contrast to the effect of MDL 100,907, ritanserin did not alter dopamine efflux. The mean extracellular dopamine concentration over the 4 h after ritanserin was 97% of the predrug level. Although DOPAC concentrations were also unchanged, ritanserin administration did alter the extracellular concentrations of HVA. The mean increase over the 4 h interval was 123% of control ($P < 0.05$, repeated measures ANOVA).

4. Discussion

The high degree of selectivity of MDL 100,907 for the 5-HT_{2A} receptor subtype makes it an extremely useful tool for examining physiological activities mediated by 5-HT. Recent data suggesting that the 5-HT_{2A} receptor and the closely related 5-HT_{2C} receptor (formerly the 5-HT_{1C}) have dramatically different effects on behaviors such as locomotor activity underscore the need for such selective agents (Hicks et al., 1993).

The increased dopamine efflux produced by MDL 100,907 in the medial prefrontal cortex of freely moving rats indicates that 5-HT_{2A} receptors regulate dopamine release in this region. Furthermore, this effect appears to occur locally as demonstrated by the enhanced dopamine efflux produced by direct infusions of MDL 100,907 into the medial prefrontal cortex. The increased release observed in the presence of an antagonist also suggests a tonic inhibition of dopamine release by prefrontal 5-HT_{2A} receptors. This conclusion is at variance with the view that the rapid down-regulation of 5-HT_{2A} receptors under even modest levels of stimulation makes them unlikely candidates for tonic activation in vivo (Leysen and Pauwels, 1990). From a therapeutic standpoint, the most important characteristic of this interaction between the serotonergic and dopaminergic systems is its apparent exclusivity to the prefrontal cortex. Both ex vivo and in vivo neurochemical studies indicate that MDL 100,907 is without effect on dopamine efflux in the rat striatum (Schmidt et al., 1992; Sorensen et al., 1993) and the nucleus accumbens (C.J. Schmidt and G.M. Fadayel, in preparation). The concept of a selective effect of 5-HT_{2A} receptor antagonists on the mesocortical dopamine system is also consistent with the results of studies conducted with the putative atypical antipsychotic, amperozide. Like MDL 100,907, amperozide has good selectivity for the 5-HT_{2A} over the 5-HT_{2C} receptor (Roth et al., 1992) and very low affinity for dopamine D_2 receptors (Axelsson et al., 1991). Dialysis studies have demonstrated a preferential effect of low doses of amperozide on dopamine efflux in the medial prefrontal cortex (Pehek et al., 1993b; Svensson et al., 1993), although higher doses of amperozide apparently increase striatal dopamine efflux via inhibition of the dopamine uptake carrier (Pehek et al., 1993b).

With the exception of the histamine H_1 receptor, clozapine has its highest affinity for the 5-HT_{2A} receptor (Leysen et al., 1993). The increase in prefrontal dopamine release produced by MDL 100,907 suggests

that the effects of clozapine in this region may be wholly accounted for by its ability to block 5-HT_{2A} receptors. The extent to which 5-HT_{2A} receptor antagonism may contribute to or underlie the therapeutic action of clozapine is unclear. However, it is apparent that clinical efficacy of clozapine cannot be accounted for by its activity at dopamine D_2 receptors alone. Positron emission tomography studies have demonstrated that clinically effective doses of typical dopamine D_2 receptor antagonists produce receptor occupancies of greater than 65%. By comparison, clinical doses of clozapine produce dopamine D_2 receptor occupancies of only 25–65% (Farde et al., 1989). However, 5-HT_2 receptor occupancies of 84–90% are achieved at clinically effective doses of clozapine (Nordstrom et al., 1993). Given the effect of 5-HT_{2A} receptor blockade on dopamine release in the medial prefrontal cortex and the hypothetical role of the prefrontal cortex and mesocortical dopamine systems in the pathophysiology of schizophrenia, it is difficult to dismiss the 5-HT_{2A} receptor antagonism of clozapine in terms of its clinical activity (Meltzer, 1992). Indeed, the greater efficacy of clozapine and its unique activity against deficit symptoms (Kane et al., 1988; Stephens, 1990) may be completely accounted for by a serotonergic mechanism.

These considerations have obvious implications for the use of a selective 5-HT_{2A} receptor antagonist for the treatment of schizophrenia. If the negative symptoms of schizophrenia are related to a deficit in prefrontal dopaminergic activity, agents capable of selectively increasing such activity should provide some amelioration of these symptoms without the exacerbation of positive symptoms observed following nonselective dopaminergic agents such as L-DOPA or amphetamine. Increases in prefrontal dopaminergic activity are also predicted to reduce the reactivity of the subcortical dopaminergic systems without affecting basal tone (Deutch et al., 1990; Rosin et al., 1992). The anticipated outcome of such an effect would be an interference with positive symptoms without the extrapyramidal side-effects associated with typical antipsychotics and dopamine D_2 receptor blockade.

The lack of any observed change in prefrontal dopamine release following ritanserin administration is difficult to explain. Direct infusions of high concentrations of ritanserin (100 μM) into the medial prefrontal cortex have been reported to increase dopamine efflux (Pehek et al., 1993a). The dose of 2.5 mg/kg ritanserin used in the present study was selected based on the activity of 0.1 mg/kg MDL 100,907 in our model and the approximately 25-fold difference in the ED_{50} of ritanserin (0.8mg/kg) and MDL 100,907 (0.03 mg/kg) for antagonism of 5-methoxy-dimethyltryptamine-induced headtwitches in mice (J.H. Kehne, personal communication). Headtwitch behavior is generally believed to be a response to the activation of 5-HT_{2A} receptors (Niemegeers et al., 1983; Kennett and Curzon, 1991). Because the effect of MDL 100,907 was modest at 0.1 mg/kg, it is possible that the dose of ritanserin used was just below that necessary to elicit release. It is also conceivable that some other property of ritanserin, such as its affinity for the 5-HT_{2C} receptor, may interfere with its effect in the medial prefrontal cortex.

Although the mechanism by which 5-HT_{2A} receptors regulate prefrontal dopamine efflux is unknown, there are relevant observations in the literature which allow for some speculation. In vitro electrophysiological studies have demonstrated that 5-HT_{2A} receptors are involved in the activation of aminobutyric acid (GABA)-containing interneurons in both the piriform cortex (Sheldon and Aghajanian, 1991) and dentate gyrus (Piguet and Galvan, 1994). MDL 100,907 has been shown to reduce the 5-HT-mediated activation of these inhibitory interneurons in slices of both the cortex (Marak and Aghajanian, 1993) and hippocampus (Piguet and Galvan, 1994). In addition, in vivo microdialysis studies in the rat have provided evidence that local release of GABA may modulate dopamine efflux within the prefrontal cortex (Santiago et al., 1993). Direct infusion of the $GABA_B$ receptor agonist, baclofen, into the medial prefrontal cortex produces a significant decrease in extracellular dopamine concentrations. Thus 5-HT_{2A} receptors could inhibit prefrontal dopamine efflux indirectly through the activation of GABA-ergic interneurons and the stimulation of $GABA_B$ receptors. Studies are now in progress to examine this possibility.

In conclusion, in vivo microdialysis studies using the selective 5-HT_{2A} receptor antagonist, MDL 100,907, indicate that cortical 5-HT_{2A} receptors tonically inhibit dopamine efflux in the medial prefrontal cortex. Evidence implicating frontal lobe dysfunction in schizophrenia suggests that the ability of MDL 100,907 to preferentially increase dopaminergic activity within the medial prefrontal cortex may contribute significantly to its therapeutic potential in this disorder.

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