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Improving Effect of Atomoxetine and Reboxetine on Memory in Passive Avoidance Task

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ÖZET:

Atomoksetin ve reboksetinin pasif sakınma testinde bellek üzerindeki iyileştirici etkisi

Amaç: Serotonin ve/veya noradrenalin geri alım inhibitörlerinin bellek üzerine etkileri çeşitli klinik ve preklinik çalışmalarda araştırılmıştır. Ancak, çelişkili sonuçlar bildirilmiştir. Bu çalışmada selektif noradrenalin geri alım inhibitörü olan atomoksetin ve reboksetinin; serotonin geri alım inhibitörü olan paroksetinin ve trisiklik antidepresan amitriptilinin farelerde bellek üzerindeki etkileri pasif sakınma testi ile karşılaştırılmalı olarak değerlendirilmiştir.

Yöntem: Çalışmada 25-30 gr ağırlığında erkek Balb-C fareler kullanıldı. Reboksetin (10 mg/kg), atomoksetin (5 mg/kg), paroksetin (10 mg/kg) ve amitriptilin (10 mg/kg) tek başlarına ve skopolamin (1 mg/kg) ile kombinasyon şeklinde uygulandı. Belleği değerlendirmek için pasif sakınma testi kullanıldı. İlk gün farelerin kazanım süresi (acquisition time) ikinci gün (24 saat sonra) ise retansiyon süresi (retention time) kaydedildi. Tüm ilaçlar ve salin, retansiyon süresinin değerlendirilmesinden 30 dakika önce intraperitoneal olarak uygulandı.

Bulgular: Tüm ilaçlar ve salin, tek başlarına uygulandıklarında retansiyon süresini bozmadılar. Ancak, skopolamin retansiyon süresini anlamlı ölçüde bozdu (p=0.003). Skopolamin ile kombine edildiğinde reboksetin, atomoksetin ve paroksetin retansiyon süresinde belirgin bir iyileştirici etki gösterdi. Amitriptilin, skopolamin ile kombine edildiğinde retansiyon süresi anlamlı ölçüde azaldı (p=0.013).

Sonuç: Atomoksetin ve reboksetinin bellek bozukluğu üzerindeki iyileştirici etkisi noradrenalin gerialım inhibisyonuna bağlı olabileceği ileri sürülebilir. Bellek bozukluğu üzerinde paroksetinin iyileştirici etkisi artmış serotonerjik aktivite ile ilişkili olabilir. Amitriptilinin bellek bozukluğu üzerinde iyileştirici etkisinin olmaması antikolinerjik yan etkisi nedeniyle olabilir. Bu ilaçların iyileştirici etkilerinin mekanizmalarını açıklamak için aynı model ve hayvan türlerini kullanarak yapılacak daha ileri çalışmalara ihtiyaç vardır.

Anahtar sözcükler: reboksetin, atomoksetin, paroksetin, amitriptilin, pasif sakınma testi

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ABSTRACT:

Improving effect of atomoxetine and reboxetine on memory in passive avoidance task

Objective: The effects of serotonin and/or noradrenaline re-uptake inhibitors on memory have been investigated in various clinical and pre-clinical studies. However, contradictory results have been reported. In this study, the effect of the selective noradrenaline re-uptake inhibitors atomoxetine and reboxetine, a tricyclic antidepressant, amitriptyline, and a selective serotonin re-uptake inhibitor, paroxetine, on learning and memory were examined alone or in combination with scopolamine in mice using a passive avoidance task.

Methods: Male Balb-C mice (25-30 g) were used. Reboxetine (10 mg/kg), atomoxetine (5 mg/kg), paroxetine (10 mg/kg) and amitriptyline (10 mg/kg) were investigated alone or in combination with scopolamine (1 mg/kg). A passive avoidance task was used to evaluate memory function. Acquisition time was recorded on the first day and retention time on the second (after 24 h). All drugs and saline were administered intraperitoneally 30 min prior to testing in order to evaluate retention time.

Results: None of the drugs or saline impaired retention time when administered alone; however, scopolamine significantly impaired retention time (p=0.003). Reboxetine, atomoxetine and paroxetine all resulted in a marked improvement in retention time in combination with scopolamine. A combination of amitriptyline and scopolamine also significantly reduced retention time (p=0.013).

Conclusion: Our results suggest that the effect of atomoxetine and reboxetine on improving memory deficit may be attributed to their inhibition of noradrenaline re-uptake. The effect of paroxetine on improving memory deficit may arise from enhanced serotonergic activity. Amitriptyline's lack of positive effect on memory deficit may be due to its own anticholinergic effect. Further studies using the same models and animal species are needed to clarify the mechanisms of the effects of each drug.

Keywords: reboxetine, atomoxetine, paroxetine, amitriptyline, passive avoidance task

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INTRODUCTION

Serotonin and/or noradrenaline re-uptake inhibitors are classified according to the neurotransmitter systems they affect[1,2]. These drugs are commonly used in various psychiatric disorders, such as depression and attention deficit hyperactivity disorder (ADHD)[2-5]. Both noradrenergic and serotonergic activity have been associated with cognitive functions, including learning and memory[6,7]. It has been suggested that noradrenaline plays a crucial role in memory processes[8] and that optimal levels of noradrenaline improve these and are necessary for memory consolidation[9]. In terms of the effect of serotonergic activity on memory, conflicting results suggest that the effects of serotonergic drugs act on different serotonergic receptors and affect re-uptake inhibition at different stages[10-12].

Limited studies have so far investigated the effects of atomoxetine[13-15] and reboxetine on memory[16,17]. Atomoxetine is a selective noradrenaline re-uptake inhibitor (NARI) and is used for the treatment of cognitive impairments in children and adolescents suffering from ADHD[4,5]. Atomoxetine has recently been reported to have an effect on improving memory deficit in animals[13,14]. Clinically, it has been suggested that atomoxetine also has a beneficial effect on memory in pre- and post-menopausal women[15]. Harmer et al. reported that another NARI, reboxetine, reversed memory impairment in depressive patients[16]. These studies suggest that NARIs might have a beneficial effect on memory.

Selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are used in the treatment of depression[18] and are some of the most commonly prescribed drugs in adults (19-21). Most depressive patients also suffer from memory problems[22,23]. An association between depression and memory problems has been suggested in many studies[24,25]. In addition to memory problems arising from depression, a growing number of studies have suggested that some antidepressant drugs might also cause memory impairment[10,26,27]. In contrast, some antidepressants have been reported to have a beneficial effect on memory[28-31]. The effect of antidepressants on memory may vary depending on the different mechanisms of antidepressants and their pharmacological properties. Further investigation is therefore needed in order to establish the mechanism by which antidepressants affect memory.

Muscarinic receptors have been shown to play a role in the regulation of cognitive functions, learning and memory, sleep and mood[32]. The non-selective muscarinic receptor antagonists scopolamine and atropine have been shown to cause cognitive impairment in humans[33,34] and rodents[35,36]. Amnesia was therefore induced with scopolamine in this study, and the effect of the drugs applied on that amnesia was then investigated. The effect of NARIs, atomoxetine and reboxetine, a TCA, amitriptyline, and a SSRI, paroxetine, on learning and memory were examined alone or in combination with scopolamine in mice using a passive avoidance task.

MATERIALS AND METHODS

Animals

Sixty male BALB/c mice, aged 6 weeks and weighing 30-35 g, were used. All animals were obtained from the Ondokuz Mayıs University Laboratory Animals Research and Application Center, Turkey. Six mice were housed in a cage. All animals were acclimatized to the laboratory environment for 2 weeks. The mice were kept at room temperature, 22±2°C, in a 12-h light/dark cycle with lights on at 06:00 am. Food pellets and tap water were provided ad libitum. Experiments were performed between 9:00 and 12:00. Experimentally naive animals were used at all times. All experiments were approved by the Ondokuz Mayıs University Local Ethics Committee for Animal Experiments and adhered to the guidelines of the Committee on Human/Animal Experimentation and the Helsinki Declaration of 1975, as amended in 1983.

Passive Avoidance Task

A step-through passive avoidance apparatus

with dark and light compartments and an automatically opening door (Ugo Basile, model 7551, Italy) was used to evaluate memory function. During the acquisition and retention trial period, the door was opened 30 s after each animal was placed in the light chamber. In the acquisition period, once the mice had crossed the dark compartment the door was closed automatically, and all mice received a 3-s 0.3 mA electric shock. After shocking, all animals were returned to their cages. Animals, that did not cross into the dark chamber within 60 s in the acquisition period were excluded from the test. The retention trial was performed 24 h after the acquisition period.

In the retention trial period, the mice were placed in the light compartment once again. We then waited for them to enter the dark compartment. No shock was applied when the animals entered the dark compartment in this trial. If the mice did not enter the dark compartment within 300 s they were returned to their cages. The latency period was thus set at 300 s. Times to crossing were recorded for all mice and were defined as the animals' memory performance.

Drugs and Experimental Design

All chemicals were freshly prepared, dissolved in 0.9% saline solution and administered by the intraperitoneal route in a volume of 2 ml/kg body weight. Paroxetine hydrochloride was donated by the Ali Raif Pharmaceutical Company (Levent, Istanbul, Turkey). Reboxetine mesylate hydrate, atomoxetine hydrochloride, amitriptyline hydrochloride and scopolamine hydrobromide trihydrate were purchased from Sigma (St. Louis, MO, USA). All drugs were administered 30 min prior to testing for evaluation of the retention trial period. Control groups were treated with 0.9% saline solution alone. We used combination (scopolamine+drugs) groups to evaluate the effect of each drug on scopolamine-induced amnesia.

The mice were divided into 10 groups of six animals each. These were classified as the saline, scopolamine (1 mg/kg), paroxetine (10 mg/kg), reboxetine (10 mg/kg), atomoxetine (5 mg/kg), amitriptyline (10 mg/kg) and paroxetine (10 mg/kg) + scopolamine (1 mg/kg), reboxetine (10 mg/kg) + scopolamine (1 mg/kg), atomoxetine (5 mg/kg) + scopolamine (1 mg/kg) and amitriptyline (10 mg/kg) + scopolamine (1 mg/kg) groups.

After drug administration, locomotor activity was measured using the locomotor activity test (Ugo Basile, 7430-Varese, Italy).

Statistical Analysis

Statistical analysis of groups without normal distribution was performed using the Kruskal Wallis test. The Bonferroni-corrected Mann-Whitney U test was used for double comparisons. Statistical analysis of groups with normal distribution was performed using One-Way ANOVA. Values were expressed as median and mean ± SD. In all tests, $p<0.05$ was considered statistically significant. Retention times in each drug group were compared with the retention time of saline.

All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Saline, scopolamine and all drug-treated mice exhibited similar results in terms of acquisition time (on the 1st day) in the passive avoidance task. Scopolamine (1 mg/kg), used as a reference drug, significantly impaired retention time (2nd day) compared to saline (Figure 1, p=0.003). None of the drug groups reduced retention time when administered alone in comparison to saline.

In the scopolamine combination groups, only amitriptyline (10 mg/kg) in combination with scopolamine (1 mg/kg) significantly reduced retention time (p=0.013) compared with saline. The effects of paroxetine (10 mg/kg), reboxetine (10 mg/kg) and atomoxetine (5 mg/kg) in combination with scopolamine (1 mg/kg) on retention time were similar to those of the saline group (p=0.153; p=0.902; p=0.153, respectively).

All the effects of treatment with drugs or saline in terms of results from the 1st day (acquisition time) and the 2nd day (retention time) are shown in Figure 1.

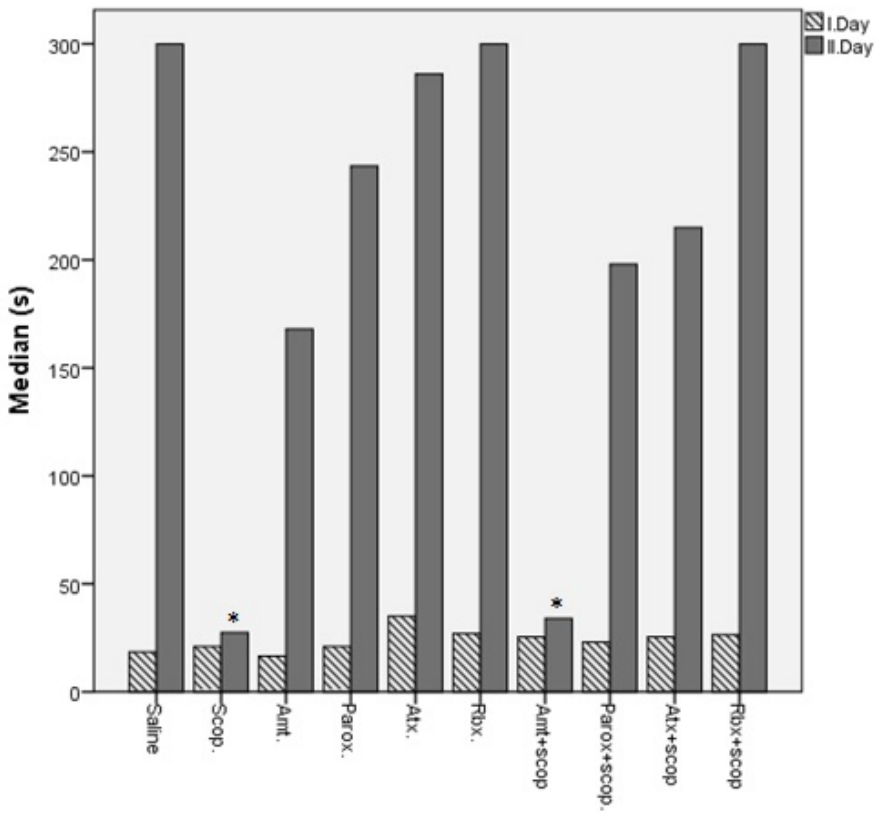

Figure 1: The effects of saline, scopolamine (1mg/kg, i.p.), amitriptyline (10 mg/kg, i.p.), atomoxetine (5mg/kg, i.p.) and reboxetine alone and the effects of antidepressants in combination with scopolamine (1mg/kg, i.p.). Scopolamine and scopolamine+amitriptyline significantly decreased the retention time as compared with saline (p=0.003; p=0.013; respectively). The effects of drugs on retention time are similar to the saline group.
Abbreviations: scop; scopolamine, amt; amitriptyline, atx; atomoxetine, rbx; reboxetine.

Table 1: Effects of drug treatment on passive avoidance response in mice

Groups	1st day Median	1st day Minumum	1st day Maximum	2nd day Median	2nd day Minumum	2nd day Maximum	p
Saline (0.5 ml)	18.5	10	29	300	255	300	
Scopolamine (1 mg/kg; i.p.)	21	11	35	27.5*	8	150	0.003
Atomoxetine (5 mg/kg; i.p.)	35	13	59	286	100	300	0.216
Paroxetine (10 mg/kg; i.p.)	21	9	40	243.5	122	300	0.153
Amitriptyline (10 mg/kg; i.p.)	16,5	8	30	168	10	300	0.153
Reboxetine (10 mg/kg; i.p.)	27	10	45	300	90	300	0.902
Paroxetine (10 mg/kg; i.p.)+ Scopolamine (1 mg/kg; i.p.)	23	11	30	198	38	300	0.153
Amitriptyline(10 mg/kg; i.p.)+ Scopolamine (1 mg/kg; i.p.)	25,5	9	29	34*	11	300	0.013
Reboxetine (10 mg/kg; i.p.)+ Scopolamine (1 mg/kg; i.p.)	26.5	16	30	300	50	300	0.902
Atomoxetin (5 mg/kg; i.p.)+ Scopolamine (1 mg/kg; i.p.)	25.5	10	30	215	33	300	0.153

*; p<0.05 (compared to the saline groups)

Table 2: Effects of drugs on locomotor activity time in mice

	n	Time (second)	p
Saline	6	75.00±5.65	0.230
Scopolamine (1 mg/kg; i.p.)	6	71.17±9.24	
Atomoxetine (5 mg/kg; i.p.)	6	63.50±10.80	
Paroxetine (10 mg/kg; i.p.)	6	70.67±13.11	
Amitriptyline (10 mg/kg; i.p.)	6	62.83±6.11	
Reboxetine (10 mg/kg; i.p.)	6	74.83±9.85	
Paroxetine (10 mg/kg; i.p.)+ Scopolamine (1 mg/kg; i.p.)	6	70.67±9.22	
Amitriptyline (10 mg/kg; i.p.)+ Scopolamine (1 mg/kg; i.p.)	6	70.67±5.95	
Reboxetine (10 mg/kg; i.p.)+ Scopolamine (1 mg/kg; i.p.)	6	71.83±8.06	
Atomoxetine (5 mg/kg; i.p.)+ Scopolamine (1 mg/kg; i.p.)	6	66.00±8.53	
Total	60	69.72±9.18	

Results are presented as mean±standard deviation. i.p., intraperitoneal

The median, minimum and maximum values of the results are given in Table 1.

No drugs compromised locomotor activity at the given doses (p=0.230).

DISCUSSION

The results show that none of the re-uptake inhibitors negatively affected memory retention when administered alone at the given doses in the passive avoidance task. The reference drug scopolamine used to cause amnesia[37] clearly impaired (p=0.003) retention time in mice at 1 mg/kg in comparison with saline. While atomoxetine, reboxetine and paroxetine clearly improved memory deficit in combination with scopolamine, amitriptyline did not.

NARIs block the membrane uptake carrier that transports noradrenaline from extracellular regions to the nerve cells. As a consequence, the synaptic concentration of noradrenaline is increased and it is assumed that NARIs increase noradrenergic transmission. Atomoxetine has been shown to improve core symptoms of ADHD[4,5], and reboxetine is approved as an antidepressant drug. However, the antidepressant effect of atomoxetine is controversial. Some studies have reported that atomoxetine exhibits antidepressive properties, but it has not been approved as an antidepressant drug by the FDA[38,39]. There are no reported findings concerning the effect of reboxetine on memory and learning using a passive avoidance task, although a few studies have been carried out with atomoxetine[13-15]. In one study, atomoxetine improved memory deficit in a passive avoidance task in rats exposed prenatally to the organic compound trimethyltin chloride, a chemical used in tests that disturbs memory[13]. Tzavara et al. have reported that atomoxetine improved memory deficit in object recognition tests and the radial arm-maze test[14]. These studies show that atomoxetine has beneficial effects on memory and learning.

Several mechanisms including the cholinergic system might be proposed to explain the effect of NARIs on improving memory deficit. The muscarinic cholinergic system is known to be associated with cognitive functions[40]. The antimuscarinic drug scopolamine has been used as a reference drug to impair memory function in tests[37]. In respect of Alzheimer's disease, in which central cholinergic cells degenerate, many studies have focused on the effect of drugs or molecules that may have a positive effect on memory[41,42]. For example, the acetylcholinesterase inhibitor physostigmine has been reported to reverse the impairing effect of amitriptyline on memory[43]. Atomoxetine has been reported to increase acetylcholine levels in cortical regions of the brain[14]. The improving effect of atomoxetine, as in our study in which, systemically applied atomoxetine improved scopolamine-induced memory deficit, may be related to the increase of acetylcholine levels in certain regions of the brain. Further studies are needed to clarify the role of acetylcholine and cholinergic system for NARIs.

Another effect of NARIs on improving memory

deficit may arise from increases in noradrenaline and dopamine in the prefrontal cortex. The prefrontal cortex receives intensive serotonergic, dopaminergic and noradrenergic afferents and plays an important role in learning and memory[44]. The interaction of neurotransmitter systems in this region affects cognitive functions[45,46]. For instance, the beneficial effect of desipramine on cognitive functions has been attributed to the alpha1-adrenergic receptors in the medial prefrontal cortex[47]. Recent studies have shown that noradrenaline has a beneficial effect on prefrontal cortex functions by activating adrenergic receptors[48]. Increased noradrenaline levels due to atomoxetine in the prefrontal cortex have been suggested as an explanation of its improving effect[49]. Like noradrenaline, dopamine also exhibits improving effects on learning and memory. While dopamine D1 receptor activation enhances learning, D2 receptor activation facilitates memory[50]. Reboxetine has been shown to increase dopamine release in the hippocampus and prefrontal cortex in healthy volunteers and in depressed patients[51,52], and to improve recognition memory by activating D1/5 receptors[53]. The beneficial effect of reboxetine may therefore also depend on dopamine interaction.

Depression is known to impair memory function[22,23]. The anticholinergic effect of some antidepressants has been implicated in the memory mechanism[27,40]. In terms of our results, amitriptyline did not impair retention time when administered alone, but in combination with scopolamine retention time decreased significantly. These results show that amitriptyline has no beneficial effect on scopolamine-induced memory deficit. According to previous studies, the impaired effect of amitriptyline on memory is related to its anticholinergic effect[26,54]. Furthermore, the acetylcholine esterase inhibitor, physostigmine has been reported to reverse the impairing effect of amitriptyline on memory[43]. These results suggest that impairment of memory depends on the anticholinergic effect of amitriptyline. Additionally, no impairing effect on memory of the serotonin and noradrenaline re-uptake inhibitors venlafaxine and duloxetine has been reported[55,56]. These drugs are known to have no or minimal anticholinergic effect, and this may contribute to their effect on memory[57,58]. We suggest that noradrenaline re-uptake inhibitors generally have an improving effect on memory deficit in a passive avoidance task if their anticholinergic effect is not pronounced. In our study, amitriptyline alone at 10 mg/kg did not affect memory. This discrepancy may be due to the relatively low doses of amitriptyline or to the species used.

Paroxetine (10 mg/kg, i.p.) did not affect memory but exhibited an improving effect in combination with scopolamine in our study. Fujishiro et al. have reported that paroxetine at 16 mg/kg and 32 mg/kg i.p. exhibited an impairing effect in a passive avoidance task[59]. Paroxetine is known to have anticholinergic effects[2]. However, in those studies in which the effects of paroxetine on memory were investigated, the positive effect of paroxetine was associated with the mild anticholinergic effect of paroxetine in comparison to amitriptyline[60,61]. We used a dose of 10 mg/kg i.p. and determined no impairment in combination with scopolamine. Our results are consistent with the results reported by Naudon et al., in which paroxetine did not impair memory in the radial arm maze test[62]. There are limited studies investigating the effect of SSRIs on learning and memory in certain brain regions such as the prefrontal cortex. In terms of the effect of variable SSRIs on memory and learning, zimelidine, citalopram and fluoxetine have been shown to impair memory in two-way active avoidance tests[63]. However, Kumar and Kullkarni suggested that fluoxetine did not exhibit any negative effect when administered alone, and furthermore reversed scopolamine-induced impairment in a passive avoidance task[26]. Chronically paroxetine-treated rats exhibited no negative effect on memory in the delayed spatial win-shift test, and it has been suggested that this effect of paroxetine was related to brain regions such as the hippocampus and prefrontal cortex, which play a critical role in memory[62]. These inconsistent results of SSRIs on memory may be due to the use of different models. Some recent studies have proposed that an increase in serotonergic activity compromised learning and memory[64]. In addition, intrahippocampal injection

of serotonin has been shown to disturb retention time in the Y-maze brightness discrimination task[65]. However, Barros et al. showed that sertraline has a positive effect on memory in a passive avoidance task and claimed that this positive effect depended on serotonin re-uptake and increases in serotonin levels in the brain[66]. Paroxetine, also used in our study, is one of the most potent serotonin re-uptake inhibitors[67], and its positive effect may be due to re-uptake inhibition of serotonin. The inconsistent results concerning the effects of serotonin and SSRIs may be attributed to the complex activity of serotonin pathways, and further studies are needed to clarify the effect of SSRIs in the modulation of learning and memory.

In conclusion, the NARIs reboxetine and atomoxetine, and the SSRI paroxetine improved memory deficit, while the TCA amitriptyline did not improve the memory deficit caused by scopolamine. The improving effect of atomoxetine and reboxetine on memory deficit may be attributed to their noradrenaline re-uptake inhibition. The lack of beneficial effect of amitriptyline on memory deficit may be ascribed to its anticholinergic effect. Further studies using the same models and animal species are now needed to clarify the improving effect of re-uptake inhibitors. Clinically, establishing a positive or negative effect of re-uptake inhibitors on memory may contribute to advances in psychiatric therapy.

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