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Pineal peptides restore the age-related disturbances in hormonal functions of the pineal gland and the pancreas

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Abstract

The purpose of this research was to study age-related changes in functioning of pineal and pancreatic glands of non-human primates, rhesus monkeys, and to elucidate the possibility of their corrections with the help of epitalon, a synthetic analogue of the pharmacopoeia drug epithalamin. In old (20–27 years) animals, the basal plasma levels of glucose and insulin were found to be higher, while the night melatonin level was lower in comparison with (6–8 years) young animals. After the glucose administration to old monkeys, a larger area under the curve of the plasma glucose response, a reduced glucose 'disappearance' rate, and a reduced insulin peak (5 min after the glucose administration) were observed in comparison with young animals in similar experiments. The epitalon administration to old monkeys caused the decrease in the basal levels of glucose and insulin and the increase in the basal night melatonin level. Additionally, in the case of old monkeys, epitalon decreased the area under the plasma glucose response curve, markedly increased the glucose 'disappearance' rate and normalized the plasma insulin dynamics in response to glucose administration. Yet, it has not affected the hormonal and metabolic changes in young animals. Thus, epitalon is a promising factor for restoring the age-related endocrine dysfunctions of primates.

Keywords: Aging; Pineal gland; Pancreas; Age-related dysfunctions; Pineal peptides; Epitalon; Epithalamin; Monkeys

1. Introduction

It is well known that the decrease in the production of melatonin, the increase of secretion of insulin, the decrease in sensitivity of peripheral tissues and of pancreatic islet β-cells to insulin are typical for aging of humans (Barbieri et al., 2002; Bellino and Wise, 2003; Ferrari et al., 1995, 1996; Touitou et al., 1981; Touitou and Haus, 2000). Many age-related diseases, such as insomnia, some neurodegenerative diseases, depression, age disturbances in the glucose tolerance, non-insulin-dependent diabetes mellitus, etc. are caused by the functional disturbances of the pineal gland and the pancreas (Ametov, 2002; Barbieri et al., 2002; Bellino and Wise, 2003; Ellis and Lemmens, 1996; Wehr, 1996). Therefore, it is of great importance to elucidate possible ways of a correction of the age-related disturbances of pineal gland and pancreas functions. In this connection, laboratory primates, which are diurnal animals and subjected to spontaneous non-insulin-dependent diabetes mellitus, like humans, are the most adequate experimental objects (Wagner et al., 1996; Cusumano et al., 2002). In our previous papers, we showed that the pineal peptide epitalon has a beneficial regulatory role on the pineal gland function (Goncharova et al., 2001, 2003; Khavinson et al., 2001). In addition, data suggest that some pineal peptides may influence on the endocrine function of the pancreas (Milcou et al., 1963). Our research was aimed at elucidating (i) how the functions of the pineal gland and of the pancreatic islet change during aging of laboratory primates and (ii) how epitalon influences the pineal gland and the pancreatic islet functions. We have shown that epitalon is a promising remedy to restore the age-related endocrine dysfunctions of primates.

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2. Materials and methods

Young adult (6–8 years, sexually mature juvenile) and old (20–27 years) non-obese healthy female rhesus monkeys (*Macaca mulatta*), 17 animals of each age, were used in the experiments. The animals were kept in the monkey colony of the Research Institute of Medical Primatology. All experiments were carried out during the period between June and September. Animals were kept in corrals or cages in groups. During the time of experiments, animals were kept in the metabolic cages under the controlled illumination (from 06.00 till 19.00). The temperature in the room was between 20 and 25 °C. The animals were fed with well balanced diet. Before the experiments, the animals were adapted to the conditions of living in metabolic cages and to the procedure of bleeding for at least 4 weeks.

Epitalon (tetrapeptide Ala-Glu-Asp-Gly) was synthesized on the basis of the amino acid analysis of epithalamin (pharmacopoeia drug, the peptide extract from the cattle pineal gland) in the St Petersburg Institute of Bioregulation and Gerontology, RAMS (Khavinson, 2002). To study the effect of epitalon on the function of pineal gland, 10 young and 10 old animals were used. The mean body weight of animals was 5.2 ± 0.2 kg (young monkeys) and 5.8 ± 0.2 kg (old monkeys). After the adaptation period, the basal levels of melatonin were evaluated for all animals. The samples of blood were taken at 10.00, 16.00, 22.00, 04.00 and 10.00 of the following day. Two weeks later, 7 young and 7 old animals were exposed to the intramuscularly injections of epitalon during 10 days (3 µkg of epitalon per day for each animal). In parallel, the control animals, 3 young and 3 old individuals, were injected with placebo (0.9% solution of NaCl in water). The blood samples were taken two times a day (at 10.00 and 22.00) on the 7th and 10th days after the beginning of epitalon or placebo administration.

To study the effect of epitalon on the function of pancreatic islets, other animals, 7 young and 7 old monkeys, were used. The mean body weights were 5.2 ± 0.3 kg for young animals and 5.7 ± 0.2 kg for old ones. To evaluate basal levels of glucose and insulin, the samples of blood were taken at 9.00–9.30 on an empty stomach. To determine the glucose tolerance, all animals on an empty stomach were intravenously injected with 40% aqueous solution of glucose (300 mg/kg b. w.) at 9.00–9.30. The blood samples were taken before the glucose administration and 5, 15, 30, 60 and 90 min after the glucose administration. A month after the glucose tolerance testing, the animals of both ages were intravenously injected with epitalon for 10 days, 10 µkg per day. The glucose tolerance testing of the same animals was accomplished on 9th day after the onset of epitalon injection, as well as 1 and 2 months after the abolition of the epitalon administration.

All blood samples were taken from the cubital and femoral vein with heparin as the anticoagulant. The blood samples were immediately centrifuged under 2000*g* at +4 °C. The plasma was separated and stored under −70 °C. Melatonin and insulin in the plasma were determined no later than 1 month after the sampling of blood. The concentrations of melatonin were measured by the immune enzyme method with preliminary purification of the hormone on chromatographic columns using the ELISA kits (IBL, Germany). The concentrations of insulin were measured by the immune enzyme method using the ELISA kits (DSL, USA). The intra- and interassay variation coefficients for melatonin did not exceed 10%. The intra- and interassay variation coefficients for insulin did not exceed and 10 and 12%, correspondingly.

To evaluate the circadian rhythm of plasma melatonin concentration, the mean diurnal melatonin concentration (pg/ml) and the amplitude of circadian rhythm were calculated. The amplitude of circadian rhythm of melatonin was calculated as the difference between its highest level (at 22.00) and its lowest level (at 16.00) in pg/ml. Additionally, it was calculated in the percent of the mean diurnal melatonin concentration.

Concentration of plasma glucose was measured by the glucose oxidize method. To evaluate the glucose tolerance, the rate of glucose 'disappearance' from the circulation was calculated during the first 15 min after the intravenous glucose administration (300 mg/kg b. w.). The rate of glucose 'disappearance' was expressed in percentage of the initial total glucose level per minute.

All the data were analyzed by the conventional statistical methods using the Student's *t* test.

3. Results

3.1. Circadian rhythm of plasma melatonin in female rhesus monkeys of different age

A typical graph of the circadian rhythm of the plasma melatonin concentration is presented in Fig. 1. The minimal levels of melatonin, registered at 16.00, were 9.00 ± 2.0 pg/ml for young animals and 9.6 ± 1.0 pg/ml for old ones. The maximal melatonin levels were detected at night and were 87.6 ± 6.9 pg/ml at 22.00 and 62.7 ± 3 pg/ml at 04.00 for young animals and 56.8 ± 4.6 pg/ml at 22.00 and 42.4 ± 2.5 pg/ml at 04.00 for old animals, respectively. The night levels of melatonin concentrations of old monkeys, detected at 22.00 and 04.00, were significantly lower than the relevant levels of young monkeys ($P < 0.001$). In addition, the mean diurnal melatonin concentration in old animals was significantly lower in comparison to young animals, 30.0 ± 2.5 and 44.2 ± 4.0 pg/ml, respectively ($P < 0.01$).

Besides the above-mentioned changes in the diurnal melatonin concentration, the amplitude of circadian rhythm also underwent the marked age changes (Fig. 1). In young animals, the absolute values of the amplitude of circadian rhythm were 78.6 ± 7.0 pg/ml in young animals and 47.2 ± 5 pg/ml in old animals ($P < 0.001$). The relative

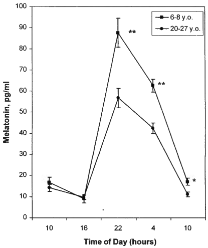

Fig. 1. Plasma melatonin circadian rhythm in female rhesus monkeys of different age (mean ± SEM, $n=7$ for each age group). $*P<0.01$, $**P<0.001$ vs old animals.

values of the amplitude (in percent of the mean diurnal melatonin concentration) were 77.8 ± 6.0% in young animals and 57.3 ± 3.0% in old animals ($P<0.01$). It means that the diurnal rhythm of plasma melatonin becomes essentially less marked with aging of animals.

3.2. Influence of epitalon on plasma melatonin level in female rhesus monkeys of different age

The data presented in Table 1 show that in the experiments with young animals epitalon has not affected the plasma melatonin concentrations. However, in the experiments with old animals, the significant increments in the night melatonin levels at 22.00 were detected on the 7th and 10th day after the epitalon administration. This marked accretion is also seen when the melatonin level in the old animals administered with epitalon is compared with the melatonin level in the animals administered with placebo (Table 1). On the 7th day and on the 10th day after the epitalon administration, the melatonin levels in the plasma of old animals have become equal to its levels in young animals. The placebo administration has not affected the plasma melatonin levels (see Table 1).

3.3. Levels of glucose, insulin, and the results of glucose tolerance testing in animals of different age in basal conditions

The data presented in Table 2 show that the basal level of glucose and the levels of glucose measured at different time points after the glucose administration (5, 15, 30 and 60 min) have been essentially higher in the case of old animals in comparison with the young ones. Fig. 2 shows that the basal insulin levels and the levels of insulin measured after 30 and 60 min of the glucose administration have also been higher in the case of old animals. However, from the same Fig. 2 one can see that, in contrast to the level of glucose, the level of insulin measured 5 min after the glucose administration has occurred to be significantly less in comparison to young animals.

Table 2 also present the results of calculations of areas under the curves of the changes of the plasma glucose level in response to administration of the standard glucose dose (the curves are not shown). From these data, one can see that the area under the curve of the glucose response for old animals in the basal conditions was significantly higher in comparison to young animals (479.6 ± 38.0 vs 294.9 ± 9.3 mmol/l min, $P<0.001$). The rate of 'disappearance' of glucose in old animals was significantly lower in comparison to that for young animals (4.3 ± 0.1% per 1 min vs 5.3 ± 0.05% per 1 min, $P<0.001$).

3.4. Effect of epitalon on basal plasma glucose and insulin levels and the results of glucose tolerance testing in animals of different age

In response to the epitalon administration, the old animals demonstrate a tendency towards a decrease of the basal glucose level (3.8 ± 0.4 vs 4.0 ± 0.4 mmol/l before the administration) and the change of the dynamics of

Table 1

Dynamics of plasma melatonin concentration in response to administration of epitalon (10 μg/animal per day during 10 days, intramuscularly) or placebo in female rhesus monkeys of different age (mean ± SEM, pg/ml)

Age, years	Before epitalon administration		On 7th day after epitalon administration		On 10th day after epitalon administration	
	Time of day, hours					
	10.00	22.00	10.00	22.00	10.00	22.00
6–8 ($n=7$)	13.9 ± 4.1	86.0 ± 7.2	14.0 ± 0.9	84.0 ± 4.1	12.8 ± 1.5	89.6 ± 7.0
20–27 ($n=7$)	10.3 ± 0.9	44.8 ± 8.0	15.8 ± 3.8	75.5 ± 8.9 [a,b]	20.0 ± 6.5	80.7 ± 9.0 [a,b]
	Before placebo administration		On 7th day after placebo administration		On 10th day after placebo administration	
6–8 ($n=3$)	15.0 ± 1.2	78.6 ± 6.0	15.0 ± 1.9	80.0 ± 4.0	13.8 ± 1.1	79.6 ± 6.0
20–27 ($n=3$)	12.3 ± 0.9	40.8 ± 6.0	14.8 ± 2.5	39.5 ± 4.9	15.0 ± 2.5	41.1 ± 6.0

[a] $P<0.05$ vs before epitalon administration; [b] $P<0.01$ vs placebo administration, n, number of animals.

Table 2
Dynamics of the plasma glucose concentration and the area under the curve of glucose level response to administration of the standard dose of glucose (300 mg/kg b. w., intravenously) in female rhesus monkeys of different age before administration of epitalon, on the background of epitalon administration (10 μg/animal/day during 10 days, intramuscularly) and 1 and 2 months later after abolition of the epitalon administration (mean ± SEM)

Age, years	Time after glucose administration, min						Area under the curve of glucose level response, mmol/l min
	0	5	15	30	60	90	
	Glucose concentration, mmol/l						
Before administration of epitalon							
6–8 ($n=7$)	3.8±0.1	9.2±0.4	5.6±0.2	3.9±0.4	3.4±0.1	3.5±0.2	294.9±9.3
20–27 ($n=7$)	4.0±0.4	12.0±0.5[b]	9.8±0.6[a]	7.8±0.9[a]	5.0±0.4[a]	4.1±0.5	479.6±38.0[a]
On 9th day after beginning of administration of epitalon							
6–8 ($n=7$)	3.6±0.3	8.9±0.7	6.1±0.6	3.9±0.6	3.8±0.3	3,7±0,5	343,3±48,2
20–27 ($n=7$)	3.8±0.4	8.4±0.6[c]	6.8±0.8[d]	5.7±0.9	3.9±0.4[e]	3.1±0.2	388.9±43.6
One month after abolition of epitalon							
6–8	3.8±0.2	8.2±0.3	7.2±0.6	4.9±0.5	3,4±0,1	4,1±0,1	353,0±19,9
20–27 ($n=7$)	4.1±0.3	9.5±0.7[c]	8.4±0.8	7.7±0.6[b]	5.2±0.5[b]	4.5±0.7	480.0±55.0[b]
Two months after abolition of epitalon							
6–8 ($n=7$)	3.7±0.3	8.4±1.1	5.9±0.5	4.1±0.5	3.2±0.1	3.1±0.1	293.2±25.0
20–27 ($n=7$)	4.2±0.4	8.6±0.7[e]	8.1±0.6[b,e]	7.4±1.0[b]	5.3±0.9[b]	4.1±0.6	451.0±46.0[b]

[a]$P<0.001$, [b]$P<0.05$ vs young animals; [c]$P<0.001$, [d]$P<0.01$, [e]$P<0.05$ vs before the epitalon administration. n, number of animals.

the glucose level (see Table 2). The glucose level in old animals significantly decreased after 5, 15 and 60 min of administration of the standard glucose dose on the background of the epitalon administration. However, in the case of young animals the basal levels and the dynamics of glucose in response to the standard glucose dose on the background of the epitalon administration did not undergo any significant changes.

The area under the curve of the plasma glucose response to the standard glucose dose in the epitalon-treatment old animals slightly decreased (388.9±43.6 vs 479.6±38.0 mmol/l min before the administration of epitalon) (see Table 2). This results in the leveling of the age differences in the areas under the curves of the glucose response, which took place in the basal conditions. The administration of epitalon has caused the significant increase of the 'disappearance' rate of glucose in the case of old animals (5.0±0.2% per 1 min vs 4.3±0.1% per 1 min before the epitalon administration, $P<0.01$) but no changes in the case of young animals (5.2±0.2% per 1 min vs 5.3±0.05% per 1 min, $P<0.05$).

During 1 and 2 months after abolition of epitalon, the basal levels of glucose, the glucose levels measured 30, 60, 90 min after the standard glucose dose administration and the area under the curve of the glucose response have reverted to their initial values (Table 2). However, the glucose levels measured 5 and 15 min after the standard glucose dose administration have still been lower compared to the initial level (Table 2). The glucose 'disappearance' rate has still been higher compared to its initial level (4.7±0.3% per 1 min in one month after the abolition and 4.96±0.20% per 1 min in 2 months after the abolition of epitalon vs 4.3±0.1% per 1 min in the basal conditions, respectively).

The data presented in Fig. 2 show that the basal insulin levels after administration of epitalon slightly decreased,

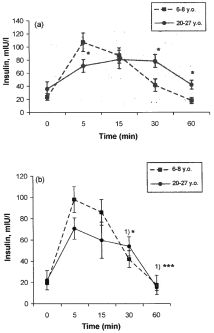

Fig. 2. Dynamics of plasma insulin level in response to glucose administration (300 mg/kg b. w., intravenously) in female rhesus monkeys of different age (mean ± SEM, $n=7$ for each age group). (a) Before epitalon administration, (b) on 9th day of epitalon administration. 1) *$P<0.05$ vs young animals; 1) ***$P<0.001$ vs before epitalon administration.

and the dynamics of insulin level in response to glucose administration in young animals looked similar to that in young animals. It must be noted that a relative increase in the insulin level in old animals 5 min after glucose administration sharply increased (320 ± 29 against $198 \pm 40\%$ before epitalon administration and $450 \pm 72\%$ in young animals) and 60 min later decreased significantly (69 ± 8 against $117 \pm 20\%$ before epitalon administration, $P < 0.05$).

4. Discussion

4.1. Age-related disturbances of pineal gland function. Effect of epitalon on melatonin secretion

Thus, the melatonin concentration in the rhesus monkeys' plasma undergoes the marked circadian rhythm with the highest values registered at night (22.00–04.00) and the lowest ones registered at approximately 16 h. The similar data were reported for humans (Touitou et al., 1981; Touitou and Haus, 2000; Ferrari et al., 1995, 1996). Moreover, absolute values of the melatonin concentrations for monkeys turned out to be similar to the absolute values of the melatonin concentrations for humans. For example, the mean diurnal concentration of melatonin for old female rhesus monkeys measured in our work is 30.0 ± 2.5 pg/ml while the mean diurnal concentration of melatonin reported for old women was 38.1 ± 2.7 pg/ml (Touitou et al., 1981).

The night melatonin concentrations and the mean diurnal melatonin concentrations in plasma of old monkeys are 1.5–2.0 times reduced as compared to young monkeys. These results are in accordance with the literature data for humans and in accordance with the data for rodents (Reiter et al., 2002; Greenberg and Weiss, 1978).

Apart from the decrease at night and mean diurnal melatonin concentrations, the amplitude of melatonin circadian rhythm of old animals is also reduced, which points to a tendency towards the flattening of the circadian rhythm of melatonin secretion with aging. This finding is probably due to the age-related impairment of noradrenergic regulation of melatonin secretion. It is in accordance with the fact of lower content of the pinealocyte membrane β-adrenoreceptors in old rats (Greenberg and Weiss, 1978). Furthermore, the marked decrease in the level of noradrenalin was observed in the various regions of brains of aged rhesus monkeys (Beal, 1993).

Thus, our experimental data testify the basic similarity in the circadian rhythms of melatonin secretion for monkeys and humans. Moreover, there is the similarity in the character of the age-related changes of melatonin secretion for monkeys and humans. Hence, rhesus monkeys may indeed be used as an experimental model to study the effects of epitalon on the melatonin secretion.

The data presented in Table 1 show that administration of epitalon to old monkeys during 10 days, 10 μkg per animal per day, resulted in statistically significant increase of the plasma night melatonin level. Epitalon can restore the age-related changes through normalization of catecholaminergic regulation of pineal function. In support of this assumption we can point to finding that the prolonged administration of another pineal peptide preparation, epithalamin, the properties of which are similar to those of epitalon, normalizes the levels of various neurotransmitters in the hypothalamus of old mice (Labunets et al., 2003).

4.2. Age-related disturbances of pancreatic islet function. Effect of epitalon

The data presented on Fig. 2 show that the basal level of glucose significantly increases with aging. There is also a tendency towards increasing the insulin level. Besides of that, the distinct age differences in dynamics of the insulin and glucose levels in response to glucose administration were observed. It points out that, despite the lack of significant differences in the basal insulin level, the marked age-related disturbances in hormonal function of the pancreas are revealed under the conditions of activation of the pancreas. First of all, it is a question of the decrease of peripheral tissue sensitivity to insulin. It is evidenced by the decrease of the rate of 'disappearance' of exogenous glucose in old animals compared to young individuals (Section 3).

However, in parallel with the decrease in sensitivity of peripheral tissues to insulin there is also the disturbance in sensitivity of β-cells of pancreatic islets to glucose. This is confirmed by the fact that the glucose concentration and the insulin concentration alter in the opposite direction 5 min after administration of glucose opposite to old animals (see Fig. 2). As a consequence, the glucose concentration in old animals 5 min after the infusion of the standard dose has become significantly higher while the insulin concentration has become lower compared to their values in young animals 5 min after the standard dose injection (Fig. 2). The similar age-related changes in the pancreatic islet functions were reported for nonhuman monkeys (Bellino and Wise, 2003; Gresl et al., 2003; Ramsey et al., 2000; Roth et al., 2001) and humans (Ametov, 2002; Bellino and Wise, 2003).

After epitalon administration, the old animals showed a tendency towards the decreasing basal glucose level and the restoring of the dynamics of the glucose level in response to glucose administration (see Table 2). It indicates that the age-related disturbance of the glucose tolerance tends to recover. Actually, epitalon significantly increases the rate of glucose 'disappearance' in old animals up to the values, which are typical for young animals (see Section 3).

After the administration of epitalon for 10 days, the old animals demonstrated recovery of both, the basal level of insulin and the dynamics of the insulin level in response to glucose administration. In particular, the increase of the insulin concentration 5 min after the glucose administration along with the decrease of blood glucose content testify that epitalon primarily exhibits its recovering effect on the first stage of insulin secretion, when the so-called pool of fast reacting insulin is secreted. It suggests an increase in sensitivity of pancreatic β-cell islets to high glucose concentrations, influenced by epitalon. Besides of the restorative action on the early stage of insulin secretion, epitalon seems to affect the second phase of the insulin secretion too, making it more plastic. As shown in Fig. 2, in the case of old animals the essential decrease in the insulin level is observed 30 and 60 min after the glucose administration compared to the basal values. Hence, when old animals are administered with epitalon, the dynamics of recovery of the insulin level in their blood in response to the glucose administration becomes similar to that of young animals. This observable fact apparently stems from the increasing sensitivity of peripheral tissues to insulin, evidenced by the findings that the level of insulin and the level of glucose simultaneously decrease with time in the experiments on administration of glucose or restoration of glucose 'disappearance' rate (see Table 2 and Fig. 2). The increase of tolerance to glucose has partly recovered in 1–2 months after abolition of the drug administration. Hence, one can conclude that the recovery effect of epitalon on pancreatic islet function and metabolism of glucose is related to the corresponding restoration of sensitivity of islet β-cells and peripheral tissues to glucose and insulin.

The recovering effect of epitalon on the pancreas function may arise from an advantageous effect of this drug on secretion of melatonin. Indeed, specific receptors to melatonin have been recently found in the pancreas (Peschke et al., 2000; Kemp et al., 2002). For example, the administration of melatonin to healthy middle-aged rats was revealed to decrease the level of basal insulin down to the values, which are typical for young animals (Rasmussen et al., 1999). The treatment of pinealectomized rats with melatonin resulted in the higher meal-induced insulin responses (la Fleur et al., 2001). There is evidence that melatonin can directly act on β-cells of the island of Langerhans in vitro (Peschke et al., 1997).

Additionally, the restoring effect of melatonin on the glucose tolerance may be mediated through stimulation of secretion of the growth hormone and somatomedins. Indeed, melatonin was revealed to enhance the exercise-induced secretion of growth hormone and secretion of insulin like growth factor-1 in healthy adult male subjects (Meeking et al., 1999). Moreover, the plasma levels of both, growth hormone and insulin like growth factor-1, essentially decrease with aging (Ferrari et al., 1996; Khan et al., 2002; Touitou and Haus, 2000). One can suggest that pineal peptides restore the pancreas function by normalization of levels of different neurotransmitters in brain and/or modulate sensitivity of the relevant receptors to neurotransmitters. In this respect, it is noteworthy that aging of primates is accompanied with deterioration of the levels of some neurotransmitters including noradrenalin and acetylcholine (Beal, 1993; Birthelmer et al., 2003), while epithalamin, the analogue of epitalon, partially restores the neurotransmitter imbalance in the central neural system (Labunets et al., 2003). In either case, epitalon obviously shows promise as a remedy to restore the age-related endocrine dysfunctions of primates.

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