Dehydroepiandrosterone and monoamines in the limbic system of a genetic animal model of childhood depression

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Abstract

Monoamines and dehydroepiandrosterone (DHEA) levels were measured in a genetic animal model for childhood depression in four subcortical structures: nucleus accumbens (Nac), ventral tegmental area (VTA), amygdala and hypothalamus. The "depressive-like" strain was the Flinders Sensitive Line (FSL), compared to their controls, Sprague-Dawley (SD) rats. Prepubertal FSL rats showed abnormal levels of only a few monoamines and their metabolites in these brain regions. This is in contrast to former studies, in which adult FSL rats exhibited significantly higher levels of all the monoamines and their metabolites measured. These different abnormal monoamine patterns between the "depressed" prepubertal rats and their adults, may help to explain why depressed children and adolescents fail to respond to antidepressant treatment as well as adults do. On the other hand, FSL prepubertal rats exhibited the same pattern of abnormal DHEA basal levels as was found in adults in previous experiments. The results from the current study may imply that treatment with DHEA could be a promising novel therapeutic option for depressed children and adolescents that fail to respond to common (monoaminergic) antidepressant treatments.

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KEYWORDS
Childhood depression; Monoamines; DHEA; Limbic system; Animal model; FSL
1. Introduction

In recent years, there has been increasing recognition of the role played by particular subcortical structures [e.g. nucleus accumbens (Nac), hypothalamus, ventral striatal area (VTA) and amygdala] in the regulation of motivation, sleep, appetite, energy level, circadian rhythms, and responses to pleasurable and aversive stimuli — domains which are prominently affected in most depressed patients (Nestler et al., 2002). These brain areas have been found to play critical roles in depression (Koob et al., 1998; Wise, 1998).

Many studies point to the Nac as the central region involved in, and mediating, activities relating to motivation and hedonia (Phillips et al., 1991; Robinson and Berridge, 1993; Breiter et al., 1997). The Nac is a target of the mesolimbic dopamine system, which arises in dopaminergic neurons in the VTA of the midbrain. These VTA neurons also innervate several other limbic structures, including the amygdala and limbic regions of the neocortex (Nestler et al., 2002). The amygdala is equally important for conditioned responses to rewarding stimuli, including substances of abuse and natural rewards (Everitt et al., 1999). Another subcortical structure with a role in depression is the hypothalamus, which has long been known to mediate many neuroendocrine and neuro-vegetative functions. Because of their unique importance and influence on depression, we focused on these four subcortical areas in the current research: Nac, VTA, amygdala, and hypothalamus [another important brain region which influences depression and should be mentioned is the hippocampus; (for review see Dranovsky and Hen, 2006; Duman and Monteggia, 2006). Since the focus of the current study was on the limbic system, we did not examine this specific region].

Childhood depression has received attention as a significant clinical phenomenon only relatively recently. Major depression in children and adolescents is common, recurrent, and associated with significant morbidity and mortality (Birmaher et al., 1996). Despite similarities in the clinical picture and longitudinal course of major depression in children, adolescents, and adults (Kovacs, 1996), there are notable differences in the neurobiological correlates and treatment response of depressed patients in these different age cohorts (Kaufman et al., 2001). Most notably, depressed prepubertal children fail to respond to antidepressant treatment as well as adults do (Hazell et al., 1995; Keller et al., 2001; Zalsman et al., 2006). For example tricyclic antidepressants have not been shown to be more efficacious than placebo for pediatric depression (Kye and Ryan, 1995; Keller et al., 2001). This may indicate that some aspects of pathophysiology in monoaminergic circuits are unique to childhood depression (Axelsson and Birmaher, 2001). In order to identify unique circuits that might be implicated in children suffering from depression and in attempt to examine potential new antidepressant approaches for childhood depression, we measured the basal levels of Dehydroepiandrosterone (DHEA) and monoamines in the limbic system in an animal model of depression.

DHEA is the most abundant adrenal androgen, functioning also as a neurosteroid (Binello and Gordon, 2003). In recent years it has been shown that DHEA has antidepressant-like effects (Wolkowitz and Reus, 2003; Hsiao, 2006; Van Broekhoven and Verkes, 2003; Schmidt et al., 2005; Strous et al., 2006) that can be explained by the interaction between the sigma 1 receptor agonist DHEAS (Maurice et al., 1996) and noradrenaline, dopamine and serotonin (5-HT) neurotransmission (Dong et al., 2007; Maayan et al., 2006). Enhancement of noradrenaline (Delgado and Moreno, 2000), serotonin (Delgado, 2000; Dubrovsky, 2005) and dopamine (Yadid et al., 2000) neurotransmission is considered to have an antidepressant effect. In vitro experiments suggest that sigma ligands inhibit noradrenaline presynaptic re-uptake in brain synaptosomes (Kinouchi et al., 1989; Rogers and Lemaire, 1991) and increase noradrenaline release (Kinouchi et al., 1989). The finding that administration of DHEA increases hypothalamic serotonin levels (Abadie et al., 1993; Svec and Porter, 1997) supports the positive relationship between DHEA and brain serotonin and its possible effect in depression. It was also shown that treatment with DHEA increased the dopamine content in the VTA and the Nac (Maayan et al., 2006) and that blockade of D1 receptor or its downstream signaling molecules (AC and PKA) with specific antagonist could completely cancel the effect of DHEAS (Dong et al., 2007). These findings support the positive relationship between DHEA/DHEAS and brain dopamine and its possible effect in depression.

In addition, it has been proposed that DHEA and DHEAS may play a role in neurodevelopment, due to a transient expression of steroidogenic enzyme P450 17-alpha hydroxylase (P450c17) (Compagnone et al., 1995) and the potential ability of DHEA and DHEAS to aid in neuronal pathway formation (Compagnone and Mellon, 1998).

Since DHEA may play an important role in depression, both because of its anti-depressive effect and it’s role in neuronal pathway formation, we measured the levels of DHEA in the limbic system of “depressed-like” prepubertal rats and their controls, trying to find out whether the juveniles of this strain show abnormal levels of DHEA as is found in depressed patients [Though peripheral DHEA and DHEAS might both have a role in depression (for review see Binello and Gordon, 2003)] we focused on DHEA levels in the limbic system because of it’s positive relationship with monoamines in these specific brain regions (Abadie et al., 1993; Svec and Porter, 1997), while avoiding the influence of various endogenous factors that can influence the synthesis of DHEA/S in the periphery, and are also impaired in depression and especially in childhood depression (Jensen and Garfinkel, 1990; Dorn et al., 1997; Birmaher et al., 1996)].

As mentioned above, serotonin, noradrenaline, and dopamine are believed to be involved in mental depression (Aghajanian, 1994; Elhweuig, 2004). According to the monoamine theory, depletion of serotonin and/or dopamine is one of the causes of depression (Pineyro and Blier, 1999). Serotonin and dopamine depletion might contribute to depression by affecting neurons in the limbic system (Nemeroff, 1998). Among the findings supporting a link between low synaptic serotonin and dopamine levels and depression is that cerebrospinal fluid (CSF) in depressed, and especially in suicidal patients contains reduced amounts of major serotonin by-products (signifying reduced levels of serotonin in the brain itself) (Cheetham et al., 1989; Mann et al., 1989). In addition, levels of serotonin and its metabolite, 5-hydroxyindole acetic acid (5-HIAA), in blood and CSF of depressed patients were reported to be relatively low in comparison with those observed in healthy volunteers (Asberg et al., 1984; Quan-Bui et al., 1984; Quintana, 1992). In accordance with the monoamine theory of depression, we measured the levels of
serotonin and dopamine in the limbic system of “depressed” prepubertal rats and their controls in order to find out whether the juveniles of the “depressed-like” lines show abnormal levels of monoamines as is found in depressed patients.

In the current study, we used a well-studied animal model of depression—the Flinders Sensitive Line (FSL). The FSL strain was selectively bred from Sprague Dawley (SD) rats. The FSL strain is a “genetic animal model” of depression; hence, it exhibits depression-like symptoms even as naïve animals (Overstreet, 1993; Overstreet et al., 2005; Yadid et al., 2000). FSL adult rats have been shown to demonstrate depression-like symptoms such as reduced body weight and disturbed REM sleep (Benca et al., 1996; Maes and Meltzer, 1995). They also displayed depression-like symptoms on several behavioral tests, e.g., increased immobility in the swim test and greater degree of “anhedonia” in response to chronic mild stress and acute stress. The increased immobility was prevented by chronic (but not acute) antidepressant treatment (Overstreet, 1993). Adult FSL rats exhibited higher levels of serotonin and dopamine and its metabolites in some regions of the mesolimbic system compared to their controls (Yadid et al., 2000). Recently, we reported that FSL prepubertal rats exhibit increased immobility in the swim test, abnormal social play as observed after 24-h of isolation and abnormal pattern of the hypothalamic–pituitary–adrenal (HPA) axis (Walkesman et al., 2006).

In the current study we attempt to determine whether prepubertal rats of this “genetic animal model” for depression exhibit, in four central regions of the limbic system (Nac, VTA, amygdala, hypothalamus), abnormal levels of DHEA in order to explore the potential role of neurosteroids as antidepressants for childhood depression. Since antidepressants developed to affect dopamine and serotonin levels fail to help children suffering from depression in the same percentage as in adults (Hazzell et al., 1995; Keller et al., 2001; Kye and Ryan, 1995), and since several studies found a strong connection between serotonin, dopamine and DHEA, we also measured the levels of these monoamines in these regions in order to examine unique developmental characteristics in the monoamines system. We measured the serotonin and dopamine levels but not noradrenaline, in an attempt to compare our prepubertal results from the current study with the adult FSL rats results reported by Yadid et al. (2000). The connection between noradrenaline, DHEA and childhood depression requires further investigation.

2. Experimental procedures

2.1. Animals

SD and FSL rats were bred in our colony at Bar-Ilan University. After weaning, juvenile rats were housed in polycarbonate cages (38 × 21 × 18 cm.), three per cage, in a temperature controlled vivarium (20–24 °C), under 14 h–10 h light:dark cycle (lights on at 0500). Food and water were available ad libitum. The study protocol was approved by the Institutional Animal Care and Use Committee and adhered to the guidelines of the Society for Neuroscience.

2.2. Brain dissection and extraction

At the age of 34–35 days, 24 rats (4–6 of each strain) were decapitated and their brains removed rapidly, and dissected as previously described (Zangen et al., 1997; Dremencov et al., 2004). Briefly, the entire hypothalamus was surgically dissected out with forceps and frozen immediately at –80 °C. The brains were then placed in a rat brain mold (constructed at Bar-Ilan University) on ice, and serial 0.5 mm sections were cut and placed on chilled microscope slides. Tissue punches (Nac, hypothalamus, VTA, and amygdala) were taken rapidly, using a stainless steel cannula with an inner diameter of 0.6 mm. The tissue samples were frozen immediately at –80 °C. Extraction was achieved by thawing the punches and subjecting them to probe sonication (80 W for 5 s with a B-12 Sonifier; Branson, Danbury, CT, U.S.A.) in 0.5 ml of a perchlorate solution (0.1 M) containing EDTA/ethanol (0.02:1%) on ice. A sample (100 μl) was removed for protein analysis and the rest was subjected to centrifugation (2000 g, 10 min, 4 °C). The resulting supernatants (the tissue extracts) were filtered (0.45 μm Acrodisc; Gelman, Ann Arbor, MI, U.S.A.) and stored at –80 °C until used for the determination of both monoamines (HPLC) and DHEA (RIA).

2.3. Analysis of monoamine content in the tissue punches

Quantitation of the 5-hydroxytriptamine (serotonin/5-HT), 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), dopamine (DA), 3,4-dihydroxy-phenylalanine (L-DOPA), and dihydroxyphenylacetic acid (DOPAC) content of the tissue punch extracts was performed as described previously (Zangen et al., 2001). Briefly, the filtered supernatants of each tissue extract were injected directly into an HPLC pump (Model 515, Waters, Milford, MA) onto a column (Merck Chemicals, Ltd; c-18, 5 μm particle size, 4.6 mm id×250 mm, 30 °C) coupled to an electrochemical detector (Digital Electrochemical Amperometric Detector, Antec-Leyden, Zeutewroude, Netherlands), and the oxidation potential was set to 0.76 V. The mobile phase (0.55 g heptane sulphonic acid, 0.2 g EDTA, 16 ml triethylamine, 12 ml 85% phosphoric acid, and 40 ml acetonitrile in 2 L of water; pH 2.6) was pumped at 0.8 ml/min. Monoamine and metabolite concentrations were expressed in relation to the protein content of the samples, which were quantified with Bio-Rad Protein Assay Kit.

2.4. DHEA determination

DHEA level was measured using a DLS 9000 Active ™ DHEA-coated tube radioimmunoassay (RIA) kit (Diagnostic Systems Laboratories, Webster, Tex, U.S.A.). 0.5 ml limbic region homogenates were extracted twice with 5.0 ml diethylether, centrifuged at 350 g for 5 min and the etheric phase was decanted into a new glass tube, evaporated till dryness and dissolved in 120 μl of standard 0 of the RIA kit. 100 μl was used for the determination of DHEA (Maayan et al., 2005).

2.5. Data analysis

DHEA basal levels were analyzed by independent t-tests comparing the FSL and SD strains separately for each brain regions (amygdala, VTA, Nac).
Nac and hypothalamus). 5-HT, 5-HIAA and, HVA, DA, DOPA, DOPAC contents of the tissue punch extracts from each brain regions (amygdala, VTA, Nac and hypothalamus) were analyzed by independent t-tests comparing the FSL and their SD controls.

3. Results

As evident from Fig. 1, FSL rats exhibited significantly lower levels of DHEA in both Nac \([t(6)=2.943; p<0.05]\) and VTA \([t(6)=3.804; p<0.05]\) compared to their control strain — SD. No significant differences in DHEA levels were found in the other brain regions [amygdala: \(t(7)=0.722;\) N.S.; hypothalamus: \(t(10)=0.233;\) N.S.].

The basal levels of monoamines in the different brain regions are presented in Fig. 2A, B, C, and D. As evident from Fig. 2A, in the Nac, FSL prepubertal rats exhibited significantly higher levels of DOPAC \([t(8)=3.159; p<0.05]\) and 5HIAA \([t(9)=2.715; p<0.05]\) compared to SD rats [DOPA: \(t(7)=0.59;\) N.S.; DA: \(t(10)=0.243;\) N.S.; HVA: \(t(7)=1.45;\) N.S.; 5HT: \(t(9)=0.373\)]. In Fig. 2B, one can see that there were no significant differences in the VTA between the FSL rats and their controls [DOPA: \(t(4)=1.41;\) N.S.; DA: \(t(5)=2.31;\) N.S.; DOPAC: \(t(6)=0.42;\) N.S.; HVA: \(t(4)=1.85;\) N.S.; 5HT: \(t(6)=0.43;\) N.S.; 5HIAA: \(t(5)=0.233\)]. In the hypothalamus, as evident from Fig. 2C, FSL showed significantly lower levels of: HVA \([t(6)=2.866; p<0.05]\) and 5HIAA \([t(8)=3.993; p<0.01]\) compared to the SD prepubertal rats [DOPA: \(t(8)=0.92;\) N.S.; DA: \(t(6)=1.34;\) N.S.; DOPAC: \(t(6)=0.489;\) N.S.; 5HT: \(t(5)=1.128;\) N.S.]. As can be noticed in Fig. 2D, there were no significant differences in the amygdala between FSL and SD prepubertal rats [DOPA: \(t(5)=1.53;\) N.S.; DA: \(t(7)=0.515;\) N.S.; DOPAC: \(t(5)=1.9;\) N.S.; HVA: \(t(4)=1.155;\) N.S.; 5HT: \(t(6)=1.4;\) SHIAA: \(t(6)=1.48;\) N.S.].

4. Discussion

The purpose of the current study was to examine whether childhood depression correlates with abnormal levels of DHEA and/or monoamines in four important regions of the limbic system in an animal model. The results showed that FSL prepubertal rats have lower basal levels of DHEA at least in some of the most important regions in the reward pathway of the limbic system, compared to their controls. FSL rats showed lower levels of DHEA both in the VTA and the Nac, compared to their control strain — SD. Several studies point to the Nac as the central region involved in, and mediating activities relating to motivation, and hedonia (Phillips et al., 1991; Robinson and Berridge, 1993; Breiter et al., 1997). The Nac is a target of the mesolimbic dopamine system, which arises in dopaminergic neurons in the VTA of the midbrain. These VTA neurons also innervate several other limbic structures, including the amygdala and limbic regions of the neocortex (Nestler et al., 2002). Though not much is known about the activity of the neurosteroid DHEA in the brain (Goodyer et al., 2001), it was recognized as having potential applications in the treatment of depression (Binello and Gordon, 2003; Wolkowitz and Reus, 2003). The antidepressive effect of DHEA can be explained, as mentioned earlier, by the interaction between the sigma 1 receptor agonist DHEAS (Maurice et al., 1996) and noradrenergic and serotonergic neurotransmission. Enhancement of serotonin (Delgado, 2000) neurotransmission is considered to have an antidepressant effect. Since DHEA has an antidepressant-like effect (Binello and Gordon, 2003; Wolkowitz and Reus, 2003), lower levels of DHEA in two important regions in the limbic system of the FSL rats may contribute to “depression like” symptoms found in the prepubertal rats of this line, such as lower basal levels of monoamines and their metabolites in the Nac and hypothalamus. 5-HT, 5-HIAA, HVA, DA, DOPA, DOPAC contents of the tissue punch extracts from each brain regions (amygdala, VTA, Nac and hypothalamus) were analyzed by independent t-tests comparing the FSL and their SD controls.

Figure 2  (A) Mean basal levels of monoamines and their metabolites in the Nac (+/− SEM) of 34–35 day old FSL and SD rats. Levels of DA, DOPAC, HVA, are divided by ten for presentation purposes. \(p<0.05\). (B) Mean basal levels of monoamines and their metabolites in the VTA (+/− SEM) of 34–35 day old SD and FSL rats. Levels of DOPA, DA, are divided by ten for presentation purposes. (C) Mean basal levels of monoamines and their metabolites in the hypothalamus (+/− SEM) of 34–35 day old SD and FSL rats. Levels of DOPA, DA, DOPAC, HVA, 5HIAA, are divided by ten for presentation purposes. \(p<0.05\). (D) Mean basal levels of monoamines and their metabolites in the amygdala (+/− SEM) of 34–35 day old SD and FSL rats. Levels of DOPA are divided by ten for presentation purposes.
as increased immobility time in the forced swim test and abnormal social play (Malkesman et al., 2006).

As mentioned earlier, administration of DHEA increases serotonin levels in the hypothalbus (Abadie et al., 1993; Svec and Porter, 1997) and Nac (Maayan et al., 2005), and treatment with DHEA increased the dopamine content in the VTA and the Nac (Maayan et al., 2006), in adult rats. In the present study we found that the prepubertal FSL rats had lower levels of the dopamine metabolite HVA. We did not find a significant difference in hypothalamic serotonin levels between the “depressed-like” rats and their controls, but in this region, the FSL prepubertal rats exhibited lower levels of the serotonin metabolite, 5HIAA, compared to controls. Since it is known that there are anatomical connections between the VTA and the hypothalamus and vice versa, e.g. projections of dopamine, and acetylcholine (Rada et al., 2000), these results may suggest that the low levels of DHEA found in the VTA and Nac of the “depressed” rats may have some negative effects on brain serotonin and dopamine, potentially reflecting decreased metabolism of serotonergic and dopaminergic neurons in these structures, as found in other studies (Abadie et al., 1993; Svec and Porter, 1997). This may support a potential role for neurosteroids as antidepressants for childhood depression.

Several studies have shown that DHEA behaves like an antiglucocorticoid by counteracting the effects of corticosterone (Hechter et al., 1997). However, in a previous study from our lab, 35-day-old FSL rats displayed “hypocortisolism” – lower basal levels of plasma corticosterone and adrenocorticotropic hormone (ACTH) – (Malkesman et al., 2006). Although the results regarding the “hypocortisolism” exhibited by the prepubertal FSL rats and the results from the current study might not fit the findings of these previous studies (Hechter et al., 1997), it is important to mention that secretion of cortisol/corticosterone and DHEA(s) are regulated by ACTH, there may be dissociation between these hormones, e.g., during (chronic) stress or medical illness (Parker et al., 1985), and DHEA levels can be regulated independently of cortisol/corticosterone (Herbert et al., 1996). In addition, Nac DHEA, measured in the current study, takes no obvious part in the HPA axis.

The pattern of results regarding the basal levels of monoamines in the limbic system suggests that FSL prepubertal rats show some serotonergic and dopaminergic abnormalities in some regions of the limbic system. In the Nac, one of the main areas responsible for control of locomotion, motivation and reward, and response to antidepressants (Yadid et al., 2001), the FSL rats had higher levels of DOPAC and 5HIAA, compared to their controls. It is known that the major degradation product of 5HT, 5HIAA, is found in the cerebrospinal fluid (CSF) as well as in the brain itself (Van Praag, 2004). Both animal (Mignot et al., 1989) and human (postmortem) studies (Stanley et al., 1985) have revealed a close correlation between brain and CSF 5HIAA. Lowered CSF 5HIAA in depression was shown to correlate positively with increased anxiety (Van Praag, 2004).

The higher levels of the serotonin metabolite found in the Nac of the prepubertal FSL rats in the current study are in accordance with the abnormal levels of this metabolite, reported previously in adult FSL rats (Yadid et al., 2000). However, while adult FSL rats exhibited in a previous study in our lab higher levels of all the monoamines and their metabolites (in Nac, hypothalamus; Zangen et al., 1997, 1999; Yadid et al., 2000), prepubertal FSL rats in the current study exhibited higher levels of only a few monoamines metabolites in the Nac (but not in the VTA and amygdala). Specifically, Zangen et al. (1997) and Yadid et al. (2000) reported that adult FSL rats exhibited higher levels of 5HT, 5HIAA, dopamine, DOPAC and HVA in the hypothalamus and the Nac, compared to their SD controls; while in the current study, prepubertal FSL rats exhibited only higher levels of 5HIAA in the Nac and lower levels of HVA and 5HIAA in the hypothalamus compared to their SD controls. These different abnormal monoamine patterns between the “depressed” prepubertal rats and their adults, may help to explain why depressed children and adolescents fail to respond to antidepressant treatment as well as adults do (Hazell et al., 1995; Keller et al., 2001). On the other hand, FSL prepubertal rats exhibited the same pattern of abnormal DHEA basal levels as was found in adult FSL rats (Maayan et al., 2005).

In sum, the results suggest that a putative genetic animal model of childhood depression, the prepubertal FSL rat, exhibited abnormal levels of DHEA (as in adult FSL rats) and monoamines (different pattern than adult FSL rats) in various regions of the limbic system. The difference in abnormal monoamine patterns between the “depressed” prepubertal rats found in the current study, and in adults (found in several studies, Zangen et al., 1997, 1999; Yadid et al., 2001) may represent the biological basis for why depressed children and adolescents fail to respond to antidepressant treatment in contrast to adults (Hazell et al., 1995; Keller et al., 2001), and might imply that other non-monoaminergic factors, such as DHEA contribute to childhood depression (Possel and Hautzinger, 2006).

Taking in consideration former results suggesting an antidepressant-like effect of DHEA in adult rats of a “depressive-like” strain (Maayan et al., 2005) and humans (Schmidt et al., 2005) and our current data, it is possible that treatment with this neurosteroid may be a promising novel therapeutic option for depressed adults and (while closely monitoring sexual maturation and androgenic effects; for review see Binello and Gordon, 2003) especially for depressed children and adolescents who fail to respond to the available monoaminergic antidepressant treatments.

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Contributors

Oz Malkesman designed the study, conducted most of the procedures and wrote the manuscript. Yoram Braw conducted the monoamine and the DHEA measurements. Edward Ram helped with the brain dissections and the DHEA measurements. Rachel Maayan helped to conduct the DHEA measurements, performed in her lab, with her guidance and under her supervision. Avi Weizman helped to design the study protocol and the DHEA determination. Noa Kinor, monoamines measurement expert, guided and helped in conducting these measurements and in their interpretation. Gal Yadid helped to design the study protocol, conducted the brain dissection and extraction. Aron Weller helped to design and write the study protocol, attain approval and funding for the project and co-edited
the manuscript. All authors contributed to the study and have approved the final draft of the manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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