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REVIEW

The impact of maternal high-fat diet consumption on neural development and behavior of offspring

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Maternal diet and metabolic state are important factors in determining the environment experienced during perinatal development. Epidemiological studies and evidence from animal models provide evidence that a mother's diet and metabolic condition are important in programming the neural circuitry that regulates behavior, resulting in a persistent impact on the offspring's behavior. Potential mechanisms by which maternal diet and metabolic profile influence the perinatal environment include placental dysfunction and increases in circulating factors such as inflammatory cytokines, nutrients (glucose and fatty acids) and hormones (insulin and leptin). Maternal obesity and high-fat diet (HFD) consumption exposure during development have been observed to increase the risk of developing serious mental health and behavioral disorders including anxiety, depression, attention deficit hyperactivity disorder and autism spectrum disorder. The increased risk of developing these behavioral disorders is postulated to be due to perturbations in the development of neural pathways that regulate behavior, including the serotonergic, dopaminergic and melanocortinergic systems. It is critical to examine the influence that a mother's nutrition and metabolic profile have on the developing offspring considering the current and alarmingly high prevalence of obesity and HFD consumption in pregnant women.

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INTRODUCTION

Obesity has a significant and deleterious effect on numerous aspects of human health. Being obese increases the risk of many serious diseases including cardiovascular disease, hypertension, diabetes and several forms of cancers.[1–3] Mounting evidence suggests that obesity is also associated with mental health disorders such as anxiety,[4] depression[4] and attention deficit hyperactivity disorder (ADHD).[5] As obesity increases the risk of many serious metabolic diseases and behavioral disorders, it has a significant impact on the quality of life and decreases life expectancy. According to the latest statistics from the National Health and Nutrition Examination Survey, a third of adult Americans are currently obese.[6] The prevalence of obesity in both adults and children has markedly increased in the United States over the past three decades;[7] childhood obesity has more than tripled in children aged 6–11 years since 1980.[8] The recent dramatic rise in the prevalence of obesity has led to a staggering increase in national health-care costs. This surge in obesity rates is likely due in part to increased accessibility to calorically dense and highly palatable foods.[9] In addition, modern technologies have decreased the amount of energy needed to complete daily tasks, and adults and children are increasingly able to choose sedentary activities such as watching television and playing video games in place of more physically active leisure activities.[9] Of dire concern, recent reports and news in the popular press have suggested that the current new generation will be the first to have a decreased life expectancy compared with their parents.[10,11] Importantly, there is increasing evidence from animal models that programming during the perinatal period contributes to the striking rise in obesity rates.[12–15]

Although there are many aspects by which maternal obesity, insulin resistance and/or diet affect fetal and adolescent development, this review will focus on the critical impact on brain development that has consequences for offspring behavior. It is our belief that negative impacts on behavior and increased risks of psychiatric disorders may have a consequence on quality of life as serious as the potential metabolic outcomes that affect life expectancy.

MATERNAL OBESITY INCREASES OFFSPRING'S RISK OF OBESITY AND METABOLIC DISEASES

A third of pregnant American women are currently obese,[8] and the majority consumes excess calories because of consumption of a diet high in fat.[16] Children who are exposed to maternal obesity during gestation have an increased risk of obesity and metabolic syndrome in adulthood.[17,18] Furthermore, gestational diabetes, which can significantly affect prenatal development, has also been well documented to increase offspring risk of adult obesity.[19] The effect of maternal obesity on the susceptibility to obesity in offspring is thought to be independent of gestational diabetes because obese mothers with euglycemia still have babies with increased adiposity.[20] Maternal obesity also increases the risk of the child developing fatty liver disease, cardiovascular disease and diabetes.[8,21] Given the high prevalence of obesity in pregnant women, it is critical to

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examine the full impact of maternal obesity on the developing offspring.

However, it should be noted that one of the limiting factors of the human studies is the inability to segregate the possible effects of the maternal metabolic phenotype versus the diet that may be causing the obesity and insulin resistance. To truly understand the relative contributions of the different aspects of metabolic complications associated with maternal obesity, we need to have better characterization of the metabolic phenotype and diet in these clinical and epidemiological studies. Much can also be learned from well-controlled animal models.

ANIMAL MODELS OF MATERNAL OBESITY

Maternal obesity is commonly simulated in animal models by feeding adult females a palatable diet that is high in fat. However, the duration of diet exposure and the composition of the diet are variable between studies. The diets most often used to induce obesity are either a refined high-fat diet (HFD) with fat in place of carbohydrates as an energy source or a cafeteria diet in which animals are provided with a selection of calorie-dense palatable food items that have a high fat and carbohydrate content along with their regular diet. The cafeteria diet is most effective in promoting obesity possibly because of the greater caloric load and/or increased consumption of carbohydrates. Differences between studies may be partly due to the carbohydrate content of the diet, as high perinatal carbohydrate consumption has been shown to have a lasting impact on neural development in rodent[22] and sheep[23] models. Rats fed a HFD through pregnancy and lactation have pups with increased body weight and adiposity, as well as higher rates of hyperglycemia compared to pups from control diet-fed mothers.[24] Murine models of chronic maternal overnutrition also find that offspring show increased adiposity due to hyperphagia and reduced locomotor activity.[25] In addition, exposure to a highly palatable junk-food diet during perinatal development results in offspring with increased preference for fatty, sugary and salty foods.[26] Our group has further confirmed these findings using a nonhuman primate (NHP) model of HFD-induced maternal obesity. Juvenile offspring from HFD-fed mothers display increased body weight and fat mass, hyperleptinemia, and the early stages of fatty liver disease.[27] Importantly, we demonstrated that the effects of maternal HFD on the offspring are independent of maternal obesity.[27] These studies confirm that in animal models, maternal overnutrition predisposes offspring to early-onset obesity and metabolic disorders. As these maternal HFD effects are independent of obesity,[27] it may be critical to provide nutritional advice to all pregnant women and not just those who are visibly obese.

MATERNAL OBESITY INCREASES OFFSPRING'S RISK OF MENTAL HEALTH DISORDERS

In recent years, maternal obesity has also been linked to an increased risk of behavioral disorders in human offspring, such as ADHD[28,29] and autism spectrum disorders (ASD).[30] Maternal obesity and diabetes are also linked with an increased prevalence of ASD and developmental delays in children aged 2–5 years old.[30] Mothers of children with ADHD are almost twice as likely to be obese than mothers of unafflicted children.[28] Similarly, prepregnancy obesity is associated with a twofold risk in ADHD symptom score in offspring, compared with the children of women who were of normal weight during pregnancy.[29] Children of mothers with maternal diabetes also showed significant deficits in expressive language.[30] These human studies indicate a potential link between having an obese mother and developing behavioral disorders, but it is unclear whether this relationship is due to genetic factors, a common postnatal environment, or the prenatal environment that offspring from obese mothers experience due to diet. Animal studies have begun to shed some light on the contribution of each of these important factors.

ANIMAL MODELS OF MATERNAL OBESITY SHOW PERSISTENT BEHAVIORAL CHANGES

Animal studies provide clear evidence that offspring behavior is affected by maternal HFD consumption. Recent studies in NHP[31] and rodent[32] models indicate that maternal HFD consumption is associated with increased anxiety. Adult male rat offspring exposed to a diet high in either saturated or trans fat during gestation and lactation displayed increased anxiety.[32] However, other studies in rodents suggest that HFD feeding decreases anxiety. It appears that this may be dependent on the composition of the diet and on the timing of consumption[33] by the mother. Offspring from mothers fed a purified HFD throughout the perinatal period displayed increased anxiety, whereas offspring exposed to a cafeteria diet during lactation displayed evidence of decreased anxiety.[33] Moreover, cafeteria diet consumption during the early postnatal period has been observed to reduce anxiety and depression-like behaviors in rodent offspring exposed to stress during gestation.[34]

By using a NHP model, our group demonstrated that maternal HFD consumption suppresses serotonergic system signaling, which predisposes female offspring to increased anxiety.[31] The finding that female NHP offspring exposed to maternal HFD consumption are more sensitive to developing anxiety than male offspring is consistent with findings in humans that indicate that females are more susceptible to anxiety than males and that the association between obesity and anxiety is stronger in women than in men.[35] However, the studies in the animal models would suggest that there could be an earlier programming event that causes a neurochemical imbalance that makes these individuals especially sensitive to social stresses later in life.

Indeed, maternal diet during the perinatal period also affects the offspring's social behavior. Rat offspring exposed to a maternal diet high in polyunsaturated fatty acids displayed increased aggression to intruders.[36] Changes in reward-based feeding have also been observed in several models of maternal HFD consumption.[26,37,38] For example, rat offspring exposed to junk food during either gestation or lactation displayed increased preference for fatty, sugary and salty foods as adults.[26,37,38] This finding is confirmed by preliminary studies using our NHP model of HFD-induced maternal obesity, which find that HFD offspring display increased preference for diets with a high sugar and fat content (Sullivan and Grove, unpublished observation). Maternal HFD consumption has also been associated with decreased behavioral sensitization to amphetamine in the offspring by altering dopamine transmission through the nucleus accumbens.[39] These studies provide compelling evidence that perinatal nutrition may have a long-term influence on reward-based behaviors such as consumption of palatable food and response to drugs of abuse.

POTENTIAL MECHANISMS FOR MATERNAL OBESITY PROGRAMMING BEHAVIOR

Several mechanisms are postulated to be contributors to the impact that maternal obesity and HFD consumption have on the development of the complex neural circuitry involved in behavioral regulation. HFD exposure has been observed to affect the development of neurotransmitter signaling pathways such as the serotonergic,[31] dopaminergic,[39,40] melanocortinergic,[41] and galaninergic systems.[42] Maternal obesity and HFD consumption are further associated with a number of potential factors that can affect brain development: placental dysfunction, increased exposure to inflammatory factors, increased circulating levels of metabolic hormones and increased levels of nutrients.

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MATERNAL OBESITY CAUSES PLACENTAL DYSFUNCTION

The increased rate of maternal obesity in humans corresponds with an increase in pregnancy complications.[18] These complications are thought to be due to placental dysfunction, as placental dysfunction has been observed in NHP[43] and ovine models[44] of maternal obesity and HFD consumption. Studies with large animal models indicate that there is a strong association between maternal diet and disruption of normal placental function. Our group has demonstrated that NHP mothers who consumed a HFD before and during pregnancy showed a 35–50% decrease in uterine artery blood flow, which was independent of maternal metabolic phenotype.[43] However, there were further complications with fetal blood flow and a higher frequency of placental infarctions and stillbirths if the mothers were obese and insulin resistant.[43] Ovine studies similarly found that overnourished ewes exhibited decreased uterine blood flow, a reduction in placental mass by one third and reduced placental capillary density.[44] Rodent models of maternal HFD consumption have also shown reduced placental mass.[45] These findings emphasize that there is a consistent relationship between HFD consumption and reduced uterine blood flow, leading to placental dysfunction.

MATERNAL OBESITY IS ASSOCIATED WITH INFLAMMATION

Obesity can be thought of as a state of chronic inflammation because it results in increased levels of circulating inflammatory cytokines in many organs, including the brain[46] and the placenta.[47,48] In human studies, the amount of adipose tissue mass is positively correlated with elevations in markers of inflammation such as C-reactive protein, interleukin (IL)-6 and IL-1β in the plasma.[46,49] These inflammatory markers are associated with an increased risk for a number of metabolic diseases: cardiovascular disease, heart disease, insulin resistance, type 2 diabetes mellitus and hypertension.[46] In patients with type 1 diabetes, who suffer from a compromised immune system, metabolic disease is associated with increased serum levels of the endotoxin lipopolysaccharide (LPS) originating from bacterial colonization of the gastrointestinal tract.[50] LPS upregulates inflammatory responses through pathways modulated by receptors such as toll-like receptor-4.[51] During pregnancy, increased levels of inflammatory cytokines secreted from adipocytes in obese women contribute to endothelial[52] and placental dysfunction.[53] As maternal obesity is associated with endotoxemia and elevated inflammatory cytokines, it increases the amount of inflammatory factors that the developing fetus comes into contact with and that affects neural development.

HFD-INDUCED INFLAMMATION RESULTS IN PLACENTAL DYSFUNCTION IN ANIMAL MODELS

As described above, maternal obesity and HFD consumption are associated with both decreased placental blood flow and an increase in circulating inflammatory cytokines. In addition, evidence from animal models indicates that consumption of a HFD increases inflammation in the placenta. The placentae of obese sheep displayed elevated levels of activated inflammatory signaling pathways and inflammatory cytokine activity compared with those of nonobese ewes.[54] Furthermore, in our NHP model, we have shown that consumption of a HFD, regardless of the metabolic state of the mother, increases the expression of placental inflammatory cytokines and that these cytokines are selectively secreted into the fetal compartment.[43] This is of grave concern, as rodent models have shown that placentally generated cytokines initiated further cytokine synthesis in the fetus, perpetuating the inflammatory environment.[55,56] Elevation of such cytokines also led to changes in growth factors that are essential for fetal development and for changes in behavior.[57]

INFLAMMATION-INDUCED NEURAL PROGRAMMING

There is strong evidence that exposure to increased circulating cytokines during fetal development affects brain development and thus is a potential mechanism by which maternal HFD consumption affects behavioral regulation. Rodent offspring from mothers consuming a HFD exhibit neural inflammation as evidenced by increased microglial activation in the hippocampus, which persists into adulthood[57] and is associated with decreased neurogenesis in the corresponding region.[58] NHP offspring from mothers consuming a HFD show an increase in circulating and hypothalamic cytokines during the early third trimester.[41] The development of neurotransmitter systems critical for regulating behavior are affected by such circulating cytokines.[46] This exposure to increased inflammatory cytokines may lead to the perturbations in the melanocortinergic[41] and serotonergic system observed in fetal offspring.[31] Maternal HFD consumption downregulates dopamine release in the nucleus accumbens of rodent offspring, leading to increased motivation to consume fatty food.[40] Rats that had decreased accumbens dopamine were more likely to be obese,[59] indicating that they may be increasing consumption to combat their lower levels of dopamine. Palatable food may therefore be overconsumed in an attempt to elevate dopamine levels. One study suggests that increasing consumption of fatty foods causes a positive feedback loop in the nucleus accumbens and hippocampus, meaning that increases in palatable food intake would increase the desire of an individual to eat fatty food.[60]

Neural inflammation has also been observed as a result of bacterial or viral infection, and this evidence demonstrates how influential inflammation is for brain development. It is well documented that when infections or illness occur during pregnancy, there is a subsequent increase in inflammatory cytokines delivered to the developing fetus, which in turn causes an inflammatory response in the fetal brain during critical periods of development.[61] For example, women who were infected with influenza during pregnancy had offspring who were at an increased risk of developing schizophrenia.[62] NHP studies show that a mid-gestational influenza infection results in atypical brain development similar to what is seen in cases of schizophrenia, such as reduced cortical gray matter and enlarged lateral ventricles.[63,64] These structural abnormalities are persistent and are likely to manifest into behavioral dysfunction, but this study was not long enough to observe the full extent of behavioral effects.[64] Offspring of NHP mothers affected by influenza during pregnancy demonstrated trouble with attention and orientation tasks from an early age.[64] Recent evidence indicates that gestational obesity may have an effect similar to gestation infection or illness, as it also elevates the levels of inflammatory cytokines that a fetus is exposed to.[43] Therefore, maternal obesity may similarly affect neural development, increasing the risk for behavioral disorders and metabolic diseases. These data demonstrate that the disruptions caused by inflammatory cytokines after infection may be similar to what is seen after maternal HFD consumption, extending beyond placental compromise into fetal brain development and offspring behavior.

HUMAN INFLAMMATION AND BEHAVIORAL ABNORMALITIES

Exposure to elevated maternal inflammatory cytokines has been indicated to have a role in human fetal brain development and consequently have a persistent impact on behavior. A number of psychopathologies, including Alzheimer's disease,[65] anxiety,[66–68] depression,[69–71] ASD[72–74] and ADHD,[75] have been linked with exposure to inflammatory cytokines. When proinflammatory cytokines cross the placenta and enter the fetal bloodstream, the fetal brain undergoes excessive neuronal growth and plasticity, termed a 'cytokine storm.'[76] Buehler[76] proposes that the inundation of

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cytokines and the subsequent neuronal growth can in turn assist the development of a state of chronic inflammation in the fetal environment and that this may explain many of the symptoms observed in individuals with ASD. Symptoms of ASD including hypersensitivity to external stimuli, repetition of heard sounds and movements, and object fixation are postulated to be a result of this mechanism.[76] HFD consumption during pregnancy has been shown to activate many of the same inflammatory cytokines that have been reported to be elevated either during gestation in mothers of children who developed ASD such as IL-4 and IL-5[72] or in children with ASD including monocyte chemotactic protein-1, RANTES and granulocyte–macrophage colony-stimulating factor.[73,74] In addition, *in utero* exposure to high levels of IL-8 results in fetal brain alterations that are consistent with the neurological structure of schizophrenia patients,[77] and thus the elevation of this cytokine in response to maternal obesity could increase the risk of schizophrenia in offspring from obese mothers. Studies that focused on obesity instead of on its consequent inflammatory response also show a link between obesity and behavioral disorders. These mechanisms propose that inflammatory cytokines and obesity affect human brain development in a way that leads to the development of behavioral abnormalities.

PSYCHOPATHOLOGIES AS PROINFLAMMATORY RESPONSES

The increased cytokine reactivity stimulated by intrauterine infection or maternal HFD consumption can be induced by administration of proinflammatory factors, further corroborating that inflammation is a mechanism responsible for the consequent alterations in fetal brain development.[56,78,79] Injection of LPS elicits increased cytokine reactivity in infant monkeys[78] and caused systemic inflammation in cats[80] and horses.[81] NHP infants from high LPS pregnancies demonstrated behavior that contained disturbances similar to what is seen in ASD and schizophrenia, such as the failure to exhibit a normal startle response.[78] These LPS infants displayed reduced gray matter,[78] which is similarly seen in NHP models of perinatal influenza,[64] and also had a significant 8.8% increase in white matter volume across many cortical regions,[78] which is similar to the increased white matter growth seen in the early development of individuals with ASD.[82,83] Offspring of rats fed a HFD had heightened response to LPS compared with controls, and these rats also displayed alterations in anxiety and spatial learning.[32] These studies of endotoxemia indicate that elevated levels of inflammatory cytokines, whether triggered by HFD consumption or infection, create a pathway that affects the development of the neurocircuitry in ways that are consistent to the neural abnormalities observed in human psychopathologies.

As exposure to inflammation during development causes a nonspecific response that affects many neurotransmitter systems, it is important for future research to directly examine the influence of maternal obesity and HFD consumption-induced inflammation on each neural pathway important in behavioral regulation. Compounds with anti-inflammatory properties, such as ursolic acid, have been found to improve the behavioral performances of mice fed a HFD.[84] This cognitive improvement was credited to the inhibition of inflammatory signaling and suggests that anti-inflammatory agents may be helpful in combating obesity-induced cognitive impairments.[84]

PROGRAMMING BY EXCESS HORMONES AND NUTRIENTS

Maternal obesity is associated with gestational diabetes

As maternal obesity is often associated with gestational diabetes,[85] rates of gestational diabetes will continue to increase as the obesity epidemic continues. Gestational diabetes is associated with the initiation of inflammation in the placenta,[47–49] and thus the same mechanisms responsible for placental dysfunction in intrauterine infection and HFD consumption are also activated by gestational diabetes.[86] Both human and rodent models point to the placenta as one target of the negative effects of maternal diabetes.[87]

Gestational diabetes is associated with hyperglycemia and hyperinsulinemia.[88] The fetus is only exposed to higher levels of glucose because glucose, but not insulin, can permeate through the blood–placenta barrier and be transferred to the fetus.[89] The fetal pancreas compensates for this hyperglycemia by increasing insulin release. As insulin is an important neural growth factor,[90] it is proposed that early exposure to hyperinsulinemia alters the development of brain circuitry regulating energy balance and behavior. This theory is supported by studies that find that insulin administration during the last term of gestation alters energy balance and produces obese offspring[91,92] and that administering insulin to the hypothalamus of rat pups during the time that projections from the arcuate nucleus to the paraventricular nucleus are developing results in elevations in body weight and insulin level, impaired glucose tolerance and increased vulnerability to diabetes in adulthood.[93]

Maternal obesity is associated with hyperleptinemia

Leptin is a satiety factor secreted by adipocytes in proportion to the amount of fat mass, and, consequently, offspring from obese mothers are exposed to increased levels of leptin. The hyperleptinemia that offspring from obese mothers experience during development is implicated in metabolic imprinting. There is substantial evidence in rodents that postnatal leptin is a critical factor in the development of neural pathways in the hypothalamus.[94–96] In addition, offspring from rodent mothers who consumed a HFD and had increased circulating leptin levels showed increased inflammation in the periphery and hypothalamus, even if they consumed a healthy diet after birth.[32] Rodent studies indicate that neonatal overnutrition increases postnatal leptin resistance in the arcuate nucleus,[97] leading to overconsumption of palatable foods.[96,97] Human studies report that leptin is elevated in obese[98] and diabetic mothers[99,100] and is lower in infants who experienced intrauterine growth restriction at term.[101] However, in human and NHP gestation, circulating leptin levels do not increase until after hypothalamic development is well advanced.[102,103] Although critical for brain development in rodents, there is limited evidence for leptin's role in the development of primate brains.[97,104] Yet, hyperleptinemia is associated with placental dysfunction,[98,99] and thus elevated leptin may affect brain development indirectly. Hyperleptinemia may also result from the effect that maternal HFD has on the leptin signaling pathway. Offspring from HFD mothers experienced reduced phospho-signal transducer and activator of transcription-3 activation as compared with control pups.[97] This suggests that leptin resistance develops during the suckling period and persists through life, increasing the susceptibility of HFD offspring to obesity.[97] To date, studies examining the role of leptin in influencing the development of neural pathways that regulate behavior have focused on feeding behavior;[105,106] however, with the increasing evidence that maternal metabolic state influences social and mental health behavior in offspring, future studies will work to determine the role that leptin has in programming mental health-related behavior.

Maternal HFD-induced suppression of the serotonin system

The serotonin (5-HT) system has an integral role in neural development, influencing neurogenesis, neuronal migration and synaptogenesis.[107,108] Furthermore, the metabolism of tryptophan (TRP), the precursor to 5-HT, through the kynurenine (KYN) pathway has a crucial role in immune function during pregnancy. During the first trimester, metabolism of TRP prevents the rejection of the fetus by suppressing the maternal immune

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response,[109] and it is involved in the regulation of blood flow between the placenta and fetus during the second and third trimesters of gestation.[110] KYN metabolites have been reported to be elevated in animal models of maternal inflammation.[111] As the KYN pathway competes with 5-HT for the substrate TRP, an increase in the KYN pathway results in less TRP availability for 5-HT synthesis. As mentioned previously, our group has demonstrated that chronic consumption of a HFD during pregnancy reduces placental blood flow, indicating the potential role of the elevated KYN levels; however, this effect is further exacerbated if the animals are obese and insulin resistant.[43] Furthermore, in humans, a suppression of brain 5-HT synthesis is associated with a number of mental health and behavioral disorders including anxiety,[112] depression,[113] ADHD[114] and ASD,[115] and thus perturbations in the 5-HT system are postulated to underlie the increased risk of offspring exposed to maternal overnutrition developing behavioral disorders.

CONCLUSION

In summary, there are several mechanisms by which maternal obesity and HFD consumption may affect the developing fetal brain and thus behavioral regulation. These mechanisms include placental dysfunction, the increased exposure to inflammatory cytokines and the higher levels of nutrients and metabolic hormones that offspring receive from obese mothers. The serotonergic system has been identified as a potential mediator of maternal HFD-induced behavioral dysregulation, and suppression in the 5-HT system has been documented in several different animal models. With the current prevalence of maternal HFD consumption and obesity, future generations are at an increased risk for behavioral and mental health disorders. Given the high rates of maternal obesity, future studies need to identify therapeutic strategies that are effective at preventing maternal HFD-induced malprogramming of offspring behavior.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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