Foetal Alcohol Spectrum Disorders and Alterations in Brain and Behaviour

Consuelo Guerri1,∗, Alissa Bazinet2 and Edward P. Riley2

1Department of Cell Pathology, Centro de Investigacion Principe Felipe, Avda Autopista del Saler, 46013-Valencia, Spain; 2Department of Psychology and Center for Behavioural Teratology, San Diego State University, San Diego, CA 92120, USA

Abstract — The term ‘Foetal Alcohol Spectrum Disorders (FASD)’ refers to the range of disabilities that may result from prenatal alcohol exposure. This article reviews the effects of ethanol on the developing brain and its long-term structural and neurobehavioural consequences. Brain imaging, neurobehavioural and experimental studies demonstrate the devastating consequences of prenatal alcohol exposure on the developing central nervous system (CNS), identifying specific brain regions affected, the range of severity of effects and mechanisms involved. In particular, neuroimaging studies have demonstrated overall and regional volumetric and surface area reductions, abnormalities in the shape of particular brain regions, and reduced and increased densities for white and grey matter, respectively. Neurobehaviourally, FASD consists of a continuum of long-lasting deficits affecting multiple aspects of cognition and behaviour. Experimental studies have also provided evidence of the vulnerability of the CNS to the teratogenic effects of ethanol and have provided new insight on the influence of risk factors in the type and severity of observed brain abnormalities. Finally, the potential molecular mechanisms that underlie the neurotological effects of alcohol are discussed, with particular emphasis on the role of glial cells in long-term neurodevelopmental liabilities.

INTRODUCTION

The idea that ethanol affects the developing brain was apparent from the first modern clinical reports describing the offspring of alcohol-abusing women (Lemoine et al., 1968; Jones and Smith 1973), where a number of brain and behavioural deficits were noted. Since these reports, a large number of well-controlled experimental studies and other clinical reports have documented the vulnerability of the developing central nervous system (CNS) to ethanol. Ethanol is considered to be one of the most common substances that impact the developing brain, and prenatal alcohol exposure is a leading preventable cause of birth defects, mental retardation and neurodevelopmental disorders (American Academy of Pediatrics, 2000).

Among the most recognized consequences of prenatal alcohol exposure is the foetal alcohol syndrome (FAS); (Jones and Smith, 1973), characterized by pre- and postnatal growth deficiencies, craniofacial anomalies and evidence of CNS dysfunction. FAS is now recognized as an important cause of intellectual disabilities, craniofacial anomalies and evidence of CNS dys-function. FAS is now recognized as an important cause of intellectual disabilities and behaviour problems in many countries (Streissguth et al., 1991; Alati et al., 2006; Autti-Rämö et al., 2006; Ceccanti et al., 2007; Spohr et al., 2007). However, over the last 30 years, it has become clear that FAS is not the only outcome resulting from prenatal alcohol exposure. Indeed, the effects of prenatal alcohol exposure lie on a continuum of physical anomalies and behavioural and cognitive deficits. The term foetal alcohol spectrum disorders (FASD) has been adopted (Sokol et al., 2003) as a nondiagnostic umbrella term to describe this range of effects. The prevalence of FASD, which can be physical, mental or behavioural, is estimated to be ~1% of all births (May and Gossage 2001).

Until recently, it was impossible to evaluate the effects of ethanol on human brain structure and function in vivo. However, novel neuroimaging techniques such as magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been employed on individuals with FASD to provide insights into the structural and functional alterations caused by prenatal ethanol exposure. Basic animal studies also provide evidence of the vulnerability of the CNS to the effects of ethanol, revealing that effects are not uniform and that some brain areas or cell populations are more vulnerable than others (Guerri, 1998, 2002).

This paper briefly reviews the current knowledge of the effects of ethanol on the developing CNS and their correlation, when appropriate, with the cognitive, behavioural and psychopathological deficits observed in individuals exposed prenatally to alcohol. Finally, potential mechanisms underlying the neurotological effects of ethanol, as well as the role of glial cells in long-term neurodevelopmental liabilities, are discussed.

Neurobehavioural disorders in individuals with FASD

Heavy prenatal alcohol exposure has been associated with widespread neuropsychological deficits across several domains, including general intelligence, memory, language, attention, learning, visuospatial abilities, executive functioning, fine and gross motor skills, and social and adaptive functioning (Mattson and Riley, 1998). The mean IQ of children with FAS is estimated in the low 70s (Mattson and Riley, 1998), and FAS is the leading preventable cause of mental retardation (Abel and Sokol, 1987). However, the majority of children with FAS are not mentally retarded, and IQ scores show a wide range (e.g. 20–120, Mattson and Riley, 1998). Individuals prenatally exposed to high levels of alcohol but without all the characteristics of FAS have IQs that average in the low 80s (Mattson and Riley, 1998). Children exposed to alcohol prenatally also have decreased academic achievement and higher rates of learning disabilities than non-exposed children (Howell et al., 2006), which may relate to impairments in verbal and nonverbal learning and memory (Mattson et al., 1996a; Mattson and Roebuck, 2002; Roebuck-Spencer and Mattson,
Influence of prenatal alcohol exposure on brain structure

Before the use of neuroimaging techniques, autopsies provided the only information about specific brain abnormalities evidenced in humans with FAS. In their initial report, Jones and Smith (1973) noted widespread damage in the brain of an infant with FAS, including microcephaly, agenesis of the corpus callosum (CC) and anterior commissure, errors in migration, and anomalies in the cerebellum and brainstem. Subsequent reports confirmed these findings and added ventricular abnormalities, CNS disorganization, and abnormalities in the basal ganglia, hippocampus, pituitary gland and optic nerve (Jones and Smith, 1975; Clarren et al., 1978; Clarren, 1986; Coulter et al., 1993).

Despite demonstrating effects of prenatal alcohol on the brain, results from autopsy studies may not be typical. Since 1992, various imaging modalities have been used to study living individuals with FASD, which has allowed the identification of more subtle brain alterations occurring in FASD. Consistent with autopsy findings, MRI studies have reported overall volume reductions in the cranial, cerebral and cerebellar vaults in FASD (Mattson et al., 1992, 1994, 1996c; Swayze II et al., 1997; Archibald et al., 2001; Sowell et al., 2001a, 2002a; Autti-Rämö et al., 2002). Furthermore, other studies have suggested that this decrease is not uniform but rather that the parietal lobe (Archibald et al., 2001; Sowell et al., 2001a, 2002a, 2002b), portions of the frontal lobe (Sowell et al., 2002a) and specific areas of the cerebellum (Sowell et al., 1996; Autti-Rämö et al., 2002; O’Hare et al., 2005) appear to be especially sensitive to alcohol insult.

Abnormalities of the CC, including complete and partial agenesis (Riley et al., 1995; Swayze II et al., 1997; Bhatare et al., 2002), hypoplasia (Mattson et al., 1992; Swayze II et al., 1997; Autti-Rämö et al., 2002; Bhatare et al., 2002), displacement in posterior regions (Sowell et al., 2001b), regional surface area reductions in anterior and posterior areas (Riley et al., 1995; Sowell et al., 2001b) and increased variability in shape (Bookstein et al., 2002a, 2002b) have also been reported. More recently, DTI has been used to examine the white matter integrity of the CC (Ma et al., 2005; Wozniak et al., 2006). One study of young adults found that individuals with FAS had decreased white matter integrity in the genu and splenium of the CC when compared to controls (Ma et al., 2005). However, another study using individuals with more moderate levels of exposure found only diffusion differences in the isthmus of the CC (Wozniak et al., 2006). Importantly, CC abnormalities have been associated with neuropsychological deficits commonly observed in alcohol-exposed populations, such as bimanual coordination (Roebuck-Spencer and Mattson, 2004), attention (Coles et al., 2002), verbal learning ability (Sowell et al., 2001b) and executive functioning (Kodituwakku et al., 2001; Bookstein et al., 2002b).

The cerebellum has also been identified as particularly vulnerable to prenatal alcohol exposure. Specifically, individuals with FASD show reduced cerebellar volume (Mattson et al., 1994; Archibald et al., 2001) and surface area (Autti-Rämö et al., 2002) as well as reduced volume and displacement of the anterior vermis of the cerebellum (Sowell et al., 1996; Autti-Rämö et al., 2002; O’Hare et al., 2005). Two studies have confirmed that the volume of the anterior cerebellar vermis, an early developing part of the cerebellum, is reduced in FASD relative to controls even after controlling for overall brain size (Sowell et al., 1996; Autti-Rämö et al., 2002). FAS subjects also show more severe displacement in the superior and anterior edges of the anterior vermis than do non-dysmorphic FASD individuals (O’Hare et al., 2005). Given that the cerebellum is responsible for the execution of motor behaviour such as posture, balance and coordination, the structural abnormalities observed may help to explain motor deficits often seen in individuals with FASD (Roebuck et al., 1998; Roebuck-Spencer and Mattson, 2004). The cerebellum is also involved in other functions, such as attention regulation (e.g. Akshoomoff et al., 1997) and classical conditioning (Woodruff-Pak et al., 2000). In accordance with this, deficits in classically conditioned eyeblink responses are noted in children with FAS (Coffin et al., 2005) and cerebellar vermis displacement is negatively correlated with verbal learning and memory in FASD (O’Hare et al., 2005).

Several studies report volumetric reductions in the basal ganglia, although only the caudate is disproportionately reduced when overall brain size is accounted for (Mattson et al., 1992, 1994, 1996b; Archibald et al., 2001). In fact, the caudate has been reported to be one of the most sensitive brain areas to prenatal alcohol insult. Abnormalities in the caudate region are hypothesized to be related to deficits in executive functioning, attention and response inhibition (Mattson et al., 1996b).

Abnormalities of grey and white matter distribution and density within specific brain regions can occur in FASD. Archibald et al. (2001) concluded that white matter decreases are greater than grey matter decreases within the cerebrum, while Sowell et al. (2002a) discovered that grey matter density was significantly increased and white matter was decreased in the perisylvian cortices and inferior parietal regions, particularly in the left hemisphere. Structural irregularities may relate to these grey and white matter abnormalities, as the parietal region is also reduced in volume in alcohol-exposed individuals (Sowell et al., 2001a; 2002a; 2002b). Sowell et al. (2002a) suggest that the increased grey matter density observed in FASD may...
be caused by an irregular cortical thinning process that occurs during development.

In addition to commonly observed structural abnormalities as described above, research is beginning to outline functional deficits in the brains of individuals with FASD. For example, a PET study has reported a subtle reduction in glucose metabolism in the thalamus and caudate (Clark et al., 2000) in young adults with FAS. Further, cerebral blood flow (CBF) as well as dopaminergic and serotonergic neurotransmission has been studied using SPECT. Decreased CBF in the left parieto-occipital region was reduced while CBF in the right frontal region was increased in FASD (Riikonen et al., 1999). There were also reduced serotonin levels in the medial frontal cortex and an increase in striatal dopamine transporter binding (Riikonen et al., 2005). Another study demonstrated reduced CBF in the temporal region relative to the cerebellum (Bhatara et al., 2002).

fMRI and MRS have also been applied to the study of prenatal alcohol exposure. Malisz and colleagues (2005) conducted an fMRI study using a spatial working memory paradigm to examine haemodynamic brain activation in exposed and non-exposed adults and children. Individuals with FASD showed increased functional activity in the inferior and middle frontal cortices when compared with matched controls. In addition, controls showed increased frontal lobe activity with increasing task difficulty, while FASD participants did not. However, Bookheimer and Sowell (2005) note that the observed activation patterns cannot be attributed to fundamental differences in brain function between groups, as alcohol-exposed individuals were less accurate and had slower reaction times than controls, and results may instead be related to performance factors. Another study of alcohol-exposed children examined activation during a response inhibition task and found that individuals with FASD displayed increased frontal and decreased caudate activation in comparison to controls despite equivalent task performance (Fryer et al., 2007b). A third study examined activation patterns during a verbal paired associates learning task. Alcohol-exposed children showed significantly less activation in left medial and posterior temporal regions and significantly more activation in right dorsal frontal regions relative to controls, even when group differences in performance were statistically controlled (Sowell et al., 2007).

Two studies have examined functional brain metabolism in alcohol-exposed populations using MRS techniques. Results of one study suggest that prenatal alcohol exposure is associated with altered brain metabolism in several anatomic regions, including lower N-acetyl-laspartate/choline (NAA/Cho) and lower NAA/creatinine (NAA/Cr) ratios in parietal and frontal cortices, frontal white matter, CC, thalamus and cerebellar dentate nucleus. Also, individuals with FASD had higher absolute levels of Cho and Cr in comparison to controls, but showed no difference in levels of NAA (Fagerlund et al., 2006). These data are indicative of a metabolic alteration in the glial cell population, rather than the neuronal cell population, associated with prenatal alcohol exposure; also, brain metabolism appears to be permanently affected (Fagerlund et al., 2006). In contrast, a second MRS study uncovered a higher metabolite ratio of NAA/Cr in the left caudate nucleus of individuals with FASD as compared to controls. Analysis of absolute concentrations suggested that this increase was due to an increase in the NAA concentration alone (Cortese et al., 2006).

Factors influencing the effects of prenatal ethanol exposure on the developing brain

The clinical data indicate considerable variability in the range and magnitude of prenatal ethanol-induced effects on brain abnormalities and behavioural outcomes. Several biological and environmental factors are known to influence the effects of ethanol on the developing brain, including dose of alcohol and exposure pattern, developmental timing of exposure, genetic background of the mother and foetus, maternal nutrition, maternal age, socioeconomic status and synergistic reactions with other drugs. Among these factors, the levels of alcohol reaching the foetal brain and the duration of exposure markedly influence the type and the extent of the damage (Maier et al., 1996). In addition, the genetic background of the mother and foetus, such as variations in ethanol metabolism, also influence the risk of ethanol-induced malformations in the foetus (Thomas et al., 1998). The more efficient alcohol dehydrogenase (ADH) allele, ADH 1B∗3, affords protection for FASD outcomes (McCárver et al., 1997), while the maternal and foetal ADH1B∗2 allele reduced the risk for FAS in a South African population (in comparison with ADH1B∗1) (see rev., Warren and Li, 2005).

The specific brain structure affected and the magnitude of the damage are also strongly influenced by the developmental timing of ethanol exposure. For example, facial dysmorphology, a salient feature of FAS (Jones and Smith, 1973), appears to arise only when high-peak blood alcohol levels occur during the embryonic stage of gastrulation (Sulik, 2005). Mice exposed to ethanol on embryonic day 7 (E7) or E8 (Sulik, 2005) and macaques exposed to ethanol on E19 or E20 (Astley et al., 1999) exhibit FAS-associated facial dysmorphism. Exposure to alcohol during gastrulation also has a negative impact on the developing brain, reducing the neural progenitors pool (Rubert et al., 2006) and causing long-term effects on the forebrain (Ashwell and Zhang, 1996; Miller, 2007) as well as on mature brainstem nuclei structures (Mooney and Miller, 2007). Human studies demonstrate that binge drinking as well as chronic alcohol abuse during the early stage of human embryogenesis (corresponding to the third week of human gestation) is associated with a greater incidence of craniofacial defects and mental disabilities (Ernhart et al., 1987).

Alcohol also affects other ontogenetic stages of brain development. For example, a second critical period is the stage of neuroepithelial cell proliferation and migration, which occurs in humans from 7 to 20 weeks of gestation (Suzuki, 2007) and from gestation day 12 (G12) to G20–21 in the rat. At this stage, most of the areas of the nervous system (except the cerebellum) begin to differentiate. Experimental studies report that ethanol exposure at this stage alters neuronal migration and affects the timing and the pattern of cell generation by reducing the number of neurons and glial cells in the neocortex, hippocampus and sensory nucleus (Gressens et al., 1992; Miller, 1995a, 1995b; Valles et al., 1997; Rubert et al., 2006). As with other neurodevelopmental disorders (Suzuki, 2007), perturbation of neuroglial proliferation and migration by ethanol could cause long-term abnormalities in the cerebral cortex and in brain size, as noted in individuals with FAS and FASD (e.g. Archibald...
et al., 2001; Sowell et al., 2001a, 2002a), and likely contribute to the cognitive defects observed in adults with FASD. Additionally, since formation of the CC and glial midline starts around 7 weeks in humans (Paul et al., 2007; Richards et al., 2004), exposure to alcohol at this stage might disrupt the early events in callosal formation, and later on might dysregulate axonal pruning, leading to agenesis, hypoplasia or abnormalities in the CC (e.g. Riley et al., 1995; Swayze II et al., 1997; Bhatarra et al., 2002). In fact, administration of a single high dose of ethanol to neonatal rats caused a marked reduction in the thickness of the CC (Olney, 2004), possibly resulting from the loss of cerebro-cortical neurons whose axons projections comprise much of the mass of the CC.

Finally, alcohol also interferes with the ‘brain growth spurt’ neonatal stage in the rat (roughly the equivalent of the third trimester of human gestation), a period characterized by glial development (astroglial and oligodendroglia), synaptogenesis and development of the cerebellum. Ethanol exposure induces microcephaly, causes neuronal cell loss in both the hippocampus and cerebellum (Goodlett and Lundahl, 1996; Dikranian et al., 2005), alters synaptogenesis and glial development (Guerri and Renau-Piqueras, 1997) and can cause learning/memory deficits, as well as long-term and neurobehavioural dysfunctions (Wozniak et al., 2004; Popovic et al., 2006). In addition, administration of a single high or moderate dose of ethanol to neonatal mice throughout the period of early synaptogenesis triggers a significant neuroapoptosis in several brain regions (e.g. forebrain, midbrain, brainstem, cerebellum, spinal cord and retina) (Ikonomidou et al., 2000; Dikranian et al., 2005; Tenkova et al., 2003), with the caudate nucleus and the frontal and parietal cortices the most vulnerable regions to the neuroapoptotic effects of ethanol (Young and Olney, 2005). In line with these data, alterations in the caudate nucleus and in the frontal cortices have also been noted in individuals with FASD (Cortese et al., 2006; Fagerlund et al., 2006).

Collectively, experimental data indicate that although ethanol can interfere with important ontogenetic stages of the mammalian brain, the levels of ethanol reaching the foetal brain and the developmental timing of ethanol exposure are important determinants of the specific brain structures affected and the resulting degree of damage.

Potential mechanisms involved in ethanol-induced brain damage during development

Several molecular mechanisms have been identified as potential candidates responsible for the range of FASD phenotypes (Guerri 1998, 2002; Goodlett et al., 2005). These mechanisms are likely to participate at different stages of development and/or with different doses of ethanol. They include (1) alterations in the regulation of gene expression (e.g. reduced retinoic acid signalling, homeobox gene expression, altered DNA methylation; Deltour et al., 1996; Rifas et al., 1997), (2) interference with mitogenic and growth factor responses involved in neural stem cell proliferation, migration and differentiation (see revs., Miller, 2006; Mooney et al., 2006; Siegenthaler and Miller, 2006), (3) disturbances in molecules that mediate cell–cell interactions (L1, NCAM, loss of trophic support; e.g. Wilkemeyer et al., 2002; Miñana et al., 2000), (4) activation of molecular signalling controlling cell survival or death (growth factors deprivation, oxidative stress, apoptotic signalling and caspase-3 activation, suppression of NMDA glutamate and GABAA receptors, withdrawal-induced glutamatergic excitotoxicity, e.g. Guerri et al., 1994; Pascual et al., 2003; Olney, 2004; Thomas et al., 2004; Young et al., 2005) and (5) derangements in glial proliferation, differentiation and functioning (Guerri et al., 2001, 2006). This last mechanism is supported by neuroimaging studies revealing global white matter reductions and abnormalities in FASD (Archibald et al., 2001; Sowell et al., 2002a). Due to the potential contribution of this mechanism to the brain damage observed in young adults with FASD, we will describe the evidence demonstrating that glial cells are an important target of alcohol teratogenesis.

Role of glial cells in the ethanol-induced brain abnormalities

Alterations in glial development are suspected to contribute to the adverse effects of alcohol on the developing brain because neuroglial heterotopias, alterations in neuronal migration and agenesis of the CC and anterior commissure (areas originally formed by glial cells) have been observed in postmortem studies of children with FAS (Clarrren et al., 1978).

Glial cells are present throughout CNS development and play critical roles in multiple developmental events. During embryogenesis, radial glia (RG) provides physical and chemical guidance for the migration of young neurons, and new data indicate that RG serves as a multipotential neural precursor cell, having the potential to self-renew and to generate neurons (e.g. Sanai et al., 2004) and oligodendrocytes (Ventura and Goldman, 2007). During synaptogenesis, glial cells and glial-derived factors promote the formation of mature functional synapses (Ullian et al., 2001), regulate neurotransmitters and energy in the brain (Magistretti, 2006) and play key roles in synaptic function (Haydon, 2001; Fields and Stevens-Graham, 2002). Disturbances of glia or of neuronal–glial communication during the well-established critical periods of brain development can cause irreversible deficits in CNS function (Lammens, 2000; Ross and Walsh, 2001; Crespel et al., 2002). Alteration of astrocytes and of neuronal–glial interactions could also affect the later generation of oligodendrocytes and myelin (Ganat et al., 2006, Ishibashi et al., 2006), causing abnormalities in white matter.

Clinical and experimental studies provide compelling evidence that foetal and/or neonatal exposure to ethanol profoundly affects glial functions (Guerri and Renau-Piqueras, 1997; Guerri et al., 2001, 2006). Experimental studies demonstrate that ethanol exposure during embryogenesis reduces the telencephalic RG progenitor pool and its transformation into neurons and astrocytes (Rubert et al., 2006) and impairs RG morphology. Ethanol also impairs astroglial proliferation, survival and functions (Guerri et al., 2001, 2006) that can affect many developmental processes, such as the availability of trophic support molecules involved in neuronal survival, modulation of the formation of mature synapses and regulation of synaptic transmission (Pascual and Guerri, 2007). Neuroimaging studies of individuals with FASD have shown more important losses in white matter structures (mainly composed of astrocytes, oligodendrocytes and myelin) than in grey matter structures (Riikonen et al., 1999; Archibald et al., 2001; Sowell et al., 2001a, 2002b). Changes in brain metabolism
have also been demonstrated in adolescents and young adults with FASD (Fagerlund et al. 2006), using MRS to evaluate neuronal and glial markers. The metabolic anomalies observed in different brain structures (parietal and frontal cortices, frontal white matter, CC, thalamus and cerebellar dentate nucleus) of FASD individuals are consistent with abnormalities in the glial cell pool, rather than in the neurons. Because astroglial cells play critical roles in the metabolic processes linked to neuronal activity such as blood flow, energy and glucose utilization (e.g. Magistretti, 2006), the results suggest that ethanol-induced glial impairment during brain development could affect neuronal activity, leading to permanent metabolic and structural brain alterations. Overwhelming evidence derived from clinical and experimental data highlights the vulnerability of human glial cells to the teratogenic effects of ethanol and the permanent consequences of these effects. Nevertheless, there may also be some neuronal-mediated effects, since some studies reported increased neuronal death as a primary effect of ethanol administration to neonatal rats (e.g. Goodlett and Lundahl, 1996; Ikonomidou et al., 2000; Olney, 2004).

SUMMARY AND CONCLUSIONS

A substantial body of evidence has emerged for the devastating consequences of prenatal alcohol exposure on the developing CNS, allowing a clearer appreciation of the specific brain regions affected, mechanisms involved and the range of effects. Prenatal alcohol exposure causes structural alterations to the shape, volume and surface area of the overall brain and particular brain regions, as well as reduced white matter and increased grey matter densities in corresponding areas. In addition, studies are now beginning to describe functional brain activation abnormalities in alcohol-exposed populations that may provide a better understanding of the underlying neural processes associated with the neuropsychological impairments that have consistently been reported in such individuals. An overall goal of this research is to provide a comprehensive picture of the associations among structural and functional brain abnormalities and observed behaviour in individuals with FASD. Another aim of this work is to identify factors that mediate the relationship between prenatal alcohol exposure and the type and severity of brain abnormalities and behavioural deficits. To this aim, experimental studies have begun to outline dosage and timing factors of alcohol use during pregnancy that contribute to changes in critical CNS developmental processes and determine, in part, the range of effects a given individual may later display. Finally, it is important to understand the molecular mechanisms that underlie alcohol’s neuroteratological effects, and research has pointed to abnormalities in glial cell proliferation, differentiation and function as one significant mechanism responsible for the adverse effects of alcohol on the developing brain. While the evidence for a neurocognitive phenotype of FASD is becoming more consistent, future research is needed to strengthen the current findings, as well as to identify additional factors that play a role in the variation of alcohol-related effects.

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