

Chapter 2

Serotonin 5-HT_{2C} Receptors: Chemical Neuroanatomy in the Mammalian Brain

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2.1 Introduction

Serotonin 5-HT_{2C} receptors belong to the 5-HT₂ family, which includes 5-HT_{2A} and 5-HT_{2B} receptors. All three share similarities in their molecular structure, pharmacology, and signal transduction pathways (Barnes and Sharp 1999; Hoyer et al. 1994). Initially named 5-HT_{1C}, based on the conventions for naming serotonin receptors at the time of its discovery, it was later renamed 5-HT_{2C} receptors after the cloning of its gene and that of 5-HT_{2A} (Pazos et al. 1984a; Prichett et al. 1988; Julius et al. 1988, 1990; Hoyer et al. 1985; Lubbert et al. 1987; Pazos and Palacios 1985) (see also Palacios et al., Chap. 1, this volume). Chemical neuroanatomical techniques were pivotal in the discovery of 5-HT_{2C} receptors, which were first identified by autoradiography after labeling of rat brain sections with the 5-HT_{2A} and dopamine D₂ receptor ligand mesulergine. This was followed by a thorough pharmacological characterization performed in pig brain choroid plexus, and the binding site was differentiated from the 5-HT_{2A} receptor. The combined use of membrane receptor binding/pharmacology and brain slice autoradiography allowed its differentiation from 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A} receptors; it was then named 5-HT_{1C}. The pharmacology and distribution of the new site differed from the existing knowledge about other receptors (Pazos et al. 1984a, b; Hoyer et al. 1985). The 5-HT_{1C} receptor was cloned soon thereafter (Julius et al. 1988). The knowledge of the messenger ribonucleic acid (mRNA) sequence and the derived protein sequence of these receptors allowed the development of new important tools for the study of their chemical neuroanatomy.

The autoradiographic localization of 5-HT_{2C} receptors had suffered from the lack of selective ligands. While mesulergine remains the ligand of choice, 5HT_{2C} sites can also be labeled by other ligands such as 5-HT self, LSD (lysergic acid diethylamide), and DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane), but

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always in combination with unlabeled ligands to block additional sites labeled by these ligands. The ability to combine in situ hybridization with radioligand binding autoradiography has allowed the establishment of the anatomical distribution of 5-HT_{2C} receptors in the brain of many animal species by different anatomical and pharmacological manipulations (Pazos and Palacios 1985; Eberle-Wang et al. 1997; Hoffman and Mezey 1989; Mengod et al. 1990a, b; Molineaux et al. 1989; Pompeiano et al. 1994). Immunohistochemistry with antibodies against parts of 5-HT_{2C} receptors has also been used to visualize the receptor protein (Clemett et al. 2000; Abramowski et al. 1995).

In this chapter I will review some of the main findings concerning the anatomical and cellular distribution of 5-HT_{2C} receptors in the brain of rodents, primates, and humans with special emphasis on recent studies on the characterization of the phenotype of the brain cells expressing these receptors and the significance of these findings for the understanding the role of the 5-HT_{2C} receptors in brain function.

2.2 5-HT_{2C} Receptors: Neuroanatomical Localization by Radioligand Binding Autoradiography, In situ Hybridization, and Immunohistochemistry in the Rodent Brain

5-HT_{2C} receptor localization is restricted to the central nervous system (CNS), unlike that of 5-HT_{2A} and 5-HT_{2B} receptors. Radioligands that label 5-HT_{2C} receptors are: [³H]mesulergine (in the presence of a selective 5-HT_{2A} antagonist), [³H]5-HT (with adequate protection with a cocktail of 5-HT₁ ligands), [¹²⁵I]SCH23982 (also dopamine D1), and [¹²⁵I]LSD (in the presence of adequate 5-HT_{2A} selective drugs). The remarkable concentration of 5-HT_{2C} receptors in the mammalian choroid plexus somehow obscures its presence throughout the CNS. Autoradiographic studies have identified this receptor in anterior olfactory nucleus, olfactory tubercle, lateral amygdaloid nucleus, cortex, nucleus accumbens, hippocampus, amygdala, caudate, and substantia nigra in addition to the choroid plexus in rat brain (Pazos and Palacios 1985). 5-HT_{2C} receptor mRNA is very abundant in the pyramidal cell layer of the ventral and posterior part of CA (cornu ammonis) 1 and CA2 fields of the hippocampus and of the anterior part of the CA3, while it is very low in the pyramidal cell layer of the dorsal and anterior region of CA1 and CA2, posterior part of CA3, and the granule cell layer of the dentate gyrus. 5-HT_{2C} binding sites show a regional distribution in agreement with that of the mRNA, being concentrated on the pyramidal cell layer of CA1 and CA2 at ventral levels and the granule cell layer of the dentate gyrus. However, receptors are also seen in the stratum lacunosum molecular of the CA1 and CA3 fields at anterior and dorsal level (Palacios et al. 1991). These localizations are illustrated in Fig. 2.1.

The distribution of [³H]mesulergine binding sites in rat brain (Pazos and Palacios 1985) are very similar to those found in mouse brain (Mengod et al. 1990a). In mouse brain, [³H]mesulergine binding sites (in the presence of spiperone to block

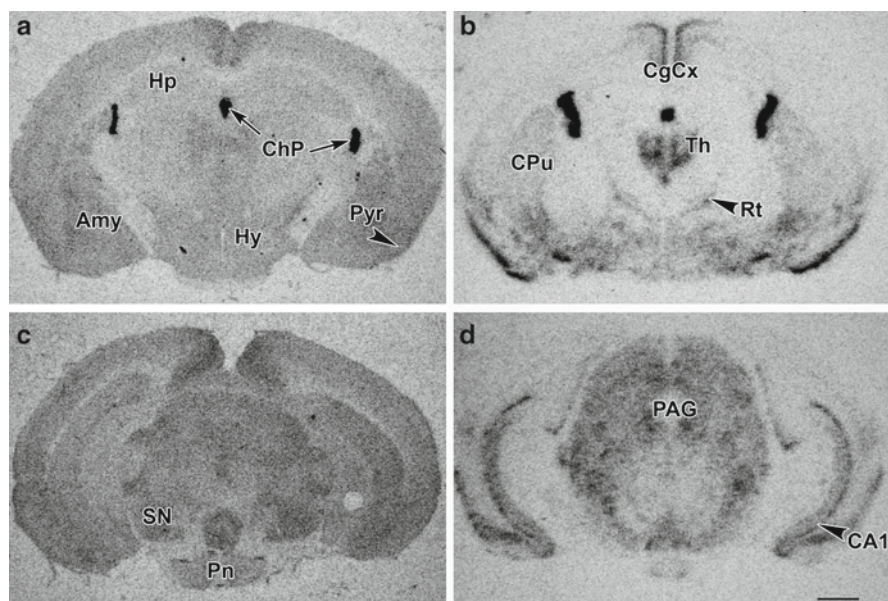


Fig. 2.1 5-HT_{2C} receptors in the mouse brain. Regional distribution of [³H]mesulergine binding sites and 5-HT_{2C} receptor mRNA in adjacent sections of the mouse brain. (a) and (c) Receptor binding sites labeled by 5 nmol/L [³H]mesulergine. (b) and (d) Hybridization signal obtained with a ³³P-labeled oligonucleotide probe complementary to the mRNA encoding 5-HT_{2C} receptors. Pictures are digital photographs from film autoradiograms. Amy indicates amygdala, CA1 CA1 field of the hippocampus, CgCx cingulate cortex, ChP choroid plexus, CPu caudate-putamen, Hp hippocampus, Hy hypothalamus, PAG periaqueductal gray, Pn pontine nuclei, Pyr pyriform cortex, Rt reticular nucleus of the hypothalamus, SN substantia nigra. Scale bar: 1 mm

binding of the radioligand to 5-HT_{2A} receptors) (Mengod et al. 1990a) are present at high densities in choroid plexus, where it is predominant, although the presence of low/very low specific [³H]mesulergine signals can be detected in nucleus accumbens, patches of the caudate putamen, olfactory tubercle, claustrum, septum, cingulate cortex, amygdala, dentate gyrus, periaqueductal gray, entorhinal cortex, and several brainstem motor nuclei. This binding is not detected in the 5-HT_{2C} receptor knockout (KO) mouse brain (López-Giménez et al. 2002), indicating that 5-HT_{2C} receptors are indeed present in the brain although at much lower densities than 5-HT_{2A} receptors (with the remarkable exception of the choroid plexus). The distribution of mRNA is very similar to that of protein or binding sites, except for high levels in the habenular nucleus; where binding site levels are very low (Mengod et al. 1990a; López-Giménez et al. 2001a). There are multiple splice and editing variants of 5-HT_{2C} receptors (Fitzgerald et al. 1999; Niswender et al. 1998), which are beyond the scope of this chapter; they are not discriminated, so far as is known, by the antagonist radioligands used in autoradiographic studies.

In monkey brain, 5-HT_{2C} mRNA is present in choroid plexus, in layer V of most cortical regions, and in nucleus accumbens, ventral anterior caudate and putamen, septal

nuclei, diagonal band, ventral striatum, and extended amygdala (López-Giménez et al. 2001a). Several thalamic, midbrain, and brainstem nuclei also contain 5-HT_{2C} mRNA. [³H]Mesulergine binding and mRNA show a good correlation across the brain supporting a predominant somatodendritic localization of 5-HT_{2C} receptors. However, in a few instances, a lack of correlation between both patterns of signal suggests a possible location of 5-HT_{2C} receptors on axon terminals. Examples of poor correlation are the septal nuclei and horizontal limb of the diagonal band (presence of mRNA with apparent absence of binding sites) and interpeduncular nucleus (presence of binding sites with apparent absence of mRNA).

2.3 Species Differences in 5-HT_{2C} Receptors Distribution: Rodent Versus Human and Nonhuman Primates

The pharmacological profile for 5-HT_{2C} receptors is very similar for human, pig and rat (Hoyer et al. 1985, 1986; Pazos et al. 1984b, 1987) both radioligand binding and autoradiographic procedures in frontal cortex, hippocampus, and choroid plexus of these species using [³H]mesulergine. The distribution of 5-HT_{2C} receptor binding sites in the human brain is somewhat different from that found in the rat brain (Pazos and Palacios 1985; Hoyer et al. 1986). In the rat hippocampus, 5-HT_{2C} receptor binding sites are located in the stratum lacunosum moleculare, whereas in the human hippocampus the pyramidal layer is enriched in these receptors.

There are also differences in [³H]mesulergine binding sites in human brain when compared with monkey (*Macaca fascicularis*) brain. High densities of binding sites are observed in the human globus pallidus and substantia nigra (Pazos et al. 1987), whereas they are absent in monkey globus pallidus and low in substantia nigra (López-Giménez et al. 2001a). In monkey neocortex, low levels of [³H]mesulergine binding sites are detected on layer V, whereas in human cortical areas binding sites are located predominately in layer III.

Although the distribution of 5-HT_{2C} receptor mRNA in monkey brain (López-Giménez et al. 2001a) is very similar to that in rat (Eberle-Wang et al. 1997; Pompeiano et al. 1994; Wright et al. 1995), mouse (Mengod et al. 1990a), and human brain (Pasqualetti et al. 1999), there are some differences. In the neocortex of mouse and rat the 5-HT_{2C} receptor mRNA are found at detectable levels only in prefrontal, cingulate, and retrosplenial cortices, whereas in monkey, mRNA is present in all neocortical areas except in the calcarine sulcus within the occipital cortex. The CA3 subfield of the hippocampus is another region of divergence: rat, mouse, and human brain contain this mRNA, and no signal is found in the monkey CA3. The rat entopeduncular nucleus contains 5-HT_{2C} receptor mRNA, whereas its equivalent in primate, the internal segment of the globus pallidus, is devoid of it. In the striatum, the hybridization signal is uniformly intense in human, rat, and mouse brain, whereas in monkey brain this signal is not uniform and is restricted to ventral aspects of the anterior striatum. The substantia nigra is another brain region that presents differences in the distribution of 5-HT_{2C} receptor mRNA among the species.

In human brain the presence of this mRNA is detected predominantly in the pars compacta of this nucleus, whereas monkey brain cells showing the hybridization signal were confined in the lateral part of substantia nigra. As in the rodent brain, there is in general a good correlation between mRNA and binding sites in human and monkey brains with the exceptions identified above. Some of these exceptions are now discussed in relationship to the cellular localization of these receptors.

2.4 Phenotype of Cells Expressing 5-HT_{2C} Receptors

The widespread distribution of 5-HT_{2C} receptors in the brain of the mammalian species studied until now suggests, as is the case for other neurotransmitter receptors, that 5-HT_{2C} receptors are expressed by neurons with different neurotransmitter phenotypes. In this section evidence is presented that suggests the presence of these receptors in neuropeptidergic, cholinergic, serotonergic, and GABAergic neurons, as well as recent studies showing the interaction of 5-HT_{2C} receptors with the cannabinoid and the dopaminergic systems.

2.4.1 5-HT_{2C} Receptors and Neuropeptidergic Neurons

In nucleus accumbens and striatum, 5-HT_{2C} receptor mRNA was found localized with each of the neuropeptides (enkephalin, substance P, and dynorphin) as shown by Ward and Dorsa (Ward and Dorsa 1996). The level of colocalization was similar among the three neuropeptides but varied by region: high levels of colocalization were observed (from 64% to 89%) ventrally, medially and scattered in patches with high expression of the receptor in the striatum, whereas lower levels of colocalization (43–54%) were observed in matrix-like areas of lower receptor expression. According to the authors this colocalization could provide an anatomical basis for earlier observations that alterations in serotonergic input can lead to changes in the levels of striatal neuropeptides (Kondo et al. 1993).

2.4.2 5-HT_{2C} Receptors and Serotonergic or GABAergic Neurons

The cellular localization of 5-HT_{2C} receptor mRNA in relation to serotonergic and GABAergic neurons has been studied in the anterior raphe nuclei of the rat (Serrats et al. 2005). In the dorsal and median raphe nuclei, 5-HT_{2C} receptor mRNA is not detected in serotonergic cells identified as those expressing serotonin (5-HT) transporter mRNA. In contrast, 5-HT_{2C} receptor mRNA is found in the majority of GABAergic cells of the anterior raphe nuclei, mainly located in the lateral and intermediolateral parts of the dorsal raphe and lateral part of the median raphe, supporting

previous hypotheses that proposed a negative-feedback loop involving reciprocal connections between GABAergic interneurons bearing 5-HT_{2A/2C} receptors and 5-HT neurons in the dorsal raphe and surrounding areas. According to this model, the excitation of GABAergic interneurons through these 5-HT_{2C} (and also 5-HT_{2A}) receptors would result in the suppression of 5-HT cell firing.

The finding of 5-HT_{2C}-immunoreactive cells in the raphe nuclei has led to the proposal that some 5-HT neurons might express these receptors (Clemett et al. 2000). In contrast, electrophysiological data suggest that 5-HT_{2C} receptors are located on local GABAergic neurons, inside or close to the dorsal raphe (Liu et al. 2000), being part of a local negative-feedback circuit that would involve reciprocal connections between GABAergic and 5-HT neurons. This model has been proposed to explain the increases in the frequency of inhibitory postsynaptic currents (IPSCs) induced by 5-HT and the 5-HT_{2A/2C} agonist DOI [1-(2,5)-dimethoxy-4-iodophenyl-2-aminopropane] when applied to rat brain slices containing the dorsal raphe.

The localization of the 5-HT_{2C} receptor in GABAergic cells has been also described in other brain areas. Immunohistochemical analyses on the 5-HT_{2C} receptor reveals that this receptor is mainly expressed in deep layers of the rat medial prefrontal cortex (Liu et al. 2007) and cortex (Abramowski et al. 1995) in agreement with the presence of the mRNA coding for this receptor in layers IV and V of PFC of mice (Mengod et al. 1990a), rat (Pompeiano et al. 1994), monkey (López-Giménez et al. 2001a), and human (Pasqualetti et al. 1999). Around 50% of the neurons expressing 5-HT_{2C} receptor immunoreactivity in the prelimbic region of the medial prefrontal cortex also expressed GAD67 immunoreactivity (Liu et al. 2007), a marker of GABAergic interneurons. We have detected abundant expression of 5-HT_{2C} receptor mRNA in layer V cells of the mouse cingulate cortex that were not GABAergic. A detail of these results is shown in Fig. 2.2.

2.4.3 5-HT_{2C} Receptors and Cholinergic Neurons

In our studies on the distribution of 5-HT_{2C} receptor mRNA in the Macaca brain (López-Giménez et al. 2001a) we remarked that several regions where cholinergic cell groups are located also contained mRNA for 5-HT_{2C} receptor. These regions of codistribution include several forebrain areas [medial septal nucleus (cholinergic group Ch1), vertical nucleus of diagonal band (Ch2), horizontal nucleus of diagonal band (Ch3), and nucleus basalis of Meynert (Ch4)], several mesencephalic nuclei [pedunculo pontine nucleus (Ch5), laterodorsal tegmental nucleus (Ch6), parabrachial nucleus (Ch8), oculomotor and trochlear nuclei], and motor nuclei of the brainstem cranial nerve. This correspondence is also observed between the distribution of 5-HT_{2A} receptor mRNA (López-Giménez et al. 2001b) and several mesencephalic and brainstem cholinergic cell groups, particularly in the latter region where the different cranial nerve motor nuclei are highly enriched in both 5-HT_{2A} receptor mRNA and ChAT mRNA.

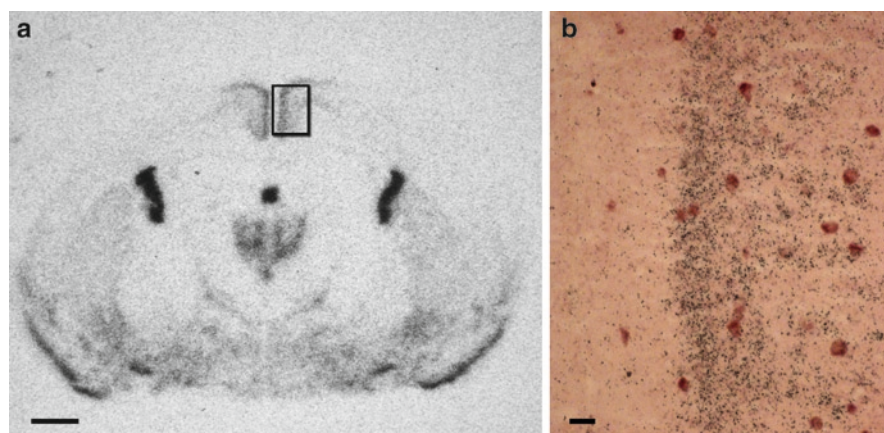


Fig. 2.2 Cellular visualization of 5-HT_{2C} receptors mRNA in the cingulate cortex. **(a)** Macroscopic visualization of 5-HT_{2C} receptor mRNA in the mouse coronal section. The inset in **(a)**, corresponding to the cingulate cortex, is shown at higher magnification in **(b)**. **(b)** Cellular localization of 5-HT_{2C} receptors mRNA (labeled with ³³P, black silver grains) in the cells of cingulate cortical layers. GABAergic cells (GAD mRNA expressing cells seen as a brown precipitate) do not display 5-HT_{2C} receptor mRNA hybridization signal. Scale bars: **(a)** 1 mm; **(b)** 20 μm

In fact, the interaction of cholinergic and serotonergic systems has been extensively studied, especially those aspects relating to the modulation of central cholinergic function by serotonin and its possible cognitive implications (See the review in Cassel and Jeltsch (1995)). Regarding 5-HT_{2C} receptors and cholinergic function, several microdialysis studies carried out in rat brain showed the effect of 1-(3-chlorophenyl)piperazine (mCPP) (an unselective 5-HT_{2C} receptor agonist) on the release of acetylcholine in rat cortex (Zhelyazkova-Savova et al. 1997) and hippocampus (Zhelyazkova-Savova et al. 1999). This effect consisted of an increase of acetylcholine release, which was shown to be mediated by 5-HT_{2C} receptors, especially in the case of the cortex, providing corroborating evidence that the effect was produced particularly via the nucleus basalis magnocellularis (Zhelyazkova-Savova et al. 1997).

2.4.4 5-HT_{2C} Receptors and the Cannabinoid Receptors System

The interaction of 5-HT_{2C} receptors with the cannabinoid system through the CB₁ receptor has been recently studied (Aso et al. 2009). CB₁ KO mice exhibited a reduction in the expression of the 5-HT_{2C} receptor in dorsal raphe, nucleus accumbens, and paraventricular nucleus, among other brain areas. In contrast, 5-HT_{2C} receptor expression was higher in the CA3 field of the ventral hippocampus of CB₁ KO mice, suggesting different roles of this receptor in these brain areas. The decreased expression of the 5-HT_{2C} receptor in the dorsal raphe of CB₁ mutant mice

could lead to a reduction in the inhibitory effect exerted by the 5-HT_{2C} receptor on 5-HT neurons through the GABAergic mechanism (Boothman et al. 2006), which supports the increased 5-HT extracellular levels in the brain areas receiving projections from the dorsal raphe observed in CB₁ KO mice. Likewise, the decreased levels of 5-HT_{2C} mRNA in CB₁ KO mice, observed within the nucleus accumbens and the paraventricular nucleus of the hypothalamus, could indicate a diminished capacity of this receptor to inhibit dopamine activity (Dremencov et al. 2006) and to stimulate corticotrophin-releasing factor release (Heisler et al. 2007), respectively.

2.4.5 5-HT_{2C} Receptors and the Dopaminergic Receptors System

Dopaminergic nuclei, such as retrorubral area, substantia nigra pars compacta, ventral tegmental area and periaqueductal gray, and dorsal striatum and nucleus accumbens, express 5-HT_{2C} receptor mRNA (Eberle-Wang et al. 1997; Mengod et al. 1990a; Pompeiano et al. 1994; Ward and Dorsa 1996). Pharmacological activation of 5-HT_{2C} receptors inhibits firing rates of ventral tegmental area neurons and dopamine release within the nucleus accumbens (Prisco et al. 1994; Di Giovanni et al. 1999; Di Matteo et al. 1998). The implication of 5-HT_{2C} receptors in the regulation of nigrostriatal dopaminergic function has been a subject of debate mainly due to controversial results obtained with different 5-HT_{2C} receptor acting molecules (Di Matteo et al. 2001; Porras et al. 2002; De Deurwaerdère et al. 2004; Navailles et al. 2004). Very recently (Abdallah et al. 2009) by using the 5-HT_{2C} receptor null mutant mice, previously generated by Tecott and collaborators (Tecott et al. 1995), it has been studied in a more direct manner the influence of this receptor subtype on functions mediated by the nigrostriatal dopaminergic pathway. Based on results generated by the combination of electrophysiological, pharmacological, neurochemical, and behavioral methods, Abdallah and coworkers have recently described that 5-HT_{2C} receptor null mutant mice displayed (1) an increment in the activity of the dopaminergic neurons of substantia nigra pars compacta, (2) an increment in the extracellular dopamine in the dorsal striatum and nucleus accumbens, (3) increased syntactic grooming chain failures and altered grooming behaviors, and (4) increased sensitivity to the stereotypic behavioral effects following selective dopamine transporter blockade. All these responses occur without phenotypic differences in the elevation of drug-induced striatal extracellular dopamine concentration, suggesting that the loss of 5-HT_{2C} receptor function may be accompanied by enhanced behavioral responses to released dopamine. The phenotypic differences these authors observe in stereotypic behavior following selective stimulation of dopamine D₁ receptors with an agonist support this hypothesis. All these findings suggest that 5-HT_{2C} receptors play a significant role in the control of nigrostriatal physiology and behavior.

2.5 Conclusions

The studies reviewed here show that 5-HT_{2C} receptors are extensive but distributed heterogeneously in the mammalian brain. Although this distribution shows a remarkable similarity among the species, there are nevertheless significant differences that have been identified. Many different neuronal populations including neuropeptidergic, cholinergic, serotonergic and GABAergic as well as the cannabinoid and dopaminergic systems have been shown to express 5-HT_{2C} receptor mRNA and/or protein. In addition, the distribution suggests the involvement of other transmitter systems such as the glutamatergic and dopaminergic, although colocalization data are still missing. All these chemical neuroanatomical studies clearly point to the role of these receptors in the functions of many brain pathways. The modulation through selective agonists or antagonists of 5-HT_{2C} receptors, an area of intensive research, will reveal the importance of these receptors as therapeutic tools.

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