Neuronal localization of the 5-HT$_2$ receptor family in the amygdaloid complex

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INTRODUCTION

The amygdaloid complex (or amygdala), a heterogeneous structure located in the medial portion of the temporal lobe, is composed of deep, superficial, and “remaining” nuclei. This structure is involved in the generation of emotional behavior, in the formation of emotional memories and in the modulation of the consolidation of explicit memories for emotionally arousing events. The serotonergic fibers originating in the dorsal and medial raphe nuclei are critically involved in amygdalar functions. Serotonin (5-hydroxytryptamine, 5-HT) regulates amygdalar activity through the activation of the 5-HT$_2$ receptor family, which includes three receptor subtypes: 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$. The distribution and the functional activity of the 5-HT$_2$ receptor family has been studied more extensively than that of the 5-HT$_{2A}$ receptor subtypes, especially in the deep nuclei. In these nuclei, the 5-HT$_{2A}$ receptor is expressed on both pyramidal and non-pyramidal neurons, and could play a critical role in the formation of emotional memories. However, the exact role of the 5-HT$_{2A}$ receptor subtypes, as well as that of the 5-HT$_{2B}$ and 5-HT$_{2C}$ receptor subtypes, in the modulation of the amygdalar microcircuits requires additional study. The present review reports data concerning the distribution and the functional roles of the 5-HT$_2$ receptor family in the amygdala.

Keywords: amygdaloid complex, pyramidal neurons, GABAergic interneurons, GABAergic projection neurons, serotonin, 5-HT$_{2A}$ receptor, 5-HT$_{2B}$ receptor, 5-HT$_{2C}$ receptor

ANATOMICAL ORGANIZATION AND MAJOR CELL TYPES OF THE AMYGDALA

The amygdala is composed of numerous nuclei and areas with different cytoarchitectonic, chemoarchitectonic, and connectional characteristics. In particular, this structure is composed of deep, superficial, and “remaining” nuclei (or areas) (Pitkänen, 2000; Pitkänen and Kemppainen, 2002). The deep nuclei include the lateral nucleus, the basal nucleus, the accessory basal nucleus, and the paralaminar nucleus (especially in primates). The lateral, basal, and accessory basal nuclei constitute the basolateral amygdala. The superficial nuclei include the anterior cortical nucleus, the nucleus of the lateral olfactory tract, the bed nucleus of the accessory olfactory tract, the medial nucleus and the posterior cortical nucleus. The remaining nuclei consist of the anterior amygdaloid area, the central nucleus, the intercalated nuclei and the amygdalohippocampal area (Pitkänen, 2000; Pitkänen and Kemppainen, 2002). Each nucleus can be partitioned into different sub divisions, as reported in Table 1 and Figure 1.

The deep nuclei consist of two types of neurons: excitatory (glutamatergic) pyramidal cells and inhibitory (GABA[y-amino butyric acid]ergic) non-pyramidal neurons (McDonald, 1992, 1998; Sah et al., 2003; Spampanato et al., 2011). Pyramidal cells have spiny dendrites, form nearly 80% of the total cell population, and act as projection neurons (McDonald, 1992, 1998; Sah et al., 2003). Non-pyramidal neurons are spine-sparse or aspiny
| Nuclei                        | Rat subdivisions                        | Monkey subdivisions                        | Human subdivisions |
|------------------------------|-----------------------------------------|-------------------------------------------|--------------------|
| Lateral nucleus (L)          | Lateral (Ldl)                           | Dorsal                                    | Lateral            |
|                              | Medial (Lm)                             | Dorsal intermediate                       | Medial             |
|                              | Ventrolateral (Lvl)                     | Ventral intermediate                      |                    |
|                              |                                        | Ventral                                    |                    |
| Basal nucleus (B)            | Magnocellular (Bmc)                     | Magnocellular                             | Magnocellular      |
|                              | Intermediate (Bii)                      | Intermediate                              | Intermediate       |
|                              | Parvicellular (Bpc)                     | Parvicellular                             | Parvicellular      |
| Accessory basal nucleus (AB) | Magnocellular (ABmc)                    | Magnocellular                             | Magnocellular      |
|                              | Parvicellular (ABpc)                    | Parvicellular                             | Parvicellular      |
| Paralaminar nucleus          | Absent                                  | No subdivisions                           | Lateral            |
|                              |                                        |                                           | Medial             |
| Bed nucleus of the accessory | No subdivisions                         | Absent                                    | Absent             |
| olfactory tract              |                                        |                                           |                    |
| Medial nucleus (M)           | Rostral (Mr)                            | No subdivisions                           | Medial             |
|                              | Central dorsal (Mcdr)                   |                                           |                    |
|                              | Central ventral (Mcv)                   |                                           |                    |
|                              | Caudal (Mc)                             |                                           |                    |
| Nucleus of the lateral       | No subdivisions                         | No subdivisions                           | No subdivisions    |
| olfactory tract (NLOT)       |                                        |                                           |                    |
| Anterior cortical nucleus    | No subdivisions                         | No subdivisions                           | No subdivisions    |
| (COa)                        |                                        |                                           |                    |
| Periamygdaloid cortex (PAC)  | Periamygdaloid cortex (PAC)             | PAC oral                                  | PAC oral           |
|                              | PAC medial (PACm)                       | PAC1                                      | PAC1               |
|                              | PAC sulcal (PACs)                       | PAC2                                      | PAC2               |
|                              |                                        | PAC3                                      | PAC3               |
|                              |                                        | PAC sulcal                                | PAC sulcal         |
| Posterior cortical nucleus   | No subdivisions                         | No subdivisions                           | No subdivisions    |
| (COp)                        |                                        |                                           |                    |
| Anterior amygdaloid area     | No subdivisions                         | No subdivisions                           | No subdivisions    |
| (AAA)                        |                                        |                                           |                    |
| Central nucleus (CE)         | Capsular (CEc)                          | Lateral                                   | Lateral            |
|                              | Lateral (CEl)                           |                                           | Medial             |
|                              | Intermediate (CEi)                      |                                           |                    |
|                              | Medial (CEm)                            |                                           |                    |
| Intercalated nuclei (I)      | No subdivisions                         | No subdivisions                           | No subdivisions    |
| Amygdalohippocampal area     | Lateral (AHAi)                          | Dorsal                                    | Lateral            |
| (AHA)                        | Medial (AHAm)                           | Ventral                                   | Medial             |

Cells, represent approximately 20% of all neurons, and constitute local circuits. These cells have axon collaterals restricted to the deep nuclei, acting as interneurons (McDonald, 1992, 1998; Sah et al., 2003; Spampato et al., 2011). However, recent tracing studies combined with immunohistochemistry have demonstrated that some GABAergic neurons in the deep nuclei originate long projections directed to the prefrontal cortex (McDonald, 1987), basal forebrain (McDonald et al., 2012) and mediodorsal thalamic nucleus (McDonald, 1987; McDonald and Mascagni, 2007). As in the neocortex and hippocampal region, interneurons in the deep nuclei can be classified into distinct subpopulations on the basis of their content of calcium binding proteins.
CB- and CR-immunoreactive (IR) interneurons are the predominant interneuronal subpopulations in the deep nuclei (Kemppainen and Pitkänen, 2000; McDonald and Mascagni, 2003). Similarly, the CR-IR interneurons can be immunopositive for CCK and/or VIP (Mascagni and McDonald, 2003). Interestingly, GABAergic projection neurons whereas non-pyramidal neurons represent local inhibitory GABAergic interneurons. These cells are not randomly organized, as in the deep nuclei, but exhibit a laminar organization (layers I, II and III) (McDonald, 1992, 1998; Sah et al., 2003). Interestingly, GABAergic projection neurons are also distributed in the superficial nuclei (McDonald et al., 2012). The medial nucleus does not contain pyramidal and non-pyramidal neurons but small- to medium-sized ovoid neurons which possess spiny dendrites (McDonald, 1992, 1998; Sah et al., 2003).

In the amygdalohippocampal area, pyramidal and non-pyramidal neurons similar to those located in the deep nuclei are the two main cell types (McDonald, 1992, 1998). Similarly, the anterior amygdaloid area contains spiny projection neurons and aspiny interneurons (McDonald, 1992, 1998). Central nucleus and intercalated masses exhibits striatal-like GABAergic neurons (McDonald, 1992, 1998; Sah et al., 2003). Moreover, neurons located in the central nucleus can be subdivided into distinct subpopulations based on their expression of neuropeptides (neurotensin, corticotropin-releasing factor, enkephalin, galanin, SOM, substance P, CCK, and VIP) (Cassell et al., 1986; Cassell and Gray, 1989).

SEROTONERGIC INNERVATION OF THE AMYGDALA AND SEROTONIN RECEPTOR

Serotonin (5-hydroxytryptamine, 5-HT) is a molecule located in the central nervous system which has the role of a neurotransmitter/neuromodulator. Serotoninergic somata are located along the midline of the brainstem in cell body groups designated raphe nuclei. The amygdala receives substantial serotoninergic innervation originating mainly from the dorsal raphe nucleus and, to a lesser extent, from the median raphe nucleus (Pralong et al., 2005; Woodruff and Sah, 2007). The CCK-IR interneurons form synapses with the somata and the proximal dendrites of the pyramidal cells. The SOM-IR neurons provide an inhibitory innervation (symmetrical synapses), especially of the distal dendritic domain (small-caliber dendrites and dendritic spines) of pyramidal cells (Muller et al., 2007a). In addition, SOM-IR axon terminals also contact SOM-, VIP- and PV-IR interneurons (Muller et al., 2007a). The VIP-IR interneurons do not innervate pyramidal cells, but form synapses with other interneurons, especially CCK-positive interneurons (Mascagni and McDonald, 2003; Muller et al., 2003).

The superficial nuclei exhibit two major cell classes: spiny pyramidal cells and spine-sparse or aspiny non-pyramidal neurons (McDonald, 1992, 1998; Sah et al., 2003). Pyramidal cells are glutamatergic projection neurons whereas non-pyramidal neurons represent local inhibitory GABAergic interneurons.

FIGURE 1 | Photomicrographs from thionin-stained coronal sections of the rat amygdala showing the various nuclei and nuclear subdivision. Scale bar = 500 μm in (F) (applied to A–F). For abbreviations see Table 1. The numbers in the lower left corner correspond to the distance from bregma according to rat brain atlas of Paxinos and Watson (1998).
Expression of 5-HT$_2$ receptor subtypes in the amygdaloid complex

The amygdaloid complex expresses moderate to high density of serotonergic receptors including 5-HT$_1$A, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, and 5-HT$_6$ (Pralong et al., 2002).

Using autoradiography, in situ hybridization and immunohistochemistry, it has been demonstrated that 5-HT$_2$ receptor family mRNA and protein are present in the amygdala. Interestingly, the expression of the 5-HT$_2A$ and 5-HT$_2C$ receptors varied during postnatal development in the rat amygdaloid complex (Li et al., 2004).

Deep nuclei

An autoradiographic study has demonstrated a 5-HT$_2$ receptor binding site in rat deep nuclei, especially in the lateral nucleus (Pazos et al., 1983). In rodents, the presence of the 5-HT$_2$ receptor in the lateral, basal and accessory basal nuclei was also verified with in situ hybridization experiments (Wright et al., 1995). Autoradiography and in situ hybridization studies have reported that binding sites and 5-HT$_2A$ receptor mRNA are present in the lateral (dorsomedial division) and basal (magnocellular division) nuclei (Lopez-Gimenez et al., 2001). Pompeiano et al. (1994) have reported the presence of the 5-HT$_3C$ receptor mRNA in rat deep nuclei, with the highest levels in the lateral nucleus. Interestingly, these Authors failed to find 5-HT$_2A$ receptor mRNA in the same nuclei. Radioactive in situ hybridization studies on the rat (Greenwood et al., 2012) and the mouse (Li et al., 2003) amygdala have shown that the 5-HT$_2C$ receptor mRNA is located in the lateral nucleus and, to a lesser extent, in the basal nucleus. Using non-radioactive in situ hybridization procedures, the highest number of cells containing 5-HT$_2C$ receptor mRNA in the rat amygdala has been observed in the lateral and accessory basal nuclei. On the contrary, only a few 5-HT$_2C$ receptor mRNA-reactive cells have been reported in the rat basal nucleus (Bonn et al., 2012, 2013). 5-HT$_2C$ receptor mRNA has been reported in the deep nuclei of the human amygdala (Pasqualetti et al., 1999).

In rat deep nuclei, immunoreactivity for the 5-HT$_2A$ receptor is located in pyramidal and non-pyramidal neurons (Morilik et al., 1993; Cornée-Hebert et al., 1999; Xu and Pandey, 2000; McDonald and Mascagni, 2007; Jiang et al., 2008; Bombardi, 2011; Bombardi and Di Giovanni, 2013). In the rat, 100% of the pyramidal cells express the 5-HT$_2A$ receptor (McDonald and Mascagni, 2007; Bombardi, 2011). The 5-HT$_2A$ receptor is abundant in the apical dendrites of pyramidal cells (McDonald and Mascagni, 2007; Bombardi, 2011) where it may amplify the impact of excitatory synaptic currents. In rat deep nuclei, 5-HT$_2A$ receptor immunoreactivity has been observed in GABAergic interneurons (in somata and dendrites) and GABAergic projection neurons (Morilik et al., 1993; McDonald and Mascagni, 2007; Bombardi, 2011). The GABAergic interneurons are present in the lateral, basal and accessory basal nuclei where the 5-HT$_2A$ receptor is expressed by 66.3, 70.6, and 66.4% of interneurons, respectively (Bombardi, 2011). These interneurons are particularly abundant in the medial subdivision of the lateral nucleus (74.7% of interneurons) and in the parvicellular and magnocellular subdivisions of the basal nucleus (73.8 and 71.9% of interneurons, respectively) (Bombardi, 2011). In the rat amygdala, 59.8% of PV-IR neurons in the medial subdivision of the lateral nucleus, and 75.6% of PV-IR neurons in the magnocellular subdivision of the basal nucleus exhibit the 5-HT$_2A$ receptor (McDonald and Mascagni, 2007). On the contrary, only 33.1% of SOM-IR neurons in the lateral nucleus (medial subdivision), and 32.6% of SOM-IR neurons in the basal nucleus (magnocellular subdivision), express the 5-HT$_2A$ receptor (McDonald and Mascagni, 2007). The GABAergic/5-HT$_2A$ receptor-IR projection neurons are especially distributed near the external and internuclear borders of the rat basolateral amygdala and project to the mediobasal thalamus (McDonald and Mascagni, 2007).

5-HT$_3C$ receptor-IR neurons, possibly pyramidal cells, have been observed in rat lateral and basal nuclei (Clemett et al., 2000).

Superficial nuclei

In the rat, 5-HT$_2$ receptor mRNA levels are moderate in every superficial nuclei (Wright et al., 1995). In rat superficial nuclei, 5-HT$_2A$ receptor mRNA is detectable only in the bed nucleus of the accessory olfactory tract where it is strongly expressed (Pompeiano et al., 1994). On the contrary, 5-HT$_2C$ receptor mRNA is located in different superficial nuclei, such as the anterior cortical nucleus, the bed nucleus of the accessory olfactory tract and the medial nucleus. In particular, 5-HT$_2C$ receptor...
mRNA levels are high in the bed nucleus of the accessory olfactory tract, intermediate in the medial nucleus and low in the anterior cortical nucleus (Pompeiano et al., 1994). Autoradiographic analyses of the rat brain have demonstrated the presence of the 5-HT2 receptor binding sites especially in the anterior cortical nucleus, but also in other superficial nuclei (Pazos et al., 1985). Immunoreactivity for the 5-HT2A receptor has been observed in every superficial nucleus of the rat amygdala. However, a high density of immunopositive neurons is present, especially in the nucleus of the lateral olfactory tract and in the bed nucleus of the accessory olfactory tract (Morilak et al., 1993; Cornea-Hébert et al., 1999; Bombardi, 2011). Using in situ hybridization procedures, high levels of 5-HT2C receptor mRNA have been observed in the medial nucleus and in the anterior cortical nucleus of the rodent amygdala (Li et al., 2003; Bonn et al., 2012, 2013; Greenwood et al., 2012). Accordingly, many 5-HT2C receptor-IR neurons are located in the rat medial nucleus (Clemett et al., 2000). A moderate level of 5-HT2C receptor-IR neurons has also been observed in the posterior cortical nucleus of the rat amygdala (Clemett et al., 2000).

As in the deep nuclei, the 5-HT2A receptor is also expressed in pyramidal and non-pyramidal neurons in the rat superficial nuclei (Bombardi, 2011). Pyramidal cells are especially distributed in the nucleus of the lateral olfactory tract (layer II), the anterior cortical nucleus (layers II and III), the periamygdaloid cortex (layers II and III) and the posterior cortical nucleus (layers II and III) (Bombardi, 2011). In these cells, the 5-HT2A receptor is strongly expressed in the apical dendrites where it may induce excitatory synaptic currents. The 5-HT2A receptor-IR non-pyramidal neurons are distributed in the nucleus of the lateral olfactory tract, the anterior cortical nucleus, the periamygdaloid cortex and the posterior cortical nucleus. These cells are heterogeneous in shape (multipolar and fusiform) and size (from small to large), and are particularly abundant in layers II and III (Bombardi, 2011). Since the cell types in the medial nucleus are not cortex-like as in the other superficial nuclei, 5-HT2A receptor-IR pyramidal and non-pyramidal neurons are not present in this nucleus (McDonald, 1992, 1998; Sah et al., 2003). Accordingly, the rat medial nucleus contains 5-HT2AR-IR principal neurons with ovoid cell bodies (Bombardi, 2011). The rat medial nucleus is the only amygdaloid area containing 5-HT2B receptor-IR neurons. These cells are numerous and show a multipolar and bipolar morphology (Duxon et al., 1997a).

Remaining nuclei

In the rat amygdalohippocampal area, the presence of the 5-HT2A receptor has been demonstrated only with immunohistochemical procedures which have revealed many 5-HT2A receptor-IR neurons with angular- and ovoid-shaped cell bodies (Bombardi, 2011). The rat amygdalohippocampal area also contains a high density of 5-HT2C receptor-IR neurons (Clemett et al., 2000). A moderate level of 5-HT2A receptor mRNA has been revealed in the rat central nucleus (Wright et al., 1995). Accordingly, immunohistochemical procedures have demonstrated the presence of many 5-HT2A receptor-IR ovoid somata in the different subdivisions of the rat central neurons (Cornea-Hébert et al., 1999; Bombardi, 2011). These cells could be GABAergic local neurons as well as GABAergic projecting neurons (Bombardi, 2011). Cells containing 5-HT2C receptor mRNA have been observed in the rat central nucleus where they are particularly numerous in the lateral capsular subdivision (Bonn et al., 2012, 2013). Both 5-HT2A and 5-HT2C receptor mRNA are present at low density in the rat amygdalohippocampal area. Accordingly, pyramidal and non-pyramidal neurons of the rat amygdalohippocampal area contain the 5-HT2A receptor (Bombardi, 2011). In the rat intercalated nuclei, 5-HT2C receptor mRNA is present at a low density while 5-HT2A receptor mRNA has not been detected (Pompeiano et al., 1994). A different distribution of the 5-HT2A receptor has been observed using immunohistochemical procedures. In fact, Xu and Pandey (2000), and Bombardi (2011) have observed that small and large neurons in the rat intercalated nuclei express the 5-HT2A receptor. The rat intercalated nuclei contain only weak 5-HT2C receptor mRNA-reactive cells (Bonn et al., 2012, 2013). These data are in disagreement with immunohistochemical studies showing that intercalated nuclei contain a high density of 5-HT2C receptor-IR neurons (Clemett et al., 2000).

EFFECT OF 5-HT2 RECEPTOR FAMILY ACTIVATION ON AMYGDALAR NEURONS AND MICROCIRCUITS

Serotonin influences amygdalar information processing by activating multiple 5-HT2 receptor subtypes. Inasmuch as the amygdaloid microcircuits are complex and the expression patterns of the 5-HT2 receptor subtypes are not fully characterized, the mechanisms by which 5-HT2 receptor subtypes modulate amygdalar neurotransmission remains poorly understood. This modulation is complex and has been studied especially for 5-HT2A and 5-HT2C receptors.

Electrophysiological studies have demonstrated that the 5-HT2A receptor activates the pyramidal cells of the deep nuclei. In fact, the local injection of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a 5-HT2A/5-HT2C receptors agonist, increases the discharge rate (Stein et al., 2000) and facilitates synaptic plasticity via an NMDA-mediated mechanism (Chen et al., 2003) in presumptive pyramidal neurons of the rat basolateral amygdala.

The 5-HT2A receptor family also modulates the excitability of GABAergic interneurons in the deep nuclei. In fact, electrophysiological studies have demonstrated that the application of α-methyl-5-hydroxytryptamine (a 5-HT2 receptor agonist) and DOI (a 5-HT2A/5-HT2C receptor agonist), induces the activation of GABAergic interneurons of the basolateral amygdala (Rainnie, 1999; Stein et al., 2000; Sokal et al., 2005). In addition, the stimulation of the 5-HT2A receptor increases the frequency and amplitude of spontaneous inhibitory postsynaptic currents (sIPSCs) recorded from the pyramidal neurons of the juvenile rat basolateral amygdala (Jiang et al., 2008). Accordingly, the inhibition of pyramidal cell firing in the lateral nucleus of the rat amygdala obtained after the local application of serotonin is blocked by the simultaneous application of bicuculline methiodide, a GABA antagonist (Stutzmann and LeDoux, 1999). The activation of GABAergic interneurons of the corticomedial amygdala has been demonstrated by iontophoretic injections of DOI (Stein et al., 2000).
Amygdala microcircuitry has not been studied as extensively as that of the neocortex and hippocampal region. However, numerous studies report that the amygdala circuit organization combines cortex-like (deep nuclei, the majority of the superficial nuclei and the amygdalohippocampal area) and striatum-like structures (central nucleus and intercalated nuclei) (McDonald, 1992, 1998; Sah et al., 2003). Since these amygdaloid areas provide numerous intra-amygdaloid and extra-amygdaloid connections, the amygdala is considered to be the interface of the information exchange between the various functional systems of the brain (Pitkänen, 2000). Traditionally, the extra-amygdaloid afferents (all the modalities of sensory inputs and polymodal inputs) target the input side of the amygdala (deep and superficial nuclei) where they are processed locally and then directed, by intra-amygdaloid connections, to the medial and central nuclei which act as an output station. The medial nucleus especially projects to the hypothalamic neuroendocrine zone whereas outputs from the central nucleus especially innervate the hypothalamic and brainstem nuclei which regulate autonomic functions (Pitkänen, 2000; Figure 2).

The distribution of the 5-HT2 receptor previously reported indicates that this receptor could modulate amygdala activity acting on projection neurons (pyramidal neurons of cortex-like structures and GABAergic projection neurons of the basolateral amygdala and striatum-like structures) as well as on inhibitory interneurons (in particular, GABAergic interneurons of the cortex-like structures). The distribution of the 5-HT2 receptor family has been studied more extensively for 5-HT2A receptor subtype, especially in the rat basolateral amygdala (Figure 3). In the microcircuits of the rat deep nuclei, the 5-HT2A receptor is located on both pyramidal and non-pyramidal neurons. The non-pyramidal neurons containing this receptor express PV and SOM (McDonald and Mascagni, 2007). As previously reported, the PV-IR interneurons innervate the perisomatic domain (cell body and proximal dendrites) of pyramidal cells (Muller et al., 2006). Moreover, these interneurons are connected by gap junctions and

![Diagram of the main extra-amygdaloid and intra-amygdaloid connections in the rat. For abbreviations see Table 1.](image-url)
constitute an inhibitory network which synchronizes the firing of pyramidal cells (Woodruff and Sah, 2007). Interestingly, most of the pyramidal neurons form intimate synapse-like contacts with the somata and dendrites (especially proximal dendrites) of the PV–IR interneurons (McDonald et al., 2005), in this way, constituting a reciprocal perisomatic connection which may be important in modulating the synchronized rhythmic activity associated with the formation of emotional memories (Paré and Collins, 2000; Paré et al., 2002; Raimie et al., 2006). In the rat basolateral amygdala, SOM–IR interneurons innervate the distal dendritic domain of pyramidal cells and could modulate synaptic mechanisms related to emotional learning, including fear conditioning (Paré et al., 2002; Muller et al., 2007a). Since the 5-HT2A receptor is located on PV–IR and SOM–IR interneurons, this receptor subtype could play an important role in the formation of emotional memories.

### 5-HT2 RECEPTOR FAMILY AND AMYGDALA-MEDIATED BEHAVIOR

The involvement of the 5-HT2 receptor family in numerous amygdala-mediated behavioral and physiological effects has been described in several reports. This receptor family plays a crucial role, especially in fear and anxiety. Local infusion of ketanserin (a 5-HT2 receptor family antagonist) induces an anxiolytic effect in the conflict test (Hodges et al., 1987). Microinjections of nefazodone (a 5-HT2 receptors antagonist) into the basolateral nucleus of the rat amygdala enhances the aversive responses induced by NMDA activation of the neural substrates of aversion in the inferior colliculus (Maisonnette et al., 2000). In different mouse models of anxiety, the 5-HT2A receptor mediates different anxiolytic-like effects (Dhonnchadha et al., 2003a,b). Moreover, bilateral injections of ketanserin (a 5-HT2A and 5-HT2C receptors antagonist) into the rat basolateral/medial amygdala produces an anxiogenic profile in an elevated plus-maze (Zangrossi and Graeff, 1994).

The 5-HT2A receptor is also implicated in kindling development from the rat amygdala since the subcutaneous injection of DOI, an agonist of 5-HT2A/2C receptors, facilitates kindling development and reduces the number of amygdaloid stimulations necessary to obtain generalized seizures (Wada et al., 1997).

It is known that direct or indirect projections from the central nucleus of the amygdala to the paraventricular nucleus of the hypothalamus mediate a stress response. In vivo microdialysis studies have demonstrated that there is an increase in serotonin release in the amygdala during stress (Kawahara et al., 1993). Accordingly, the 5-HT2A receptor located in the central nucleus of the rat amygdala is able to activate the hypothalamo-pituitary-adrenocortical axis (Feldman et al., 1998). Finally, in the rat basolateral amygdala, the 5-HT2A receptor-mediated serotoninergic facilitation of GABAergic synaptic transmission is impaired by stress (Jiang et al., 2008).

The 5-HT2B receptor is also involved in amygdala-mediated behavior. In fact, the activation of this receptor subtype causes anxiolysis in social interaction tests in the rat (Duxon et al., 1997b).

### CONCLUSIONS

The present review reported that the 5-HT2 receptor family plays a crucial role in regulating the activity of amygdalar microcircuits and projections. In fact, as in the cerebral cortex and the hippocampal regions (Williams et al., 1997; Hamada et al., 1998; Jakab and Goldman-Rakic, 1998, 2000; Corne-Hébert et al., 1999; Clemett et al., 2000; Xu and Pandey, 2000; Jansson et al., 2001; Miner et al., 2003; Lüttgen et al., 2004; Bombardi, 2012), excitatory as well as inhibitory neurons in the rat amygdala express the 5-HT2 receptor family. Nevertheless, the exact role of the 5-HT2 receptor family in the modulation of amygdala activity is still poorly understood and requires additional study. In this way, detailed knowledge of the cellular mechanism underlying the modulation of amygdalar activity mediated by the 5-HT2 receptor family could provide valuable information for better understanding the pathogenesis of affective disorders and for utilizing a more specific pharmacological treatment.

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