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What is the amygdala?

Larry W. Swanson and Gorica D. Petrovich

'Amygdala' and 'amygdalar complex' are terms that now refer to a highly differentiated region near the temporal pole of the mammalian cerebral hemisphere. Cell groups within it appear to be differentiated parts of the traditional cortex, the claustrum, or the striatum, and these parts belong to four obvious functional systems – accessory olfactory, main olfactory, autonomic and frontotemporal cortical. In rats, the central nucleus is a specialized autonomic-projecting motor region of the striatum, whereas the lateral and anterior basolateral nuclei together are a ventromedial extension of the claustrum for major regions of the temporal and frontal lobes. The rest of the amygdala forms association parts of the olfactory system (accessory and main), with cortical, claustral and striatal parts. Terms such as 'amygdala' and 'lenticular nucleus' combine cell groups arbitrarily rather than according to the structural and functional units to which they now seem to belong. The amygdala is neither a structural nor a functional unit.

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SLICES THROUGH THE TEMPORAL POLE of the human cerebral hemispheres reveal an almond-shaped mass of gray matter that Burdach[1] discovered and called the amygdalar nucleus in the early 19th century (Fig. 1). Starting about 50 years later, the microscopic examination of histological tissue sections began to reveal more and more structural differentiation in the amygdala; and the extent of its outer border, and number and classification of its subdivisions, remain controversial today. In this article, we present a model of amygdalar architecture based on recent embryological, neurotransmitter, connectional and functional data. When placed in the context of cerebral hemisphere architecture as a whole,

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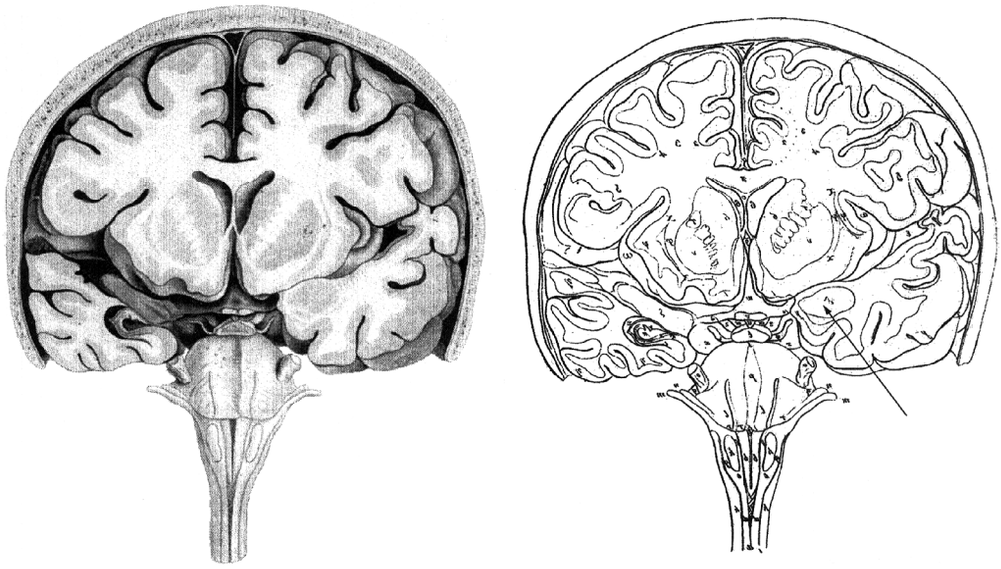

Fig. 1. ***The first illustrations of the 'amygdalar nucleus' (Mandelkern), in the human cerebral hemisphere.*** *An arrow has been added to the outline drawing on the right to indicate the amygdalar nucleus as drawn by Burdach. Comparison with a standard modern textbook (see Figs 66 and 92 in Ref. 2) shows that Burdach was referring to the basolateral complex. Later workers added adjacent olfactory cortex, and the medial and central nuclei, to form the 'amygdalar complex', which has been extended recently to include the bed nuclei of the stria terminalis (BST) and parts of the substantia innominata.* Reproduced, with permission, from Ref. 1.

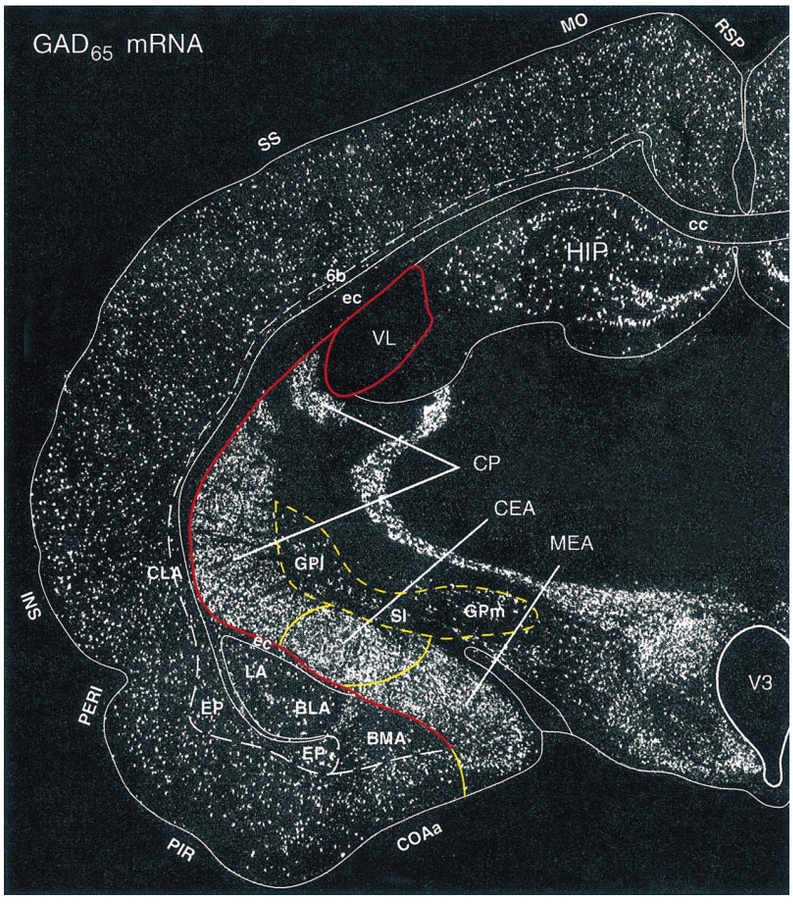

Fig. 2. ***The distribution of glutamic acid decarboxylase (GAD_{65})-expressing neurons in the rat forebrain.*** *This low-power photomicrograph of a transverse section through the left half of the rat forebrain shows the distribution of GAD_{65}-expressing neurons, which are especially dense in the caudoputamen and central nucleus of the amygdala (CEA), and to a somewhat lesser extent in the medial nucleus of the amygdala (MEA). The red line extending ventrally from the lateral ventricle, just deep to the external capsule, indicates the location of the obliterated lateral ventricle (see Fig. 3). Yellow lines outline different parts of the basal nuclei (ganglia). See text for details and Box 1 for abbreviations.* In situ *hybridization, darkfield illumination of an autoradiograph.*

the results suggest that, however defined today, 'amygdala' and 'amygdalar complex' refer to an arbitrarily defined set of cell groups.

Historical background

Meynert's claim in 1867 that the amygdala of Burdach is a ventral, temporal lobe extension of the claustrum (according to Meynert the deepest layer of cortex)[3] sparked a more than 50 year controversy about how to classify the amygdala in terms of basic parts of the cerebral hemisphere (telencephalon, endbrain). Equally distinguished neuroanatomists soon proposed, instead, that the amygdala is part of the lenticular nucleus (a gross anatomical term for the globus pallidus and putamen – two different cell groups in the basal nuclei or ganglia, rather than in the cortex), and observed that the amygdala is rimmed ventrally by olfactory cortex of the piriform lobe[4]. In 1923, J.B. Johnston[5] introduced the fundamental description of amygdalar structure in widest use today, based on detailed analysis of comparative vertebrate material. He proposed that the amygdala is divided into a primitive group of nuclei associated with the olfactory system (central, medial and cortical nuclei, and nucleus of the lateral olfactory tract), and a phylogenetically new group of nuclei (lateral and basal).

Interest in classifying the amygdala and its various parts in terms of cerebral hemisphere subdivisions and phylogeny waned in the last 50 years as attention shifted to determining input/output relationships of each neuronal group, and the neurotransmitter/receptor systems contained within these pathways. Currently available data are much more extensive and reliable than those available to Johnston, and when taken together suggest that the amygdala is a heterogeneous region, one part of which is a specialized ventromedial expanse of the striatum (central and medial nuclei, and anterior area), a second part of which is caudal olfactory cortex (nucleus of the lateral olfactory tract, cortical nucleus, and postpiriform and piriform–amygdalar areas), and a third part of which is a ventromedial extension of the claustrum (lateral, basal and posterior nuclei). Major evidence for this view will now be considered. The structural nomenclature is based on literature cited elsewhere[6].

Neurotransmitter evidence: the central and medial nuclei

Immunohistochemistry for GABA (Refs 7,8) and *in situ* hybridization for glutamic acid decarboxylase[9] (GAD), the enzyme converting glutamate to GABA, reveals a characteristic, very dense band of labeled neurons that extends ventrally and uninterrupted through the caudoputamen, the central amygdalar nucleus (CEA) and then the medial amygdalar nucleus (MEA), where it ends along the ventromedial edge of the cerebral hemisphere (Fig. 2). In contrast, other

parts of the amygdala contain only scattered GABA neurons, most of which are probably involved exclusively in the formation of local circuits[10]. This anatomical evidence, together with less complete electrophysiological data[11], suggests that the extrinsic projections of the CEA and MEA are predominantly GABAergic (like the dorsally adjacent caudoputamen), whereas the major extrinsic connections of the remaining amygdala are not, but instead are presumably glutamatergic. This supports the general conclusion that part of the amygdala is striatal (CEA and MEA) and the rest cortical.

The suggestion that the CEA and MEA form caudoventral differentiations of the striatum is supported by histochemical evidence (1) that most amygdalar neuropeptide expression is found in them[12,13], (2) that many of the same peptides are also expressed in other striatal regions including the caudoputamen (dorsal striatum), nucleus accumbens and olfactory tubercle (ventral striatum), and lateral septum (medial striatum)[14,15], and (3) that limited peptide expression in the basolateral complex is restricted mostly to interneurons[10] rather than to projection neurons. Topographically, the MEA lies just caudal to the olfactory tubercle, which is now regarded as a part of the ventral striatum with GABAergic projection neurons[16]. As we shall see below, the olfactory tubercle receives a direct input from the main olfactory bulb, whereas the MEA receives a direct input from the accessory olfactory bulb[17]. Based on a similar group of arguments, we would also include the anterior amygdalar area (AAA) within the striatal group, along with the bed nucleus of the accessory olfactory tract, which could easily be a tiny ectopic part of the MEA.

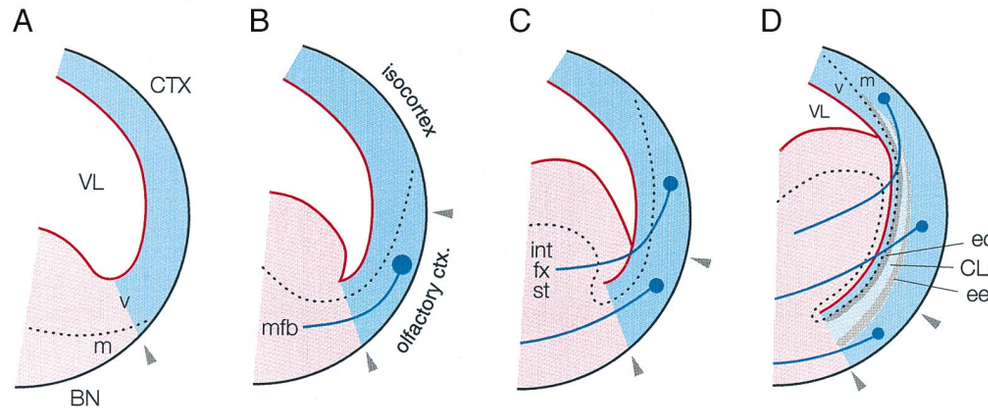

Fig. 3. ***Schematic drawings to illustrate basic features of telencephalic vesicle differentiation in the early embryo at mid-rostrocaudal levels.*** *Mantle layer formation begins ventromedially in the ventricular ridges (the partial ridge shown in* **A** *in pink, adjacent to the cortical part of the vesicle, is the striatal ridge), and then gradually extends dorsally through presumptive cortical regions. Rapid growth of the ventricular ridges (forming the basal ganglia) begins obliterating ventral regions of the lateral ventricle. Ventral neurons send axons directly through the basal nuclei as a component of the medial forebrain bundle* **(B)**, *whereas more dorsal neurons* **(C,D)** *send their descending axon across the obliterated lateral ventricle into the internal capsule (lateral forebrain bundle), as well as the stria terminalis and fornix. The cortical plate is separated from the external capsule by the incipient extreme capsule (and its extensions), with the claustrum lying between* (D). *See Box 1 for abbreviations.* Adapted from Ref. 22.

Considerable evidence now indicates that most, if not all, cortical projection neurons (pyramidal cells) use glutamate as a neurotransmitter (with peptide expression concentrated in interneurons), whereas descending projections of the striatum (and of the globus pallidus) use GABA as a neurotransmitter[14]. If this is true, it implies that non-GABA-projecting regions of the amygdala are part of the cortex.

Box 1. Abbreviations

AAA, anterior amygdalar area; ACB, nucleus accumbens; AIp, agranular insular area, posterior part; alv, alveus; amc, amygdalar capsule; ANS, brainstem autonomic centers; AOB, accessory olfactory bulb; AUDv, ventral auditory areas; AV, anteroventral nucleus thalamus; BLAa,p, basolateral nucleus amygdala, anterior, posterior parts; BMAa,p, basomedial nucleus amygdala, anterior, posterior parts; BN, basal nuclei (ganglia); BSTpr, bed nuclei stria terminalis, posterior division, principal nucleus; CA3, field CA3, Ammon's horn; cc, corpus callosum; CEA, central nucleus amygdala; CLAvm, claustrum, ventromedial part; COAa,pl,pm, cortical nucleus amygdala, anterior part, posterior part, lateral zone, posterior part, medial zone; CP, caudoputamen; cpd, cerebral peduncle; CTX, cerebral cortex; CTXolf, olfactory cortex, amygdalar component; d, medial hypothalamic defensive behavior system; DA, dopamine; ec, external capsule; ECT, ectorhinal area; ee, extreme capsule; ENTl, entorhinal area, lateral part; EPd,v, endopiriform nucleus, dorsal, ventral parts; fi, fimbria; FS, fundus of the striatum; ft, claustrum, frontotemporal component; FT, frontotemporal components of amygdala; fx, columns of the fornix; GABA, gamma-aminobutyric acid; GLU, glutamate; GPl,m, globus pallidus, lateral, medial segments; HIP, hippocampal region; i, medial hypothalamic ingestive behavior system; IA, intercalated nuclei amygdala; ILA, infralimbic area; INS, insular region; int, internal capsule; LA, lateral nucleus amygdala; LHAcl, lateral hypothalamic area, caudolateral part; lot, lateral olfactory tract; m, mantle layer (neural tube); MDm, mediodorsal nucleus thalamus, medial part; MEA, medial nucleus amygdala; mfb, medial forebrain bundle; MO, motor areas; MOB, main olfactory bulb; MRN, mesencephalic reticular nucleus; NLOT, nucleus of the lateral olfactory tract; olf, claustrum, olfactory component; OLF, olfactory components of amygdala; opt, optic tract; PA, posterior nucleus amygdala; PAA, piriform–amygdalar area; PAGvl, periaqueductal gray, ventrolateral part; PAL, pallidum; PERI, perirhinal area; PIR, piriform area; PRN, pontine reticular nucleus; PVT, paraventricular nucleus thalamus; r, medial hypothalamic reproductive behavior system; rf, rhinal fissure; RSP, retrosplenial area; RT, reticular nucleus thalamus; SI, substantia innominata; SNc, substantia nigra, compact part; SS, somatosensory areas; SSs, supplemental somatosensory area; st, stria terminalis; STN, subthalamic nucleus; STR, striatum; TEv, ventral temporal association areas; THpg, thalamus, perigeniculate region (includes medial geniculate complex, posterior limiting nucleus, and parvicellular subparafascicular nucleus); TR, postpiriform transition area; v, ventricular layer (neural tube); V3, third ventricle; VAL, ventral anterior-lateral complex thalamus; VISC, visceral area; VL, lateral ventricle; VM, ventral medial nucleus thalamus; VPL, ventral posterolateral nucleus thalamus; VPM, ventral posteromedial nucleus thalamus; ZI, zona incerta.

Olfactory cortex of the caudal piriform lobe

It now seems clear that the cortical amygdalar 'nucleus' (COA) and the 'nucleus' of the lateral olfactory tract (NLOT) are in fact distinct areas of the olfactory cortex (forming the caudal end of the piriform lobe), partly because they lie on the surface of the hemispheres ventral to the rhinal sulcus and display a laminated organization with radially oriented pyramidal cells[18], and partly because they lie caudally adjacent to the piriform area and receive differential inputs from the main and accessory olfactory bulbs. Like the piriform area, the NLOT, anterior cortical nucleus (COAa) and posterolateral cortical nucleus (COApl) receive inputs from the main olfactory bulb, whereas the posteromedial cortical nucleus (COApm) receives an input from the accessory olfactory bulb[17]. Thus, traditional names for these parts of the amygdala are misnomers if they are cortical areas rather than nuclei.

Based on topographic considerations, two adjacent cortical areas should probably also be included within the amygdalar olfactory cortical group. One is the postpiriform transition area (TR), which has often been included in the entorhinal area. It lies adjacent to the COA and also receives a massive input from the main olfactory bulb[17], and recent *Phaseolus vulgaris*-leucoagglutinin (PHAL) analyses indicate that it does not project to the dentate gyrus, but instead generates a massive input to the CEA (G.D. Petrovich, PhD thesis, University of Southern California, 1997; S. Shammah-Lagnado, pers. commun.). The other is the piriform–amygdalar area (PAA), which also lies adjacent to the COA, receives a dense main olfactory bulb input, and projects to several parts of the amygdala (Ref. 19; L.W. Swanson and G.D. Petrovich, unpublished observations). Thus extended, the cortical division of the amygdala contains the COApm (accessory olfactory bulb input), as well as the rest of the COA, the NLOT, and areas TR and PAA (main olfactory bulb input).

The basolateral complex and the claustrum

This leaves us with the basolateral complex, which is the most problematic in terms of classification; it corresponds to the region originally called amygdala by Burdach, and identified as a temporal extension of the claustrum by Meynert and others in the last century. Based on embryological considerations and adult topographic relations, we suggest that Meynert was correct in his assignment of what are now referred to as the lateral and basal nuclei to the deepest layer of cortex, along with the dorsally adjacent claustrum proper (and endopiriform 'nucleus').

Early morphological features and homeobox gene expression patterns in the developing telencephalic vesicle clearly distinguish a dorsal presumptive cortical region from a ventral (or basal) presumptive nuclear region[20,21] (Fig. 3). The claustrum proper is the deepest part of the insular cortex. During embryogenesis its neurons are separated by an incipient fiber layer known in the adult as the extreme capsule. Thus, the claustrum proper may form at least part of the subplate or deepest layer of the insular cortex, between the external and extreme capsules.

The endopiriform nucleus, which is commonly described as a ventrolateral, olfactory, extension of the claustrum, almost certainly forms the deepest layer of the piriform area, and it too is separated from more superficial layers by a very broad fiber system that has not been named but appears to be a ventrolateral extension of the extreme capsule system. We suggest that the basolateral complex forms at least part of the subplate layer for regions of the temporal, piriform and perhaps frontal lobes. This deepest layer is separated from more superficial layers of cortex by a fiber lamina often mis-identified as the external capsule[6] when it is really a component of the extreme capsule system that we have recently called the amygdalar capsule[23] (Fig. 4).

The topographic relationship of the claustrum proper and endopiriform nucleus to the insular cortex and piriform area, respectively, is obvious. However, the relationship of basolateral complex cell groups to other regions of the cortical mantle is not always so clear in the adult, partly because fundamental structural relationships become extremely distorted (stretched and curved) near the temporal pole during mantle layer differentiation. Nevertheless, the lateral nucleus (LA) does lie deep to ventral temporal cortex caudally (Fig. 4D), and the basomedial (BMA) and posterior (PA) nuclei clearly lie deep to amygdalar olfactory cortex.

Recent detailed morphological analysis indicates that neurons in the basolateral amygdala share many features in common with cortical neurons[10]. Unfortunately, however, a great deal more needs to be learned about the morphology and connections of neurons in the claustrum proper (and endopiriform nucleus) before its relationship to the basolateral amygdala can be considered to be established.

The medially and dorsally extended amygdala

Alheid and Heimer[16] have argued for extending the amygdala both medially and dorsally. First, they suggest that because the amygdala innervates the bed nuclei of the stria terminalis (BST) and intervening regions of the substantia innominata (ventral pallidum), and because the latter two regions share with the amygdala similar patterns of descending projections, the BST and caudodorsal regions of the substantia innominata belong to the (extended) amygdala as well (but see Ref. 24). Somewhat indirect embryological evidence suggests that the BST are derived from the pallidal ridge along with the adjacent substantia innominata[20], so that this division would be pallidal. Moreover, they regard scattered neurons along the length of the stria terminalis to a point just before it enters the BST as a dorsally extended part of the amygdala. On embryological grounds[21], these cells appear to form a dorsal extension of the MEA along the sulcus terminalis, and would thus be striatal according to the present model.

Organization of major amygdalar connections

The evidence reviewed thus far, together with the connections we shall now review, suggest the arrangements of amygdalar cell groups illustrated in Figs 4 and 5. Structurally, these cell groups are differentiated parts of the striatum, cerebral cortex and claustral complex, whereas functionally they belong to the olfactory, autonomic and frontotemporal cortical systems.

The literature on amygdalar connections is vast, complex, contradictory and incomplete, and cannot be reviewed thoroughly here. Instead, we shall focus on major pathways established with reliable methods

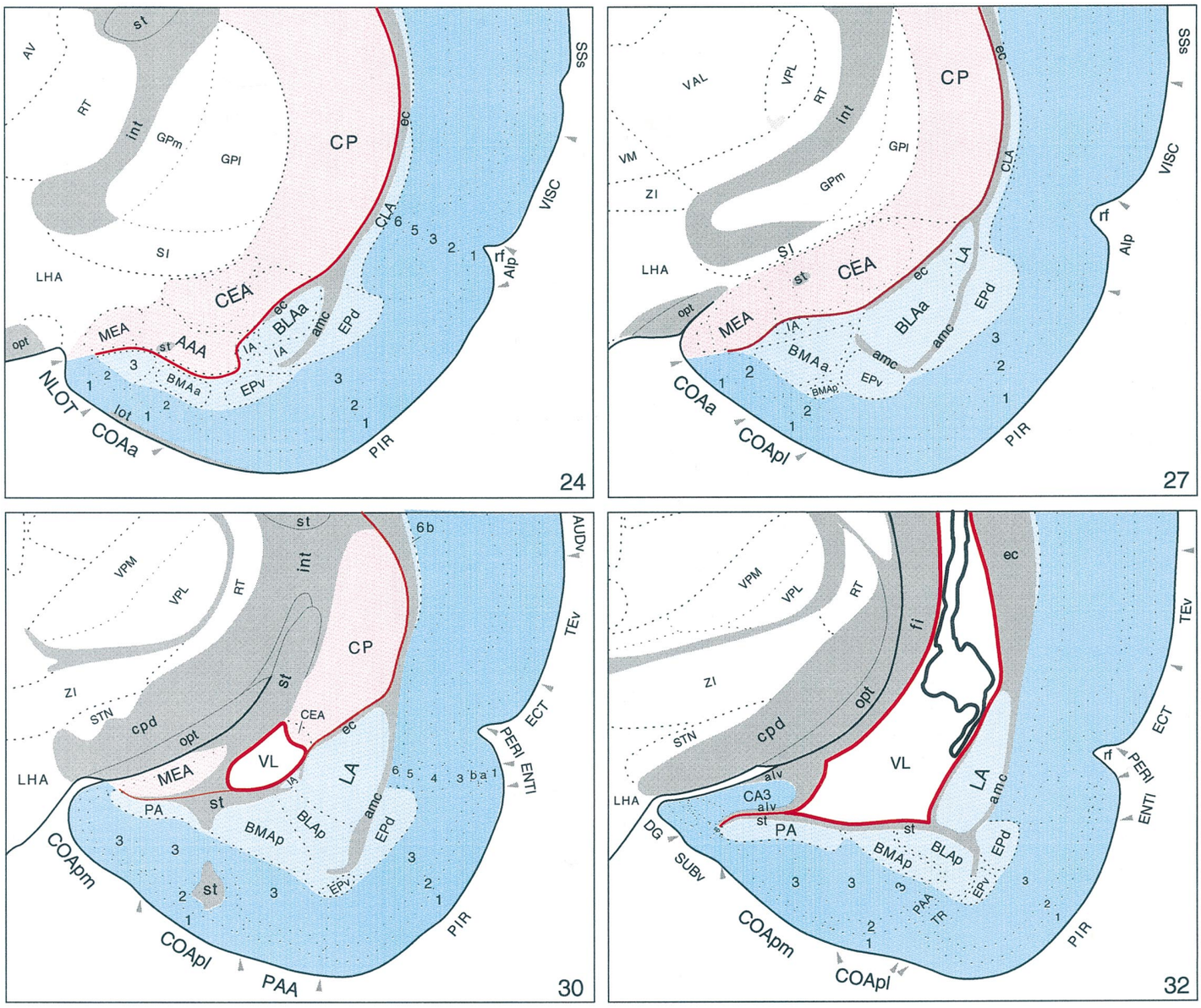

Fig. 4. ***The arrangement of amygdalar and adjacent cell groups in the adult rat.*** *The drawings of transverse sections (right side of the brain) are modified from Swanson[23], with level numbers indicated. Assignment to cerebral hemisphere subdivisions is based on developmental, neurotransmitter and connectional evidence reviewed in the text. Arranged from rostral (24) to caudal (32). See Box 1 for abbreviations.*

in the rat that clarify amygdalar circuitry at the systems level – especially in view of the subdivisions proposed in Fig. 5. It is especially important to consider whether putative cortical, claustral and striatal regions of the amygdala display basic connectional features of accepted cortical, claustral and striatal regions, as well as how they may be specialized or differentiated. All of the amygdalar projections cited here have been confirmed in a collection of about 125 PHAL experiments with injections centered in all of the amygdalar cell groups, except the NLOT and intercalated nuclei (Refs 24–27; G.D. Petrovich, PhD thesis, University of Southern California, 1997; unpublished observations).

The accessory olfactory system component

The most obvious place to start is with the MEA and COApm (Fig. 6A), which are the only major projection fields of the accessory olfactory bulb[17]. If the accessory olfactory bulb is the primary sensory cortical area for pheromonal information (as Brodmann[28] held, in principle), then the present interpretation indicates that it projects in turn to the striatum (MEA) and to another cortical area (COApm), which might be involved in the perception of pheromonal stimuli. This is similar to projections from the main olfactory bulb to the rostroventral striatum (olfactory tubercle) and the rest of the cortical amygdalar division[17]. It is also similar to connections of the primary visual area, except that here optic nerve information is transmitted through the lateral geniculate nucleus rather than directly to the primary sensory cortical area – which, in the case of area 17, projects to the dorsal striatum and to other visual cortical areas. This component is completed with the PA, which shares massive bidirectional connections with, and lies just deep to, the COApm, and also has bidirectional connections with the MEA (Refs 24,25). Thus, local connections include bidirectional pheromonal pathways between cortical, claustral and striatal parts.

Other major inputs to the accessory olfactory component arise in the main olfactory system[29], in the

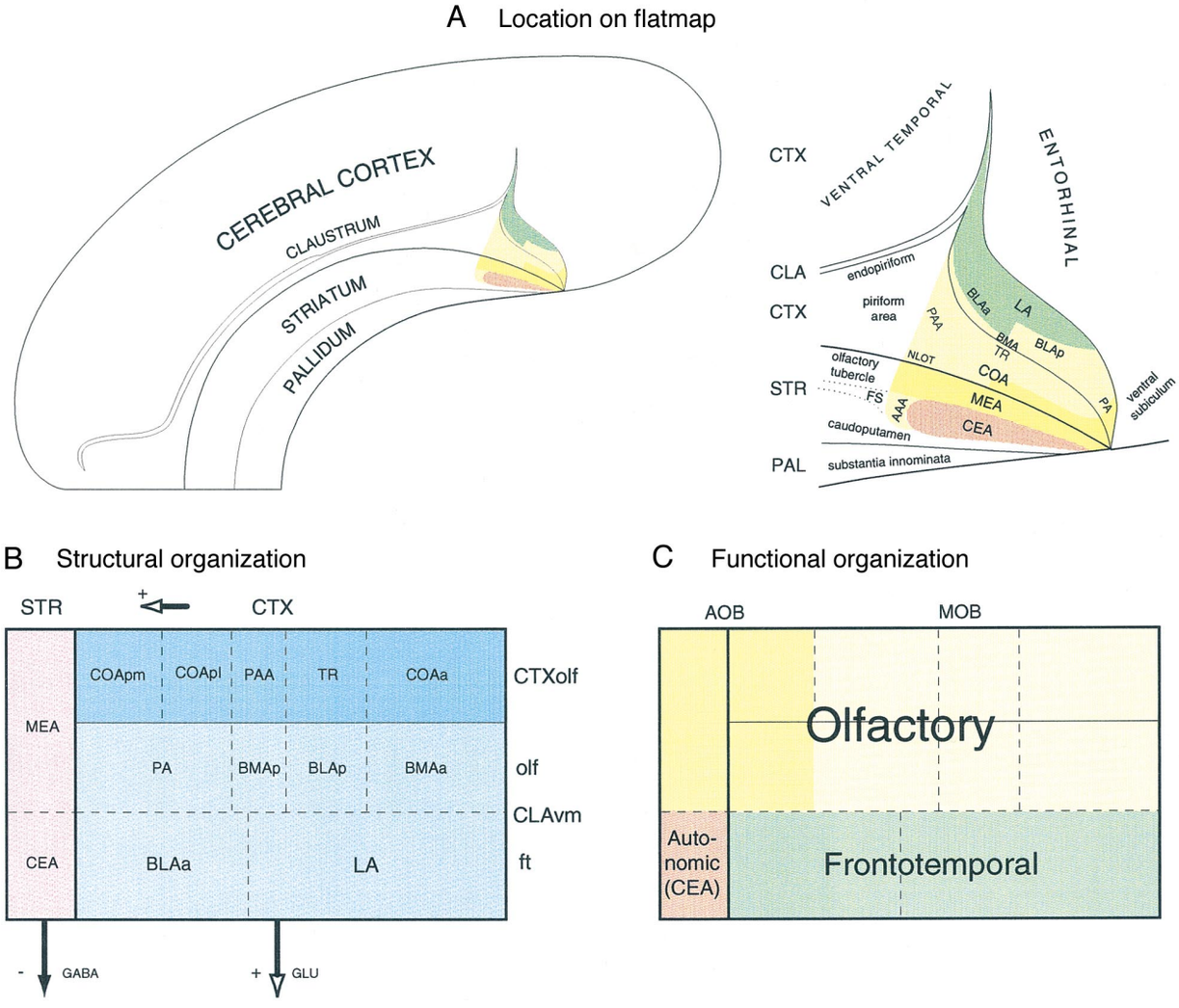

Fig. 5. ***Schematic views of rat amygdalar organization.*** **(A)** *The general location of the amygdala* (left) *and amygdalar subdivisions* (right), *displayed on a flat map of the rat cerebral hemisphere.* Adapted from Swanson[23]. **(B)** *A schematic view of amygdalar parts based on structural criteria (Figs 3 and 4). Projections of the cortical parts apparently use glutamate as a neurotransmitter, whereas striatal parts apparently use GABA.* **(C)** *A schematic view of amygdalar parts based on functional criteria reviewed in the text. For clarity, the nucleus of the lateral olfactory tract, anterior amygdalar area, and intercalated nuclei have been omitted from* B *and* C. *See Box 1 for abbreviations.*

medial prefrontal[30,31] and agranular insular[31] cortical regions (which process visceral, olfactory and gustatory information), in the ventral subiculum of the hippocampal formation[32,33], and in the medial hypothalamus[34,35]. Obviously, the accessory olfactory component of the amygdala does not deal exclusively with unimodal sensory information. Instead, it is dominated by pheromonal information (from the vomeronasal organ and nerve), and its cortical parts are probably more accurately referred to as 'pheromonal association'.

The accessory olfactory component of the amygdala has four major known outputs. One is to the cerebral cortex (back to essentially the same olfactory, prefrontal, insular and hippocampal areas that project to it), the second is to differentiated regions of the striatum (the nucleus accumbens and CEA), the third is to the medial hypothalamus, and the last is to the medial part of the mediodorsal thalamic nucleus[24,25,29,36,37]. The innervated region of the mediodorsal nucleus projects back to medial prefrontal and agranular insular cortical areas[38], whereas accessory olfactory amygdalar projections to the medial hypothalamus are especially prominent and selectively innervate parts of three systems that control the expression of partly innate reproductive, defensive and ingestive behaviors[39]. This projection is modulated by a 'relay' through the principal nucleus of the BST (Ref. 13).

The main olfactory system component

This consists of five distinct cortical areas, each with an apparently associated part of the claustral complex with which it shares connections (Fig. 6B). The cortical fields are heavily interconnected (association projections), whereas the claustral parts are not (G.D. Petrovich, PhD thesis, University of Southern California, 1997).

The major input to the cortical areas is the main olfactory bulb[17]. However, the cortical areas also receive inputs from other parts of the main olfactory system and the accessory olfactory system[24–26,29,32], and from medial prefrontal[30–32], agranular insular[31,32], perirhinal[40] and hippocampal cortical areas[32,33,41]. In addition, the COAa/BMAa receive ascending inputs from the parabrachial nucleus[42] (visceral and possibly gustatory information) and caudal thalamic regions in and near the medial geniculate nucleus[43,44] (possibly auditory and somatosensory information). Analogous to the accessory olfactory component, this component of the amygdala should probably be regarded as 'main olfactory association cortical areas' (including their claustral components).

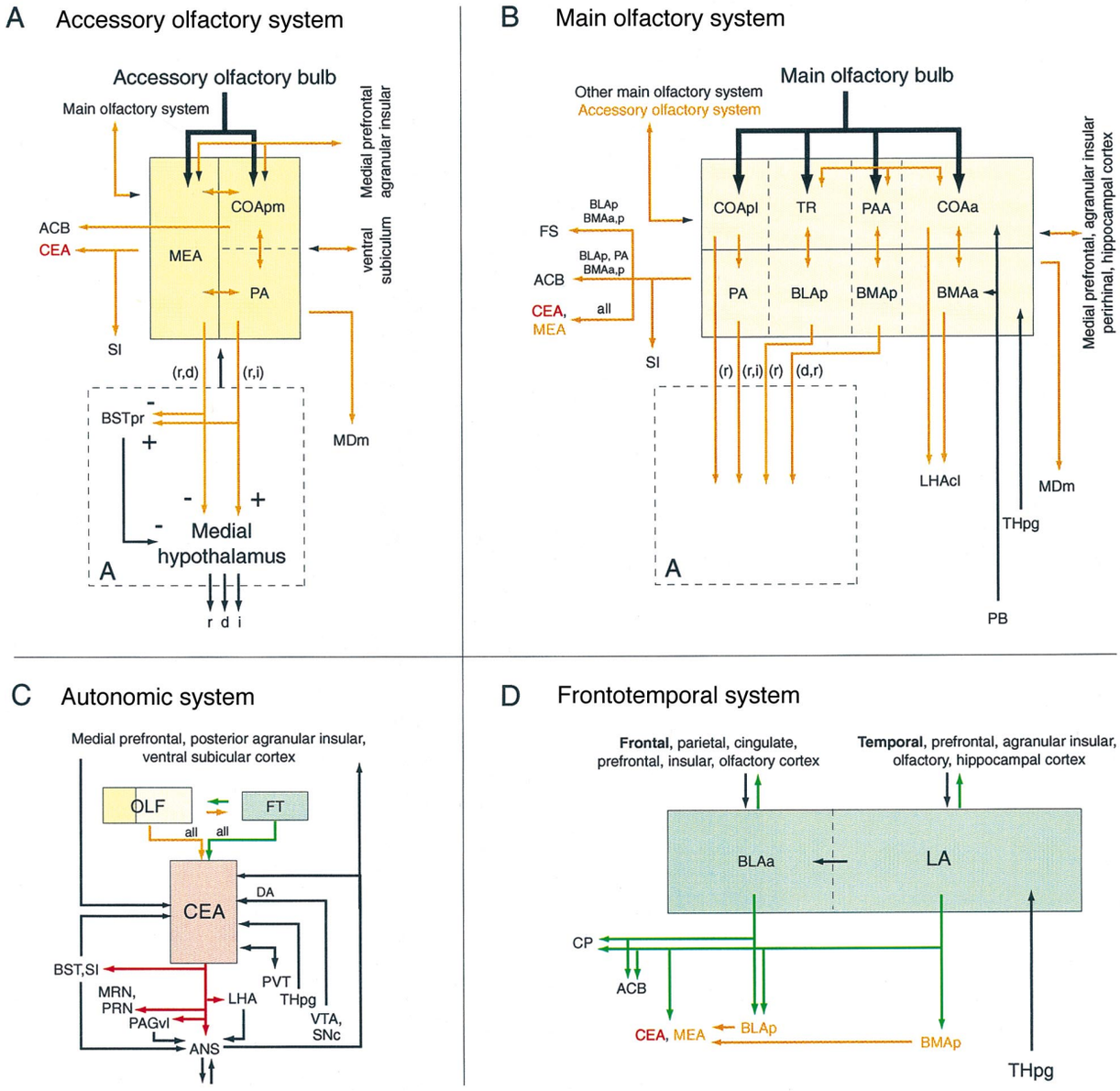

Fig. 6. ***Major neural inputs and outputs of the four functional systems associated with the amygdala.*** *Note especially that the accessory* **(A)** *and main* **(B)** *olfactory systems project topographically to reproductive, defensive and ingestive behavior systems in the medial hypothalamus, and that the central nucleus* **(C)** *projects to autonomic centers in the brainstem, while the frontotemporal system* **(D)** *projects widely to the striatum, and it does not seem to innervate directly hypothalamic behavioral systems. See text for details and Box 1 for abbreviations.*

The outputs of the main olfactory component are similar to those from the accessory component. They include projections: (1) back to regions of cortex from which it receives inputs[25,26,29,45–47]; (2) to the striatum[19,25,26,32,36,47–49]; (3) to the pallidum (BST and substantia innominata)[25,26,36]; (4) to the medial mediodorsal nucleus[25,26,37,45]; and (5) to the hypothalamus[25,26,36]. Specifically, in the striatum, all parts of this component project to both the MEA and CEA; the BMAa, BMAp and BLAp also project to the striatal fundus; and the BLAp and BMAp also project to the nucleus accumbens. In the hypothalamus, the COApl and PA, BMAp and BLAp innervate selectively the three medial hypothalamic drive controllers mentioned above, whereas the COAa and BMAa project directly to a caudolateral region of the lateral hypothalamic area.

The autonomic system component

We suggest that the CEA is that region of striatum specialized for modulating autonomic motor outflow because it has characteristic brainstem projections to autonomic-related centers, including the dorsal motor nucleus of the vagus nerve, nucleus of the solitary tract and parabrachial nucleus[50] (Fig. 6C), as well as to regions of the lateral hypothalamic area (Ref. 50; G.D. Petrovich, PhD thesis, University of Southern California, 1997) and periaqueductal gray[50,51] thought to modulate autonomic responses, and a region of the pontine reticular nucleus thought to modulate acoustic startle[52], nictitating membrane[53] and perhaps other reflexes. Obviously, the dorsal striatum (caudoputamen) is specialized for modulating somatic motor outflow.

The CEA receives a wide range of sensory information from descending cortical inputs and ascending thalamic and brainstem inputs (including a dopaminergic input from the ventral midbrain[54]). More specifically, the CEA receives inputs from main and accessory olfactory systems (including all those in the amygdala)[19,24–26,29,32,49], from medial prefrontal[30–32], agranular insular[31,32] and ventral subicular[32,33] cortical

regions, from the nucleus of the solitary tract[55] and parabrachial nucleus[42] (probably involving visceroceptive, nociceptive and gustatory information), and from the perigeniculate thalamus (probably transmitting somatosensory and auditory information[43,44]). In addition, the CEA receives inputs from the thalamic paraventricular nucleus[56] (which receives massive inputs from the hypothalamus, including the suprachiasmatic nucleus[39]) and from the LA and BLAa, to be considered next.

The frontotemporal cortical component

This leaves us with the LA and BLAa, which we suggest together form a ventromedial extension of the claustrum related most closely with the temporal and frontal lobes (Fig. 6D). Both cell groups also share bidirectional connections with the olfactory system and with the prefrontal and insular regions[31], whereas the LA is distinguished by such connections with temporal and hippocampal regions (Refs 40,57; G.D. Petrovich, PhD thesis, University of Southern California 1997; unpublished observations) and the BLAa is distinguished by such connections with somatosensory-motor areas in the frontal and parietal lobes[58–60].

The striatal projections of this component are unusual in that both parts innervate the caudoputamen as well as the nucleus accumbens (Refs 36,48,60; G.D. Petrovich, PhD thesis, University of Southern California, 1997). The LA also innervates the CEA directly (as well as indirectly via the BMAp and BLAp)[19,49], whereas the BLAa is atypical in the sense that it is the only part of the amygdala that has little if any direct projection to the CEA (G.D. Petrovich, PhD thesis, University of Southern California, 1997).

This component of the amygdala is also unusual in that it sends little if any projection through the stria terminalis. Thus, it generates little if any direct projection to the BST and hypothalamus.

The role of connections between the LA and CEA in at least some aspects of fear conditioning to auditory conditioning stimuli has been reviewed recently[19]. In this context, it is interesting that Penfield's human patients reported the experience of fear only when inferior regions of their temporal lobes were stimulated electrically[61].

What is the amygdala?

However one chooses to define the precise borders of the amygdala, it is a structurally and functionally heterogeneous region of the cerebral hemispheres. We have attempted to classify the various parts of the amygdala (as currently understood) in terms of larger cerebral hemisphere divisions, to provide a reasonable list of parts in each division, and to review the major neural inputs and outputs of the various parts. Overall, the evidence suggests that it is necessary to ask whether the concept of a structurally and functionally defined amygdala is indeed valid, or whether the concept is hindering attempts to understand general principles of telencephalic architecture by imposing an arbitrary classification on heterogeneous structures that belong to different functional systems.

We suggest that the latter is the case. First, a major part of the amygdala is an integral component of the olfactory system. Along with the accessory olfactory bulb, the MEA, COApm and PA form the core of the vomeronasal sensory-motor system, which is sexually dimorphic[62], whereas the rest of the COA, the NLOT, areas PAA and TR, and the BMA and BLAp are integral components of the main olfactory system. Second, the CEA is a specialized region of the striatum that projects to visceral centers in the brainstem. It receives inputs from prefrontal, insular, temporal and olfactory cortical areas, as well as from almost all other parts of the amygdala, from brainstem viscerosensory and nociceptive centers, and from parts of the caudal thalamus transmitting auditory and somatosensory information. Third, the LA and BLAa appear to form a ventromedial extension of the claustrum for large regions of the frontal and temporal lobes. It also projects to widespread, differentiated regions of the striatum, including the caudoputamen, nucleus accumbens and CEA.

This interpretation is broadly consistent with Johnston's original parcellation, except that his primitive group is now divided into an olfactory group or part, and an autonomic part (the CEA). The dynamics of information flow through the circuits outlined here by and large remain to be characterized. Furthermore, insufficient connectional data are available to specify with any certainty what homologies there may be among components of the basolateral complex (claustral division) in rats and primates[26,33].

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PERSPECTIVES ON DISEASE

Mutations in RNA: a first example of molecular misreading in Alzheimer's disease

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In the past decade, considerable progress has been made in the understanding of the neurodegenerative changes that occur in Alzheimer's disease (AD). Knowledge about this disease is based mainly on studies of inherited forms of AD, although most cases of AD are of the non-familial type. Recently, a novel type of mutation in 'vulnerable' dinucleotide repeats in messenger RNA was discovered in AD patients: in this type of mutation a mutated transcript is produced from a correct DNA sequence, a process that we call 'molecular misreading'. The resulting mutated '+1 proteins' are prominent neuropathological hallmarks of AD and they are present in most elderly non-demented people also. This suggests that the dinucleotide deletions in transcripts could be one of the earliest events in the neuropathogenesis of AD and an important factor in normal aging.

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IN THE ADULT mammalian nervous system, the proliferation of neurons is rare, except in the olfactory epithelium[1] and the hippocampal dentate gyrus of rodents[2]. In primates, neuronal proliferation is even more limited, apart from mitosis-associated mutations and site-specific recombinations[3,4]. Consequently, mutation rates in the neuronal genome are very low[5], and the capacity of neurons to broaden the phenotypic repertoire as is seen in lymphocytes[3], is reduced. However, modification of expression is possible by alternative splicing and mRNA editing[6]. Indeed, in the nervous system, substitutional mRNA editing has been reported, in which specific nucleotides in RNA are modified post-transcriptionally[7].

Some years ago, when investigating the presence of vasopressin (VP) precursor products that theoretically could not exist[8,9], we discovered a novel type of transcript variability in homozygous Brattleboro rats[10]. These rats suffer from hypothalamic diabetes insipidus as a result of a single-base germ-line mutation in the *VP* gene that encodes an aberrant VP precursor. Surprisingly, we found that an additional mutation (ΔGA) in their VP transcripts results in restoration of the wild-type reading frame and the synthesis of a functional VP protein that can enter the secretory pathway and undergo axonal transport[10,11]. Two sites of the dinucleotide deletion (ΔGA) were found that occurred preferentially in GAGAG motifs of the VP mRNA. Moreover, the mutation rate

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