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A Short History Of The 5-HT_{2C} Receptor:

From The Choroid Plexus To Depression, Obesity And Addiction Treatment

Jose M. Palacios¹, Angel Pazos², and Daniel Hoyer^{3,4,5}

1: Frontera Biotechnology SL, Barcelona, Spain.

2: Universidad de Cantabria, Instituto de Biomedicina y Biotecnología de Cantabria, CSIC-UC-IDICAN, CIBERSAM, Santander, Spain.

3: Department of Pharmacology and Therapeutics, School of Biomedical Sciences, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, Victoria 3010, Australia.

4: The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, 30 Royal Parade, Parkville, Victoria 3052, Australia.

5: Department of Chemical Physiology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA.

*Address correspondence and reprint requests to: d.hoyer@unimelb.edu.au

ABSTRACT

This paper is a personal account on the discovery and characterization of the 5-HT_{2C} receptor (first known as the 5-HT_{1C} receptor) over 30 years ago and how it translated into a number of unsuspected features for a G-protein coupled receptor (GPCR) and a diversity of clinical applications. The 5-HT_{2C} receptor is one of the most intriguing members of the GPCR superfamily. Initially referred to as 5-HT_{1C}R, the 5-HT_{2C}R was discovered while studying the pharmacological features and the distribution of [³H]mesulergine labelled sites, primarily in the brain using radioligand binding and slice autoradiography. Mesulergine (SDZ CU-085), was at the time best defined as a ligand with serotonergic and dopaminergic properties. Autoradiographic studies showed remarkably strong [³H]mesulergine-labelling to the rat choroid plexus. [³H]mesulergine-labelled sites had pharmacological properties different from at the time known or purported 5-HT receptors. In spite of similarities with 5-HT₂ binding, the new binding site was called 5-HT_{1C}, because of its very high affinity for 5-HT itself. Within the following ten years, the 5-HT_{1C}R (later named 5-HT_{2C}) was extensively characterized pharmacologically, anatomically and functionally: it was one of the first 5-HT receptors to be sequenced and cloned. The 5-HT_{2C}R is a G protein coupled receptor (GPCR), with a very complex gene structure. It constitutes a rarity in the GPCR family: many 5-HT_{2C}R variants exist, especially in humans, due to RNA editing, in addition to a few 5-HT_{2C}R splice variants. Intense research led to therapeutically active 5-HT_{2C} receptor ligands, both antagonists (or inverse agonists) and agonists: keeping in mind that a number of antidepressants and antipsychotics are 5-HT_{2C}R antagonists/inverse agonists. Agomelatine, a 5-HT_{2C}R antagonist is registered for the treatment of major depression. The agonist Lorcaserin is registered for the treatment of aspects of obesity and has further potential in addiction, especially nicotine/ smoking. There is good evidence that the 5-HT_{2C}R is involved in spinal cord injury-induced spasms of the lower limbs, which can be treated with 5-HT_{2C}R antagonists/inverse agonists such as cyproheptadine or SB206553. The 5-HT_{2C}R may play a role in schizophrenia and epilepsy. Vabicaserin, a 5-HT_{2C}R agonist has been in development for the treatment of schizophrenia and obesity, but was stopped. As is common, there is potential for further indications for 5-HT_{2C}R ligands, as suggested by a number of preclinical and/or genome wide association studies (GWAS) on depression, suicide, sexual dysfunction, addictions and obesity. The 5-HT_{2C}R is clearly affected by a number of established antidepressants/ antipsychotics, and may be one of the culprits in antipsychotic-induced weight gain.

Keywords: 5-HT_{2C} receptor, GPCR, GWAS, receptor autoradiography, in situ hybridization, species differences, human brain, RNA editing, receptor homomers, heteromers, depression, anxiety, obesity, smoking cessation, spinal cord injury, drug addictions, schizophrenia, suicide, mesulergine, agomelatine, lorcaserin, vabicaserin, sertindole.

THE EARLY DAYS: 1983-1988. 5-HT_{1C/2C} RECEPTORS CONTRIBUTE TO 5-HT RECEPTOR SUBTYPE AWARENESS:

The discovery of 5-HT_{2C} receptor took place more than 30 years ago, in the middle of a revolutionary period of change in receptor pharmacology (see Lefkowitz, 2004; Palacios et al. 2010). The realization that single entities such as neurotransmitters or hormones were acting through a multiplicity of receptors, which can each take additional forms either by splice or editing variants as is the case for the 5-HT_{2C} receptor was “new”, and as discovered later, became even more complex, with the notion of variable constitutive activity and eventually differential coupling or signalling bias. The concept of receptors was initially postulated in the early 1900's by Paul Ehrlich as “selected binding sites for chemotherapeutic agents” and evolved further as JN Langley formulated the concept of “receptive substances” (see, Bennett 2000).

For much of the 20th century, receptors were defined in functional assays based on responses collected in isolated tissues to chemical series and translated in pharmacological effects in animal models and from there extended to the therapeutic use of such new molecular entities. This concept is the basis for the development of still about half of the current therapeutic targets and for the discovery of innumerable drugs.

Despite many decades of receptor pharmacology and related drug discovery, the existence of receptors as actual molecular entities was still debated in the 70's. The introduction of radioligand binding and affinity labelling which led to the solubilization and purification of receptor proteins, e.g. in the labs of Jean Pierre Changeux and Robert Lefkowitz, (see Lefkowitz 2004) opened the “molecular era of receptor research” and to the cloning of the first receptors: i.e. the cholinergic nicotinic and the β adrenergic receptors which represent the two big families of receptors, i.e. ligand-gated channels and GPCRs. These discoveries led ultimately to Nobel Prizes for the discovery of GPCRs and their structure by Brian Kobilka and Robert Lefkowitz (Chemistry, 2012). Earlier, the Nobel Committee, whether in Physiology/Medicine or Chemistry, recognized the discovery of odorant receptors (Richard Axel and Linda Buck, 2004), the transmitters activating these receptors and playing multiple roles in disease, such as acetylcholine, noradrenaline, dopamine and serotonin or neuropeptides (Sir Bernard Katz, Ulf von Euler and Julius Axelrod, 1970) (Roger Guillemin, Andrew Schally and Rosalyn Yalow, 1977) (Arvid Carlsson, Paul Greengard and Eric Kandel, 2000), the prostaglandins (Sune Bergstrom, Bengt Samuelsson, Sir John Vane, 1982), drugs acting through these receptor (Sir James Black, Gertrude Elion and George Hitchings, 1988), signaling molecules such as cAMP (Earl Sutherland, 1971) and NO/cGMP (Robert Furchgott, Louis Ignarro and Ferid Murad, 1998) or the role of G proteins in GPCRs (Alfred Gilman and Martin Rodbell, 1994).

The development of rapid and simple techniques using radiolabeled ligands (radioligands) to identify receptors in cell-free preparations pioneered by Changeux, Lefkowitz and others, opened new possibilities to study receptors. Radioligand binding was expanded later to intact tissue sections for the localization of receptors in situ at the light microscope level and eventually to whole body imaging in vivo. The combination of these two methods, in addition to second messenger studies and in situ hybridization, constituted the workhorse of much of our work for the next 10 years, until recombinant technologies allowed to investigate cloned receptors. These methodologies revealed many unexpected

features of drug and neurotransmitter receptors. One, which raised tremendous opposition in the beginning, was the multiplicity of receptors for a single neurotransmitter. It was generally considered that the number of receptors for a given neurotransmitter should be limited (to 1 or 2), and some of the resistance to change was nearly dogmatic. From the extreme: "one transmitter-one receptor" to the "liberal": "one transmitter-two receptors". Examples: acetylcholine-nicotinic and muscarinic, noradrenaline-alpha and beta adrenergic receptors, histamine-H1 and H2, metabotropic vs ionotropic receptors (e.g. this duality was accepted for acetylcholine, but much less so for 5-HT or GABA receptors). Proposing more than two receptors for a single neurotransmitter was considered non practical by some, heretical by others, and if the proposal was based on radioligand binding, and/or second messengers / electrophysiology, doubly heretical. In other words, radioligand binding was a rather obscure side product of biochemical pharmacology, especially if combined with second messenger studies and/or electrophysiology. Along the same lines, the effects of guanine nucleotides on agonist binding (Laduron 1983), were merely considered as detergent-like effects of GTP and the likes, rather than on active vs. inactive states of the receptor (a few years later in 1994, the Nobel Prize was awarded for the discovery of G-Proteins, see above). However results were accumulating making it difficult to artificially constrain the size of receptor families.

With respect to serotonin, 2 receptors were considered to be optimal in 1983/1984, when we started collaborating on this subject: José María Palacios (JMP), Angel Pazos (AP) and Danny Hoyer (DH). The receptor molecular biology era was only to start a few years later with successful cloning of the β_2 receptor. There was an interesting twist: by homology screening, the cloning of the β_2 receptor lead to that of G_{21} /5-HT_{1A} receptor and then to the β_1 receptor. This was not surprising as 5-HT_{1A} receptors have high affinity for beta blockers such as pindolol, as revealed in our binding studies, and of course 5-HT and beta receptors share structural homologies (see Wang et al. 2013; Wacker et al. 2013). Thus in the brain, one would distinguish between 5-HT₁ and 5-HT₂ binding sites (Peroutka and Snyder 1979), labelled by [³H]5-HT and [³H]spiperone or [³H]ketanserin, respectively; keeping in mind that [³H]LSD would label both. In the guinea pig ileum, 5-HT-M and 5-HT-D receptors had been known since the mid 1950's (the effects of 5-HT on receptors were first reported in the gastro intestinal tract), but there were no binding studies in the GI tract, primarily since this was the field of physiologists and electro-physiologists (Gaddum and Picarelli 1957; Bradley et al. 1986; Hoyer et al. 1994). It was becoming clear that 5-HT₂ sites and 5-HT-D receptors were very closely related, if not overlapping (Engel et al. 1984). This lead to reconsider the whole nomenclature. In 1984, there was agreement to name these receptors "5-HT₁-like", 5-HT₂ (5-HT-D) and 5-HT₃ (5-HT-M). The Bradley scheme was born and the first receptor nomenclature group was in its infancy (Bradley et al. 1986). The 5-HT₄ receptor had already been recognised by Pramod Saxena and colleagues, but it was not an integral part of the new nomenclature, neither were subtypes of 5-HT₁ or 5-HT₂ receptors. There had been at times confusion between 5-HT₃, 5-HT₄ and 5-HT_M, receptors, not surprisingly since the tools/ligands used to characterise these receptors were still in their infancy (Hoyer, 1989) and these receptors were primarily investigated in the guinea pig ileum. The ileum is extremely complex, since most known 5-HT receptors are expressed functionally in the gut, although the proportions, localisation and distribution of the various receptors change along the alimentary tract and vary across species.

[³H]-Mesulergine: A Dopamine D₂ Receptor Ligand That Defines A New 5-HT Binding Site.

The discovery of the 5-HT_{1C} (later 5-HT_{2C}) receptor took place at Sandoz (now Novartis) in Basel, Switzerland. Sandoz had a long tradition of working with ergot derivatives with multiple useful pharmacological activities. Semi-synthetic ergot compounds had been developed over the many years in many therapeutic areas, with famous scientists such as Stoll and Hoffman who discovered many ergot alkaloids and eventually LSD in the 1920-1940s (see Giger and Engel 2006). One of the later ergoline-like compounds was CU-32085, also known as mesulergine. It presented interesting dopaminomimetic activities in animal models and was being developed as an anti-parkinsonian drug (Markstein 1983; Enz et al. 1984). Radioligand binding studies with [³H]mesulergine were carried out by Dr. Annemarie Closse. Somewhat surprisingly given its dopaminergic profile, [³H]mesulergine showed high affinity binding to 5-HT₂ receptors in the rat brain (Closse 1983). It must however be kept in mind that a number of these ergolines like [³H]LSD and [¹²⁵I]LSD, have high affinity for both 5-HT₁ and 5-HT₂ receptors, and we will see later that [¹²⁵I]LSD does indeed label 5-HT_{2C} receptors. In 1983, having just set up receptor autoradiography developed in Michael Kuhar's laboratory at Johns Hopkins University to label brain tissue sections with radioligands and study brain receptor distribution and pharmacology, JMP decided to investigate the localization and nature of [³H]mesulergine binding sites in the brain of various species. Thus, rat brain sections were incubated with [³H]mesulergine to generate autoradiograms. When the films were developed, there was disappointment: at first glance the film appeared "empty", as it happens when exposure is short. Similar stories get repeated: when we did the first 5-HT₃ receptor autoradiographic studies with [³H]ICS-205930, exposure time reached 5.5 months (!) before we could detect relevant binding in the brain (Waeber et al. 1988). A closer look though, revealed that [³H]mesulergine labelled some dark lines which did not correspond to any known neuronal structures or nuclei, namely the choroid plexus. This binding was selectively blocked by co-incubation with low concentrations of "cold" 5-HT. We knew from our own experience that [³H]5-HT also labelled intensely the choroid plexus, as well as many other brain areas, but no special attention had been paid to the choroid plexus, as it was not a target for CNS research: for transporters and brain penetration yes, but not for the study of future drug targets in the general field of neurology or psychiatry.

Thus, while one could expect some 5-HT₂ binding as well as dopamine D₂ binding with [³H]mesulergine, our first studies were pointing to a very different pattern. Competition studies suggested that we had identified a "new 5-HT-related site". Preliminary autoradiographic data were further confirmed by AP, a postdoctoral fellow who had just joined JMP's team.

These results were first presented at a meeting of the British Pharmacological Society in 1984 in Birmingham and were received with amused comments from established researchers in the field. This coincided with the first nomenclature group to meet and agree on the existence and naming of "5-HT_{1-like}", 5-HT₂ and 5-HT₃ receptors; the group convened by Professor Philipp Bradley, precisely in Birmingham (Bradley et al. 1986).

A full description of the pharmacological profile and characteristics of the 5-HT_{1C} receptor was published in 1984, and their detailed anatomical distribution, compared to 5-HT_{1A} and

5-HT_{1B} and 5-HT₂ receptors, was published a year later. Those studies have been cited extensively (Pazos et al. 1984a; Pazos and Palacios 1985; Pazos et al. 1985), as of today 661, 1395 and 899 times respectively.

Characterization Of 5-HT_{1C} Binding Sites In Pig Choroid Plexus:

Classical membrane radioligand binding studies are a simple way to study the kinetic features as well as to fully characterize the pharmacological profile of a new binding site with a large number of drugs. In 1983, high throughput screening did not yet exist, and testing 3 Mio compounds in 2.5 days using fluorescent imaging plate readers (FLIPR®) sounded like science fiction. Pipetting was done by hand, the reaction was carried out in 12.5ml tubes incubated in water baths at 37°C, each tube filtered individually, and each filter placed by hand into another large vial which then needed about 10 ml of scintillation fluid, all introduced single handedly into scintillation counters: no 96, 384 or 1536 plates, fed and handled by robots! DH had just joined Sandoz in 1983 following his postdoctoral training in Perry Molinoff's lab (U of Pennsylvania). His PhD thesis dealt with the discovery and development of two highly utilised radioligands for the study of alpha₁ ([¹²⁵I]BE-2254 also known as [¹²⁵I]HEAT) and beta-adrenoceptors ([¹²⁵I]ICYP, which will be used later to characterize 5-HT_{1B} receptors). Thus, radioligand binding was used massively in the characterization of 5-HT_{1C/2C} and other 5-HT receptors in a variety of species. In order to characterize the pharmacological profile of a new binding site, one needs a source of tissue rich in the sites of interest, that can be easily obtained and in sufficient amounts. Since the putative new 5-HT receptor had been initially identified in the choroid plexus, (we later demonstrated its presence in other brain regions), we decided to study its pharmacology by using radioligand binding in choroid plexus membrane preparations. The rat choroid plexus is small and in order to save animal numbers and costs, we turned to the pig plexus. It was indeed cheaper to collect brains from the local slaughterhouse. To obtain a homogeneous choroid plexus membrane preparation was not trivial, since the plexus is primarily a tight mix of vessels and harsh connective tissue. Eventually, we managed to obtain acceptable membrane fractions, allowing to perform regular radioligand binding studies with adequate quality (Pazos et al. 1984a, 1984b; Hoyer et al. 1985a, 1985b). Parallel autoradiographic studies were carried out to define the brain distribution of what was to become the 5-HT_{2C} receptor in various species (see below).

Thus, we compared the profiles of [³H]mesulergine, [³H]5-HT and [³H]LSD labelled sites in choroid plexus membranes. The very first studies with [³H]mesulergine added an additional surprise. We found that mesulergine had a unique binding profile in the choroid plexus, different from its pharmacology in the rest of the brain. In addition, species differences in the pharmacology of [³H]mesulergine binding became evident, a new feature in receptor studies, adding further complexity to the field. A few years later, it was recognized that such differences are real and dictated by the gene structure of these receptors (Hoyer and Middlemiss 1989; Hartig et al. 1996). In essence, human and pig receptors were different from rodent receptors, and we struggled with designing appropriate experiments as well as "selling" the new concept to management, since rodents were/are very commonly used in drug development.

In rat cortex, [^3H]mesulergine- and [^3H]ketanserin-labelled sites were indistinguishable (thus classical 5-HT₂ binding); in contrast, porcine and human cortex [^3H]mesulergine binding sites were pharmacologically distinct from [^3H]ketanserin-labelled sites, in other words the rank orders of affinity of a great number of compounds although close were clearly different. On the other hand, in the choroid plexus of the three species, [^3H]mesulergine-, [^3H]5-HT- and [^3H]LSD- labelled sites were highly similar, yet different from 5-HT₂ binding e.g. those labelled by [^3H]ketanserin. [^3H]mesulergine binding sites in the choroid plexus were named 5-HT_{1C}, as our results clearly demonstrated that they were distinct from the 5-HT_{1A} and 5-HT_{1B} binding sites, the latter two were well characterized as separate entities at that time in our labs. 5-HT_{1C} sites had low to very low affinity for a range a “classical” 5-HT₂ ligands such as ketanserin, spiperone, cinanserin or pirenperone, and high affinity for 5-HT. Further, 5-HT_{1C} sites were labelled by [^3H]5-HT, the prototypical 5-HT₁ radioligand. As more receptor families were characterised, it became clear that high affinity [^3H]5-HT binding was by no means specific for the 5-HT₁ family, but this was one the agreed features of 5-HT₁-like receptors at the time preceding receptor cloning (Hoyer et al. 1994).

5-HT Receptor Autoradiography: The Power Of Anatomical Resolution

In parallel to the studies carried out in membranes, we performed a detailed autoradiographic characterization of the whole suite of 5-HT binding sites, first in the brain, later in peripheral tissues. We did also compare various species, since we were primarily interested in human pharmacology, yet needed to know about the pharmacology of the commonly used laboratory animals. We were not interested in developing rodent selective drug candidates. Studies were first designed to identify brain areas specially enriched in the different proposed subtypes of 5-HT₁ receptors, in order to reinforce the specificity of 5-HT_{1C} sites as a separate entity from the other 5-HT sites/receptors. At that time, 5-HT₁ binding was divided into 5-HT_{1A} and 5-HT_{1B} (Pedigo et al. 1981). 8-OH-DPAT had just been reported as a 5-HT_{1A} selective agonist (Hjorth et al. 1982; Gozlan et al. 1983; Middlemiss and Fozard 1983). [^3H]8-OH-DPAT was shown to label a more restricted population of sites in the brain than [^3H]5-HT (Pazos and Palacios 1985; Hoyer et al. 1986b). We used [^3H]5-HT, [^3H]mesulergine, other radioligands and 8-OH-DPAT, SDZ 21-009, (a very useful beta blocker picked by Guenter Engel), and mesulergine itself as the main competing ligands. We identified anatomical areas particularly enriched in each of the 5-HT₁ and 5-HT₂ receptor subtypes: the dentate gyrus of the hippocampus for 5-HT_{1A}, the substantia nigra for 5-HT_{1B} and, of course, the choroid plexus for the “new” 5-HT_{1C} site. These studies contributed to establish a clear separation between 5-HT_{1C}, 5-HT_{1A} and 5-HT_{1B} sites both in terms of pharmacological profile and brain localisation. We also characterized the pharmacological profile of the new receptor at the microscopic level, by constructing autoradiographic competition curves: these studies revealed a pharmacological profile fully comparable to the one found in membranes (see below). They also revealed the first picture of the distribution of this subtype throughout the rat brain: the choroid plexus presented, by far, the highest binding density, but clearly detectable levels of 5-HT_{1C} sites were found over the olfactory system, hippocampus (CA1 field), thalamic nuclei, substantia nigra and spinal cord (external); lower levels were detected in neocortex (piriform, cingulate, frontal), putamen, globus pallidus, hypothalamus (ventromedial) and nuclei of the brainstem (i.e., spinal trigeminal nucleus). The autoradiographic studies highlighted the true power of combining the anatomical

dimension to the classical membrane binding strategies: without the initial identification of a region enriched in one class of receptors, it would have been rather unlikely to perform the detailed studies in choroid plexus membranes that eventually led to the full description of the finally re-named 5-HT_{2C} receptors. Again, the choroid plexus as opposed to hippocampus or cortex or striatum is not a brain region that would be commonly studied, and in fact is rather difficult to process; almost like performing binding in blood vessel preparations. Later we also used antibodies to localise the new receptor, although one must confess that anti GPCR antibodies have led to a lot of dubious data (Abramowski et al. 1995).

Further Characterisation Of 5-HT₁ And 5-HT₂ Sites

We subsequently showed (Hoyer et al. 1985b) that brain 5-HT₁/ [³H]5-HT binding could be displaced in a tri-phasic manner by the beta blocker SDZ 21-009: high affinity for 5-HT_{1B} sites, intermediate for 5-HT_{1A} and very low affinity for 5-HT_{1C} sites. Our autoradiographic data had also demonstrated the ability of this compound to selectively bind to 5-HT_{1B} sites in specific brain areas (Hoyer et al. 1985a; 1985b). Some further indole beta blockers turned out to be very important tools for the delineation of 5-HT₁ receptor subtypes. Indeed, we noticed that [¹²⁵I]ICYP ([¹²⁵I]iodocyanopindolol), a very potent antagonist at β -adrenoceptors, which is still the most popular radioligand for labelling these receptors (Engel et al. 1981; Hoyer et al. 1982), was also labelling brain sites sensitive to 5-HT and other serotonergic ligands. Although, the radioligand was initially described as highly specific for beta receptors, we had to admit that it was perfectly suitable to label 5-HT_{1B} receptors in rodents. But not in other species, certainly not in pigs or primates, or rabbits; again highlighting species differences.

Using an iterative process, we put bits and pieces together comparing the binding profiles of radioligands known to interact with 5-HT/Dopamine D₁-D₂/5-HT₂ or mixed 5-HT₂/D₂, beta receptor ligands, and the one that seems to label pretty much everything, [³H]LSD and its derivative [¹²⁵I]LSD (Hoyer et al. 1986c). Incidentally, [¹²⁵I]SCH23982 a “selective” dopamine D₁ ligand, and [¹²⁵I]LSD were found to label 5-HT_{1C} sites in the choroid plexus (Hoyer and Karpf 1988). We also used [³H]8-OH-DPAT which at the time was (and still is) an exquisite tool to define 5-HT_{1A} sites, whereas [³H]ketanserin turned out to be another valuable tool for labelling 5-HT₂ receptors. Both membrane binding and autoradiographic studies allowed to define the pharmacological profile / rank order of affinities on the new receptor, with the drugs available at that time. In addition to 5-HT and mesulergine, LSD, methysergide and mianserin showed high or very high affinity for 5-HT_{1C} receptors; ketanserin, pirenperone and methergine bound to the new site with an intermediate affinity; by contrast, 8-OH-DPAT, (-) SDZ 21-009 and spiperone had low or very low affinity for 5-HT_{1C} receptors.

The iterations were multiple: radioligand binding was performed in brain membranes, including choroid plexus, receptor autoradiography in brain slices of various species, and functional models such as contractions of the guinea-pig ileum (Engel et al. 1984; Kalkman et al. 1986), inhibition of 5-HT release in the cerebral cortex (Engel et al. 1986), stimulation or inhibition of cAMP production in hippocampus (Markstein et al. 1986; Schoeffter et al. 1989), in the substantia nigra (Hoyer and Schoeffter 1988; Schoeffter et al. 1988; Schoeffter and Hoyer 1989; Schoeffter et al. 1989), stimulation of PLC

production in choroid plexus (Hoyer et al. 1989) or in smooth muscle cells, contraction or relaxation of various blood vessels (Kalkman et al. 1984; 1986; Doyle et al. 1986; Hoyer 1988a, 1998b; Schoeffter et al. 1989) and in vivo (Kalkman et al. 1984; Doods et al. 1988).

5-HT Receptor Binding And Autoradiography In The Human Brain

After characterizing the properties of the new site in animal brain (mouse, rat, guinea-pig, pig, bovine and many others), we went on with the characterization and localization of 5-HT_{1C} receptors in postmortem human brain tissue. Taking advantage of the fact that Dr. Alphonse Probst, a pathologist at the University of Basel, shared a collaboration with the JMP group aimed to visualize and analyse neurotransmitter receptors in human tissue, we applied similar experimental procedures both in membranes and sections from a series of human brains, although confronting the specific limitations associated to the work with postmortem material. By the end of 1985 the anatomical distribution and pharmacological profile of 5-HT₁ and 5-HT₂ receptors in the human brain were obtained, proving to be relatively similar to that reported in animals (choroid plexus starring again). However species differences were highlighted again: the marked differences in 5-HT_{1B} pharmacology complicated for quite a while the exact delineation of the distribution of 5-HT_{1C} sites in non-choroid plexus areas (Pazos et al. 1987a; 1987b; Hoyer et al. 1986a, 1986b). The high density of 5-HT_{1C} receptors in the choroid plexus of all the species investigated was calling for an examination of their potential functional role in the volume and composition of cerebrospinal fluid. We cannulated rat cerebral ventricles and using perfusion with artificial CSF and radiolabeled inulin, examined alterations in the volume of CSF. We found effects of 5-HT and other drugs, but the system was too complex to carry out detailed studies and we did not progress enough to publish. However, Lindvall-Axelsson et al (1998) performed a detailed study in the rabbit, a better suited model, reporting inhibition of CSF production by 5-HT which was blocked by ketanserin.

In Situ Hybridization Complements Autoradiography:

The cloning of 5-HT_{1C/2C} receptor (see below) allowed for the visualization of mRNA coding for this receptor by in situ hybridization histochemistry in brain: 5-HT_{1C/2C} binding and mRNA distributions were largely overlapping in mammalian brain (Hofman and Mezey 1989; Palacios et al. 1990; Mengod et al. 1990; Pompeiano et al. 1994; Lopez-Gimenez et al. 2001; Serrats et al. 2005; Mengod et al. 2010). There is the occasional mismatch as has been reported for other GPCRs. For instance, high levels of mRNA are found in the habenular nucleus, whereas binding levels are low. The monkey brain was then studied extensively: 5-HT_{2C} mRNA is present in choroid plexus, in layer V of most cortical regions, in nucleus accumbens, ventral anterior caudate and putamen, septal nuclei, diagonal band, ventral striatum, and extended amygdala (López-Giménez et al. 2001). Several thalamic, midbrain, and brainstem nuclei also express 5-HT_{2C} mRNA. In general, [³H]mesulergine binding and mRNA showed a good correlation across the brain, in agreement with a somatodendritic localization of 5-HT_{2C} receptors. When there was lack of correlation, this was compatible a possible location on axon terminals, such as in 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). 5-HT_{2C} receptors are also present in the spinal cord

(see below). There has been no evidence for 5-HT_{2C} binding or mRNA in peripheral tissues.

The 5-HT_{1C} Receptor Defines A New 5-HT Receptor Family

It became clear that 5-HT₂ receptors were acting via the PLC/PKC/Calcium pathway, whereas 5-HT₁ receptors were negatively modulating cAMP production (Hoyer 1988a). There was no evidence for cAMP modulation in the choroid plexus (Palacios et al. 1986), whereas stimulation of PLC activity had a 5-HT_{1C} profile (Conn and Sanders Bush 1986; Conn et al. 1986; Hoyer et al. 1989). We also suggested that 5-HT_{1C} receptors were present in the stomach fundus, and attempted to correlate both activities (5-HT_{1C} binding and 5-HT-mediated contraction), with little success. Further, the 5-HT_{2B} receptor is expressed in the fundus (Foguet et al. 1992a; 1992b) and there is no evidence that 5-HT_{1C} receptors are expressed in the periphery. With the tools available at the time, a pharmacologic differentiation between the two receptors was not easy. Right from the beginning, the pharmacological similarity between 5-HT_{1C} and the classical 5-HT₂ receptors in terms of pharmacological profile was rather striking. We thus suggested these receptors to be closely linked (Hoyer 1988a) as confirmed subsequently.

POST 1988. THE CLONING OF 5-HT RECEPTORS: 5-HT_{1C} BECOMES 5-HT_{2C}.

The 5-HT_{1C} receptor, one of the first of the 5-HT family, was cloned before the 5-HT₂ receptor (Lubbert et al. 1987), although the full length 5-HT_{1C} sequence came somewhat later. The 5-HT_{1C} gene has a rather complex structure (Julius et al. 1988; Saltzman et al. 1991; Yu et al. 1991; Milatovich et al. 1992; Stam et al. 1994). The 5-HT₂ receptor was cloned in close succession (Pritchett et al. 1988; Julius et al. 1989; Foguet et al. 1992a; 1992b). The 5-HT₂ receptor family was then extended, when the fundus receptor was sequenced and cloned, named first 5-HT_{2F}, (for fundus), to become 5-HT_{2B}. Together, these three receptors showed some marked sequence similarities (Julius et al. 1989; Foguet et al. 1992b) and thus formed a group structurally distinct from the 5-HT_{1R} family, which eventually expanded to 5-HT_{1B/1D}, 5-HT_{1E} and 5-HT_{1F} (Hoyer et al. 1994; Hartig et al. 1996).

Logically, the serotonin receptor nomenclature committee agreed that subtypes existed for 5-HT₁ and 5-HT₂ receptors (cloning had strongly supported these views): it was then decided to place the 5-HT_{1C} receptor within the 5-HT₂ family. Thus, 5-HT_{1C} was re-named 5-HT_{2C}, which was the least disruptive move (Humphrey et al. 1993; Hoyer et al. 1994) and the 5-HT_{1C} spot remains unassigned.

The availability of recombinant receptors in homogeneous cell population allowed for relatively selective 5-HT_{2C} receptor agonists and antagonists to be synthesized, and clinical development followed for conditions such as depression, obesity, addiction, schizophrenia (see Table 1, and Cryan and Lucki 2000; Fletcher et al. 2002a; 2002b; 2004; 2008; 2001; 2012; Kennett et al. 1994; 1996; 2000; Grottick et al. 2000; 2001; 2015; Lee and Meltzer 1994; Niswender et al. 2001; Millan et al. 2003; 2005; 2008; 2011; Millan 2003; 2005; Miller 2005; Higgins et al. 2012; Rauser et al. 2001; Marquis et al. 2007; Cunningham et al. 2011; 2013; Cunningham and Anastasio 2014; Anastasio et al. 2014a, 2014b; 2015).

The progress in the field has been compelling, due to major advances in molecular biology, the availability of selective tools and their judicious use, a lot of 'out of the box' thinking and some neglect for dogmas imposed by self-named experts. Yet, the gene encoding the 5-HT_{2C}R is extraordinarily complex and it has taken quite some time to obtain the full sequence (see Lubbert et al. 1987; Julius et al. 1988; Saltzman et al. 1991; Yu et al. 1991; Milatovich et al. 1992; Stam et al. 1994). There are three splice variants of the 5-HT_{2C}R: the full length receptor, and two severely truncated forms (Canton et al. 1996; Xie et al. 1996; Liu et al. 1999; Wang et al. 2000; Kishore and Stamm 2006; Kishore et al. 2010; Shen et al. 2013; Bombail et al. 2014), thought to be inactive, although they may serve as chaperones and seem to be affected in disease (Dracheva et al. 2003; 2008a; Flomen et al. 2004; Martin et al. 2013).

5-HT_{2C} Receptor mRNA Editing.

Quite exceptionally for a GPCR, the primary transcript of the 5-HT_{2C}R is subjected to multiple RNA editing (Burns et al. 1997; Niswender et al. 1999; 2001; Rueter et al. 1999; Fitzgerald et al. 1999; see also Dracheva et al. 2003; 2008a; 2008b; 2009; Camel et al. 2012; Du et al. 2006; 2007; Di Narzo et al. 2014; 2015). So far editing is only known for ionotropic glutamate AMPA receptors. In rodents, there are four editing sites within the coding region of the 5-HT_{2C}R, whereas in humans a fifth editing site is present. Together they may produce up to 32 different mRNAs and 24 different proteins. The 5-HT_{2C}R is characterized by constitutive activity, the level of which decreases as editing increases (Herrick Davis et al. 1999). For instance, RNA encoding the human 5-HT_{2C}R undergoes adenosine-to-inosine RNA editing at five positions, resulting in alterations of amino acids in the second intracellular loop. Edited 5-HT_{2C}Rs show reduced G-protein coupling compared to the non-edited isoform, and the fully edited variants (VSV and VGV) show lowest levels of constitutive activity and the unedited form (INI) the highest level. Editing also leads to a loss of the active state of the receptor (Niswender et al. 1999) and a delay in agonist-stimulated calcium release in the fully edited isoforms (Price and Sanders Bush, 2001). The unedited receptor couples to both Gq/11 and G13, whereas editing reduces or eliminates coupling to G13 (Price et al. 2001). Thus, editing may serve to stop constitutive activity by reducing coupling to G proteins. The multiple editing and some splice variants of the 5-HT_{2C} receptor are probably not discriminated by antagonist radioligands used in binding/ autoradiographic studies; however, agonist binding such as [³H]5-HT, will only label receptors in an active state which depends much on the levels of editing.

5-HT_{2C} Receptor KO And Knock Down, Transgenic Models:

5-HT_{2C}R-KO or -mutated mice show hyperphagia, late-onset obesity, insulin resistance, and type 2 diabetes (Tecott et al. 1995; Heisler et al. 1998; Nonogaki et al. 1998; Tecott and Abdallah 2003; Wade et al. 2008). Interestingly, fenfluramine has reduced satiating effects in 5-HT_{2C}R KO mice (Vickers et al. 1999), suggesting a major role for the 5-HT_{2C} receptor in the reduced food intake produced by fenfluramine, norfenfluramine, benfluorex and possible effects on insulin/diabetes of these drugs (Wade et al. 1998). 5-HT_{2C}R-KO or -mutated mice also have spontaneous and audio-induced seizures (Brennan et al. 1997; Heisler et al. 1998; 2002) and show locomotor hyperactivity via 5-HT_{1B}R (Heisler and Tecott 2000; Rocha et al. 2002). The 5-HT_{2C}R knock down produces motor

impulsivity and increased cocaine sensitivity (Anastasio et al., 2015), that may result from an imbalance with the 5-HT_{2A} receptor in the medial prefrontal cortex. Further evidence from KO mice and other models suggest a role for the 5-HT_{2C} receptors in neuroendocrine responses to stress and an anxiolytic phenotype (Rocha et al. 1993; 1994; Heisler et al. 2007a; 2007b). Interestingly, the effects of 5-HT uptake blockade are reinforced in 5-HT_{2C}R KO mice (Cremers et al. 2004). 5-HT_{2C}R-selective expression in POMC neurons of 5-HT_{2C}R KO mice (Xu et al. 2008; 2010) reverses hyperphagia and restores insulin levels. These studies have been instrumental in directing the preclinical and clinical development of a number of drug candidates, and eventually some clinical translation, although much more work is in progress, especially in the addiction field (see below).

5-HT_{2C} Receptor Homomers And Heteromers.

Several members of the 5-HT receptor family, including the 5-HT_{2C}R, have been reported to form homodimers (see Herrick-Davis 2013, for a review). 5-HT_{2C}R homodimer formation occurs in the endoplasmic reticulum during receptor biosynthesis (Herrick-Davis et al. 2006) and the dimer is then transported through the Golgi complex to the plasma membrane. 5-HT_{2C}R homodimers do not form higher order complexes (tetramers or higher) following agonist or inverse agonist treatment (Herrick-Davis et al. 2004; 2007; 2012). The 5-HT_{2C}R homodimer interacts with a single G protein, with both active protomers needed for signaling to occur (Herrick-Davis et al. 2005). Homodimerization occurs with both the unedited INI and the fully edited (VSV and VGV) isoforms (Herrick-Davis et al. 2007; 2012). Heterodimers can form between the different editing isoforms of the 5-HT_{2C}R. In HEK293 cells, INI/VSV, INI/VGV and VSV/VGV isoform pairs have been reported (Herrick-Davis and Farrington 2011). The native choroid plexus 5-HT_{2C}R is expressed as homodimers on the apical surface of the epithelial cells (Herrick-Davis et al. 2015).

Heterodimers between the 5-HT_{2C}R and the 5-HT_{2A}R are likely to exist, but have not been demonstrated, although 5-HT_{2A}R and 5-HT_{2C}R protein co-localize in rat medial prefrontal cortex (Anastasio et al., 2015). Furthermore, combination 5-HT_{2A} antagonist / 5-HT_{2C} agonist seem to act in synergy, which support the claim by Cunningham's group to develop dual compounds for the treatment of various forms of addiction. Thus, subthreshold doses of the 5-HT_{2A}R antagonist M100907 combined with the selective 5-HT_{2C}R agonist WAY163909 synergistically suppressed cocaine-evoked motor impulsivity, hyperactivity and cocaine-seeking behavior (Cunningham et al. 2013).

The 5-HT_{2C}R and ghrelin receptor appear to form heterodimers when overexpressed in HEK293 cells. Further, the two receptors colocalize in cultured primary rat hypothalamic and hippocampal neurons (Schellekens et al., 2015). Interestingly, activation and blockade of 5-HT_{2C}R *in vivo* attenuated and potentiated, respectively, the orexigenic effects of ghrelin. It remains to be seen whether compounds such as fenfluramine, norfenfluramine or benfluorex act primarily on these receptor heterodimers or preferentially on 5-HT_{2C}R homodimers.

The formation of 5-HT_{2C}R and melatonin MT₂R heterodimers has been reported in transfected cells, and importantly human cortex and hippocampus (Kamal et al., 2015).

The antidepressant / anxiolytic agomelatine displays 5-HT_{2C}R antagonist and MT₁ and MT₂ receptor agonist properties. Whether the receptor heterodimer is the target of agomelatine and other antidepressants / anxiolytics remains to be investigated.

The glutamate *N*-Methyl-D-aspartate (NMDA) receptor subunit GluN2A co-localizes with the 5-HT_{2C}R in rat spinal cord neurons and synaptosomal fractions (Bigford et al., 2012). 5-HT_{2C}R activation enhanced NMDA-evoked motoneuron depolarization (Bigford et al., 2012), suggesting the existence of 5-HT_{2C}R / NMDA hetero complex in the spinal cord.

THE MODERN ERA: THERAPEUTIC CONSIDERATIONS.

The clinical relevance of 5-HT_{2C}R editing has been linked in genome wide association studies (GWAS), animal models or clinical samples, to suicidality (Niswender et al. 2001), schizophrenia (Sodhi et al. 2001; 2005; Reynolds et al. 2003; 2005; Zhu et al. 2012), anxiety (Hackler et al. 2006; 2007; Heisler et al. 2007b), depression (Iwamoto and Kato 2003; Yang et al. 2004; Iwamoto et al. 2005; 2011), spatial memory (Du et al. 2007), obesity (Yuan et al. 2000; Pooley et al. 2004), antipsychotic-induced weight gain (AIWG) (Basile et al. 2002; Tsai et al. 2002; Templeman et al. 2005; Wallace et al. 2011), addiction or impulsivity (Rocha et al. 2002; Filip and Cunningham 2002; Winstanley et al. 2004; Anastasio et al. 2014a), although it is fair to say that replication failure is frequent and contradictory data are not uncommon in GWAS. 5-HT_{2C} receptors have been shown to modulate mesolimbic dopaminergic function, where they exert a tonic inhibitory influence over dopamine neurotransmission (Bubar and Cunningham 2007; Bubar et al. 2011). Therefore, the interest in this receptor as a therapeutic target for treating substance abuse (Bubar and Cunningham 2006; 2008). The 5-HT_{2C}R is also believed to mediate the effects of antidepressants, e.g. mirtazapine or agomelatine (Cremers et al. 2004; 2007; see Millan 2003), possibly by stimulating neurogenesis, as well as that of atypical antipsychotics (Berg et al. 1999; Herrick Davis et al. 2000). 5-HT_{2C}R are expressed in the amygdala, and fMRI data have demonstrated that 5-HT_{2C}R agonists lead to its neuronal activation (Hackler et al. 2007). Other therapeutic indications relate to obesity and possibly epilepsy (Tecott et al. 1995; Brennan et al. 1997; Heisler et al. 1998; 2007a; Tecott and Abdallah 2003) as observed in the first series of receptor transgenic mice and later with 5-HT_{2C}R selective ligands (Venzi et al. 2016; Bagdy et al. 2007; Jakus et al. 2003; Isaac 2005). It is still a challenge to synthesise 5-HT_{2C}R selective agonists, devoid of significant interactions with the other 5-HT₂ receptor subtypes, since 5-HT_{2B} receptor activation results in detrimental cardiac effects such as valvulopathies (see Fitzgerald et al. 2000; Roth 2007), whereas 5-HT_{2A}R activation leads to hallucinations (Nichols 2004).

Depression And Anxiety: Agomelatine And Others.

Agomelatine (Valdoxan®, Melitor®, Thymanax®), a selective 5-HT_{2C}R antagonist and melatonin_{1/2}R agonist, was approved by the EMA and in other countries (but not FDA), for the treatment of major depressive disorders. It has also been considered in the treatment of sleep disorder, generalized anxiety disorders and adjunctive therapy in obsessive compulsive disorders. The recommended dose is 25 mg to be taken at bedtime, the dose may be doubled after 2 weeks if efficacy is lacking. There are some safety issues since liver enzymes are increased in a significant number of patients, although the compound is

generally well tolerated. Thus, the 5-HT_{2C}R is involved in the serotonergic regulation of generalized anxiety, depression and possibly bipolar disorders. It has been known for some time that mCPP and MK212 induce anxiogenic-like behaviours in rodents (Kennett et al. 1989; Benjamin et al. 1990; Shepherd et al. 1994; Bilkei-Gorzo et al., 1998; Millan 2003; 2005; Martin et al. 1998; Di Giovanni et al. 2001) and these compounds have been used as tools to induce anxiety and panic in humans (Lowy and Meltzer 1988; Kahn and Wetzler 1991; Sevy et al. 1994; Southwick et al., 1997; Gatch 2003). The anxiogenic effects are likely due to the activation of the 5-HT_{2C}R. 5-HT_{2C}R knockout mice exhibit an anxiolytic-like phenotype (Heisler and Tecott 2000; Heisler et al. 2007b). Moreover, desensitization of the 5-HT_{2C}R in SERT KO mice reduces the anxiety phenotype (Martin et al. 2015) and show antidepressant-like effects (Prisco and Esposito, 1995; Di Giovanni et al. 2006). The situation is however more complex: although, mCPP induces anxiety in mice (Kennett et al. 1989; Nic Dhonnchadha et al. 2003), it has antidepressant-like properties in the anhedonia model in rats (Moreau et al. 1996) and is apparently anorexigenic without inducing anxiety/depression in humans (Thomas et al. 2014). RO60-0175, a 5-HT_{2C}R agonist, shows antidepressant and anxiolytic/anti-compulsive like effects in some rodent models (Cryan and Lucki 2000; Nic Dhonnchadha et al. 2003). It seems that anxiogenic-like features of RO60-0175 (Martin et al. 2013; Martin et al. 2014) may be related to its sedative properties (Kennett et al. 2000). Yet, all compounds are not equal: CP809101 is not anxiogenic in some models (Siuciak et al. 2007) but anxiogenic in others (Strong et al. 2009; 2011; Christianson et al. 2010), suggesting that pathway selection may be at play. Thus, some 5-HT_{2C}R antagonists have strong anxiolytic/antidepressant properties in numerous tests (Kennett et al., 1994; 1996; 1997; 2000; Wood et al. 2001; Millan, 2005; Harada et al., 2006). On the other hand and surprisingly, both 5-HT_{2C}R agonists and antagonists have been reported to have anxiolytic/antidepressant properties, in the chronic mild stress-induced anhedonia and olfactory bulbectomy models of depression. It has been suggested that selective 5-HT_{2C}R agonists would be more appropriate to treat depression, obsessive-compulsive disorder or panic attacks, while antagonists would be better suited for generalized anxiety and obsessive-compulsive disorder (Jenck et al. 1998; Millan 2003; 2005). However, the atypical antidepressants mirtazapine and mianserin (Hayasaka et al. 2015) and the recently developed antidepressant agomelatine (Millan et al. 2003; 2011; Millan 2005) have clear antagonistic 5-HT_{2C}R profiles. Local activation of the 5-HT_{2C}R in the basolateral amygdala is anxiogenic (Campbell and Merchant 2003), whereas 5-HT_{2C}R activation in the dorsal periaqueductal grey is anxiolytic (Yamashita et al. 2011). Be it is at it may, agomelatine is a 5-HT_{2C}R with additional melatonin 1 and 2 receptor agonism that has been registered for the treatment of major depression in Europe and a number of other countries, but not in the USA. Interestingly, the 5-HT_{2C}R receptor may form heterodimers with melatonin receptors (Kamal et al 2015), although the functional consequences for the therapeutic effects of agomelatine need to be clarified. It is clear that other antidepressants display potent 5-HT_{2C}R antagonism, e.g. mirtazapine or mianserin, although their receptor profile is by no means selective.

Appetite, Satiety And Obesity: Lorcaserin, Fenfluramine And Others.

There is ample evidence that the 5-HT_{2C}R plays a role in the management of hunger, food intake and satiety (Lucki 1998; Blundell 1999; Halford et al. 1997; 1998; Halford and Blundell 2000; Voigt and Fink, 2015). Lorcaserin (Belviq®) is a selective, high-efficacy 5-

HT_{2C}R agonist (Thomsen et al. 2008; Smith et al. 2009; 2010) marketed for weight reduction in patients with a body-to-mass (BMI) index of >30 or with a BMI >27 comorbid with type-2 diabetes, hypertension or dyslipidemia (FDA (2012): <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm>). The development of Lorcaserin was based on the knowledge accumulated with previously developed selective ligands such as the agonists RO60-0175 (Fletcher et al. 2004), WAY163909 (Dunlop et al. 2005; 2006) or the antagonist SB242084 (Bromidge et al. 1997) and SB206553 (Kennett et al. 1996), but also from older compounds such as fenfluramine, dexfenfluramine, mCPP or MK212, which act as 5-HT_{2C}R agonists and various antipsychotics or cyproheptadine which act as 5-HT_{2C}R antagonists. The 5-HT releaser d-fenfluramine and its active metabolite d-norfenfluramine, other preferential 5-HT_{2C}R agonists such as mCPP or MK212, evoke hypophagia and increase satiety in rodents, keeping in mind that mCPP has anxiogenic effects. The effects on food intake are blocked by 5-HT_{2C}R antagonists or by the constitutive 5-HT_{2C}R KO (Kennett and Curzon 1988; Tecott et al. 1995; Halford et al. 1997; Vickers et al. 1999; Dalton et al. 2006; Nonogaki et al. 1998; 2008). Selective 5-HT_{2C}R agonists such as lorcaserin, RO60-0175 or WAY163909 do consistently suppress food intake (Clifton et al. 2000; Hewitt et al. 2002; Somerville et al., 2007; Thomsen et al., 2008; Grottick et al. 2000; 2015; Higgs et al. 2016). Interestingly, WAY163909 decreased food intake in normal Sprague–Dawley rats, obese Zucker rats and diet-induced obese mice without the anxiogenic effects of mCPP (Dunlop et al. 2005; 2006). Constitutive 5-HT_{2C}R knockout mice show hypophagia and increased body mass in the context of both insulin resistance and late-onset obesity (Tecott et al. 1995; Nonogaki et al. 2008). Some 5-HT_{2C}R antagonists such as cyproheptadine disrupt the satiety sequence and increase appetite (Chinuck et al. 2007; Bergen 1964; Ishii et al. 2003). Weight gain and a greater relative risk of metabolic dysfunction and diabetes is associated with atypical antipsychotics with 5-HT_{2C}R antagonist properties, such as clozapine and olanzapine in both patients and animals (Wirshing et al. 1999; DeLuca et al. 2007; Kirk et al. 2009). Thus 5-HT_{2C}R antagonism may lead to highly detrimental side effects and explains in part the lack of compliance seen with some atypical antipsychotics. However, the situation may be somewhat more complex, since selective 5-HT_{2C}R antagonists may increase (Bonhaus et al. 1997; Higgs et al. 2016;) or decrease food intake depending upon the rodent preclinical model (Kennett et al. 1997; Murotani et al. 2011; Higgs et al. 2016). What is clear however, is that 5-HT_{2C}R agonism has positive effects in preclinical models of food intake and satiety, and that such effects may also translate positively with respect to diabetes; keeping in mind that all 5-HT_{2C}R are not equal, more specifically with respect to biased signalling. Thus, d-fenfluramine and RO60-0175 reduce the rate of feeding and meal size and increase the latency to feed (Clifton et al., 2000). The effects of d-fenfluramine are markedly reduced in 5-HT_{2C}R KO mice (Vickers et al. 1999). Lorcaserin reduces the number of licking bouts probably by promoting satiety (Higgs et al. 2016; Davis et al. 2001). The sites of action of lorcaserin and other selective 5-HT_{2C}R ligands in the mechanisms underlying satiety are to be found in hypothalamic and midbrain/hindbrain circuits that modulate energy balance and glucose homeostasis in concert with the periphery (Gautron et al. 2015; Voigt and Fink 2015). Multiple hypothalamic nuclei express 5-HT_{2C}R (van de Kar and Lorens 1979; Peyron et al. 1998; Hoffman and Mezey 1989; Molineaux et al. 1989; Mengod et al. 1990; Pompeiano et al. 1994). Indeed, arcuate nucleus POMC neurons expressing 5-HT_{2C}R are activated by d-fenfluramine and mCPP (Heisler et al. 2002; Lam et al. 2008; Xu et al. 2008; 2010), which translates into

the synthesis of α -MSH. α -MSH in turn, acts on melanocortin 4 receptors in the hypothalamic paraventricular nucleus to promote satiety, weight loss and glucose regulation (Heisler et al. 2007a; Zhou et al. 2007; Xu et al. 2008; 2010; Berglund et al. 2013). Mice with a selective 5-HT_{2C}R KO in POMC neurons, have normal body weight, and are insensitive to d-fenfluramine- or mCPP-evoked hypophagia; these mice develop a metabolic syndrome, with hyperinsulinemia, hyperglucagonemia, hyperglycemia, and insulin resistance (Berglund et al. 2013). This syndrome can be reversed by re-expressing the 5-HT_{2C}R in POMC neurons (Xu et al. 2008). Interestingly, female mice appear to be different in that respect, leading to speculation about possible sex differences in the prevalence of obesity (Burke et al. 2016). Another interesting interplay has been reported between the 5-HT_{2C}R and the leptin system. Co-administration of mCPP and leptin results in an additive reduction in body weight in diet-induced obese mice (Yan et al. 2015). 5-HT_{2C}R KO mice show leptin-independent hyperphagia and a diabetic phenotype (Nonogaki et al. 1998; 2008), whereas double leptin and 5-HT_{2C}R KO mice show a synergistic disruption of glucose homeostasis and a profound diabetes phenotype (Wade et al. 2008). Transgenic overexpressing leptin and 5-HT_{2C}R KO mice have a lean phenotype on a chow diet; by contrast, on a high fat diet, these mice become markedly obese (Wang and Chehab 2006). Stimulation of the 5-HT_{2C}R activates the same POMC neurons activated by leptin (Qiu et al. 2007; 2010). Thus, the 5-HT and leptin systems may function independently, but within POMC neurons of the hypothalamus, they may control satiety and energy reserves in a coordinated fashion (Halford and Blundell 2000).

Schizophrenia: Vabicaserin, Sertindole And The Others.

Both selective 5-HT_{2C}R agonists and antagonists have been suggested for the treatment of schizophrenia, however so far, the clinical outcome has been disappointing. 5-HT_{2C}R antagonism may be effective in suppressing positive symptoms, while 5-HT_{2C}R agonism may be correcting the negative symptoms and cognitive impairments (Wood et al. 2001; Rosenzweig-Lipson et al. 2007a; 2007b; 2012) with placebo like motor side effects (Di Giovanni et al. 2006; Di Giovanni and De Deurwaerdere 2016). The features of some atypical antipsychotics led to 5-HT_{2C}R blockade as a strategy to improve the efficacy of dopamine antagonists in long-term treatments (Meltzer, 1999). On the other hand, one of the great expectations was that 5-HT_{2C}R agonists would have antipsychotic effects without inducing AIWG and altering glucose homeostasis, a negative feature of a number of atypical antipsychotics. Further, experimental evidence suggested that 5-HT_{2C}R agonism might increase the efficacy of typical and atypical antipsychotics, allowing dose-sparing with a reduction of motor side-effects (Grauer et al. 2009). However, Vabicaserin a potential antipsychotic and anorectic with high agonist efficacy at the 5-HT_{2C}R (Dunlop et al. 2011), although improving positive symptoms (Shen et al., 2014), did not meet the primary efficacy endpoints (see ClinicalTrials, 2014: <https://clinicaltrials.gov/ct2/show/results/NCT00563706?term=vabicaserin&rank=2>). Its clinical development by Pfizer was terminated. On the other hand, Sertindole, (Juruena et al. 2011) a potent 5-HT_{2C}R inverse agonist, and dopamine D₂, α_1 -adrenergic receptor and 5-HT_{2A}R antagonist (Herrick-Davis et al. 2000; Hietala et al. 2001), was either not registered (USA) or withdrawn from the market (Europe), due to cardiovascular side effects. Sertindole was effective in reducing anxiety, improving cognition/memory and brain plasticity, most probably by reducing 5-HT_{2C}R tonic activation (Hietala et al., 2001).

In other words, clinical data have not conclusively proven or disproven the therapeutic potential of 5-HT_{2C}R modulating ligands in schizophrenia, thus the jury is still out.

RNA Editing, Spinal Cord Injury And More: A Case For Inverse 5-HT_{2C} Receptor Agonists

Spinal cord injury (SCI) patients suffer from paralysis of muscles innervated by motor neurons below the injury site. Weeks to months following injury, some restoration of motor neuron excitability may take place which may be associated with some recovery of motor function. However, that recovery is often accompanied by marked muscle spasms that may be spontaneous or can be triggered by various stimuli. A number of SCI studies (Murray et al. 2010) suggest a role for constitutive activation of the 5-HT_{2C}R (and possibly 5-HT_{2B}R) in this process in both SCI patients and rodents (rats and mice) subjected to SCI (Fouad et al. 2010; Murray et al. 2011; Husch et al. 2012). In rats, following chronic SCI, electrical stimulation of the tail results in sustained muscle spasms; administration of a neutral 5-HT_{2C}R antagonist does not affect these spasms, whereas the 5-HT_{2C}R inverse agonists SB206553 and cyproheptadine inhibit the spasms most probably by blocking constitutively active 5-HT_{2C}R. These effects can be reproduced in the isolated spinal cord in vitro, ruling out a role for local 5-HT in the spasms. Along these lines, chronic SCI was associated with a fourfold increase in expression of the unedited, constitutively active isoform of the 5-HT_{2C}R. In SCI patients, leg muscle spasms evoked by cutaneous stimulation to the foot are significantly reduced by oral administration of cyproheptadine. These data suggest the use of 5-HT_{2C}R inverse agonists (and possibly 5-HT_{2B}R antagonist) to manage SCI spasticity. However, recovery of locomotion in rats following partial SCI was also inhibited by SB206553, implying that constitutive 5-HT_{2C}R activity is needed for normal locomotion. Thus a therapeutic window is to be considered when using such agents.

5-HT_{2C}R RNA editing is not limited to SCI, a number of attempts have been made to relate editing to psychiatric disorders and suicide (e.g. Niswender et al. 2011; Gurevich et al. 2002; Lyddon et al. 2013). It is clear that in some brain regions and depending on state, native 5-HT_{2C}R display constitutive activity which can vary largely (Di Giovanni et al. 1999; Di Matteo et al. 2000; Gobert et al. 2000; Leggio et al. 2009; Navailles et al. 2004; 2013a; 2013b). A number of antipsychotics behave actually as inverse agonists (Berg et al. 1999; Herrick-Davis et al. 2000; Rauser et al. 2001; Navailles et al., 2004; Aloyo et al. 2009; Sullivan et al; 2015) and if the 5-HT_{2C}R is a target, their effectiveness may depend on the level of constitutive activity of the receptor (Navailles et al. 2013b). A complicating factor is that constitutive activity may vary with transduction pathway (Berg et al. 1994; 1998a; 1998b; 2001; 2008a; 2008b; Moya et al. 2007; Wang et al. 2000; Werry et al. 2005; 2008; Berg and Clarke 2009), receptor desensitization and trafficking may be at play as well (Berg et al. 1999; Marion et al., 2004) and different ligands may possess different pathway selectivity. In other words, the situation may be even more complex than ever envisaged and again the status of the receptor may well be disease- and cell-type dependent.

Addiction And Substance Use Disorders: Lorcaserin.

The role of the 5-HT_{2C}R in various addictive processes has been amply investigated. 5-HT_{2C}R agonists suppress nicotine intake and nicotine-seeking in preclinical models (Grottick et al. 2001; Levin et al. 2011; Fletcher et al. 2012; Higgins et al. 2012) leading to clinical trials with lorcaserin in nicotine abuse (Eisai, 2014: <http://www.eisai.com/news/news201465.html>). The early clinical data suggest lorcaserin given 10 mg twice daily, to increase abstinence from nicotine modestly but significantly, as may be expected from preclinical studies dealing with other substance abuse paradigms such as cocaine and other psychostimulants, ethanol and opiates as well as factors involved in relapse, impulsivity and cue reactivity (Cunningham et al. 2011; 2013; Cunningham and Anastasio, 2014; Rezvani et al., 2014; Howell and Cunningham 2015; Harvey-Lewis et al. 2016). Cocaine administration elevates 5-HT in the Nucleus Accumbens (NAc) (Parsons and Justice 1993; Parsons et al. 1995; Howes et al. 2000). 5-HT_{2C}R KO mice show an increased motivation to self-administer cocaine and cocaine-induced elevation in dopamine in the NAc (Rocha et al. 2002). A 5-HT_{2C}R agonist, enhances, whereas a 5-HT_{2C}R antagonist inhibits, the elevated dopamine efflux in the NAc evoked by cocaine administration (Navailles et al. 2004; 2008; Cathala et al. 2015). Selective 5-HT_{2C}R agonists e.g. RO60-0175 or WAY163909 suppress voluntary intake of cocaine (Grottick et al. 2000; Fletcher et al. 2002a; 2004; Neisewander and Acosta 2007; Cunningham et al., 2011) probably via NAc dopamine increases. 5-HT_{2C}R stimulation dose-dependently suppresses cocaine-evoked or exposure to cocaine-associated cues (Grottick et al. 2000; Neisewander and Acosta 2007; Burbassi and Cervo 2008; Fletcher et al. 2002a; 2004; 2008; 2011; Cunningham et al. 2011; Swinford-Jackson et al. 2016). Selective 5-HT_{2C}R blockade produces opposite effects on self-administration of low doses of cocaine (Fletcher et al. 2002a) and enhances cocaine-evoked reinstatement of drug-seeking in rodents (Fletcher et al. 2002a; Pelloux et al. 2012). In non-human primates, 5-HT_{2C}R agonism attenuated the stimulant, reinforcing and reinstatement effects of cocaine, which are blocked by the 5-HT_{2C}R antagonist SB242084 (Manvich et al. 2012a; 2012b; Ruedi-Bettschen et al. 2015). SB242084 itself may induce modest stimulant effects in primates (Manvich et al. 2012a; 2012b), although this data is open for discussion (Ruedi-Bettschen et al., 2015). The 5-HT_{2C}R mediated inhibitory tone on cocaine reward and cue reactivity may originate in the medial prefrontal cortex (mPFC) as suggested by local administration studies (Cunningham and Anastasio 2014; Howell and Cunningham 2015; Di Giovanni and De Deurwaerdere 2016). The 5-HT_{2C}R functional status in the orbitofrontal cortex may also be a contributor to the vulnerability of impulsive rats to cocaine reward and cue reactivity (Besson et al. 2013). Altogether, the data suggest that the functional status of the cortical 5-HT_{2C}R system may be a mechanistic driver in the generation of cocaine use disorder and relapse phenomena, and abstinent cocaine users exhibit lower sensitivity to the effects of 5-HT_{2C}R agonists (Lee and Meltzer 1994; Buydens-Branchey et al. 1997; Patkar et al. 2006; Liu et al. 2011; 2012; Anastasio et al. 2014a). Stimulation of the 5-HT_{2C}R is also suppressing ethanol self-administration (Maurel et al. 1999; Tomkins et al. 2002; Kasper et al. 2013; Rezvani et al. 2014) and reinstatement in rodents (Kasper et al. 2013). Further, ethanol vapor exposure leads to an increased corticostriatal and hypothalamic 5-HT_{2C}R mRNA, increased 5-HT_{2C}R protein in the NAc and 5-HT_{2C}R pre-mRNA editing (Yoshimoto et al. 2012; Watanabe et al. 2014). The behavioral effects of d-amphetamine (O'Neill et al. 1999; Rippberger et al. 2015; Wöhr et al. 2015), 3,4-methylenedioxymethamphetamine (MDMA) (Bankson and Cunningham 2002; Fletcher et al. 2002b), methamphetamine (Steed et al. 2011; Graves and Napier 2012), and the marijuana alkaloid Δ⁹-THC (Ji et al. 2006) can be modulated

by the administration of 5-HT_{2C}R agonists, thus extending the potential therapeutic value of selective 5-HT_{2C}R agonists in the treatment of substance abuse. Systemic administration of dexfenfluramine blocks heroin self-administration in rats (Wang et al. 1995). Selective 5-HT_{2C}R activation reduces opioid-induced behavioral sensitization (Wu et al. 2015; Zhang et al. 2016). Finally, pre-clinical data presented at the ISSR 2016 meeting in Seattle by Kathy Cunningham's group suggest that lorcaserin may be effective in alleviating oxycodone addiction in human subjects.

CONCLUSION

The discovery of the 5-HT_{2C}R resulted from a good mix of experimental design and serendipity and excellent collaborative spirit: having at hand a number of (radio)ligands was essential as was the use of autoradiography that pointed to the choroid plexus. This is not a tissue neuroscientist in big Pharma used to work with, unless one has a dedicated interest in blood brain barrier. Thus seeing the high receptor expression in the brain attracted our attention and allowed the characterization of a binding site that was clearly different from what had been described previously. The pharmacological characterization of the then called 5-HT_{1C} receptor, led us to rethink the nomenclature of 5-HT receptors, starting with the 5-HT₁ receptor subfamily. This was a rather controversial subject, since some experts at the time barely recognized the existence of 5-HT₁ receptors: Bradley and colleagues limited that family to the general but rather vague concept of "5-HT₁-like". We had already made up our mind that subtypes of 5-HT₁ receptors existed, 5-HT_{1A}, 5-HT_{1B}, rapidly expanding to 5-HT_{1D}, although the latter two were largely species variants as suggested in binding, 2nd messengers and functional studies across species (Hoyer and Middlemiss 1989), as confirmed by cloning (Hartig et al. 1996; Hoyer et al. 2002). For a short while we thought that the functional correlate to the 5-HT_{1C/2C} site was the receptor described by John Vane in the stomach fundus, but although similar, it became evident following its cloning that 2C and 2B were indeed different! Many years later, (drug development can be a very long enterprise), it becomes clear that the original 5-HT_{1C} site did make relevant contributions to modern pharmacology, not only to nomenclature. The development of selective 5-HT_{2C}R selective drugs has pioneered the demonstration of the capability of certain ligands to differentially activate different signal transduction pathways (Berg et al. 1998a; 1998b; 2003): this evidence has been instrumental for the concept of "ligand-dependent functional selectivity". In addition to challenging the dogma of classical pharmacology, this concept has a clear impact on drug discovery (Millan et al. 2003). The 5-HT_{2C}R is undoubtedly one of the most complex members of the GPCR superfamily, given its multiple editing and splice variants, yet it is clearly the target of a number of drugs which may act rather differently in health and disease. The clinical development of agomelatine as an antidepressant as a potent 5-HT_{2C}R antagonist and melatonin receptor agonist aimed at improving sleep, is a first illustration of what selective modulation of 5-HT_{2C}R can achieve clinically. With the marketing of the high-efficacy 5-HT_{2C}R agonist lorcaserin (Belviq®) for obesity (and possibly smoking) and the active investigation of its potential therapeutic value for addictive disorders and epilepsy, for example, the field is gaining valuable information concerning the clinical opportunities for 5-HT_{2C}R agonists. Some of the unwanted effects on body mass of both older and newer antipsychotics may be explained by their 5-HT_{2C}R antagonism and this knowledge should help to design better antipsychotics devoid of massive weight gain and metabolic syndrome, which limits compliance for otherwise reasonably good medications. However, the situation is

probably more complex since not all 5-HT_{2C}R antagonists induce weight gain (e.g. agomelatine). The 5-HT_{2C}R may well be one of the two primary targets of fenfluramine/dexfenfluramine/benfluorex and explain their effects of weight loss, due to 5-HT_{2C}R agonism. Obviously, their 5-HT_{2B}R agonism represented a major and dramatic “side” effect and led to their discontinuation and that of other 5-HT_{2B}R agonists (Roth 2007). Surprisingly, it would seem that 5-HT_{2C}R agonism (Vabicaserin), may also be an approach to treat different aspects of schizophrenia, although more robust clinical data are needed before drawing firm conclusions. Also surprising, is the fact that both 5-HT_{2C}R agonists and antagonists have been reported to have antidepressant activities in animal models; is this related to pathway selection, inverse agonism or disease model? The complexity of the 5-HT_{2C}R is even greater than just expected from RNA editing and splicing: 5-HT_{2C}R are able to form homodimers that seem necessary for signal transduction and heteromers with e.g. NMDA or melatonin or ghrelin receptors (Herrick-Davis 2013; Herrick-Davis et al. 2004; 2005; 2006; 2007; 2012; 2015; Herrick-Davis and Farrington 2011; Bigford et al. 2012; Kamal et al. 2015; Schellekens et al. 2015). The latter raise further questions about the actual target of drugs such as agomelatine or lorcaserin and their effects in depression or eating behaviour. 5-HT_{2C}R as many others have a complex pattern of interactions with multiple GIPs (GPCR interacting proteins, see e.g. Becamel et al. 2001; 2002; 2004; Parker et al. 2003; Gavarini et al. 2006; Labasque et al. 2008; Maillet et al. 2008; Kleene et al. 2015). Finally, 5-HT_{2C}R antagonists (or at least inverse agonists), may help in controlling involuntary movements / muscle spasms that result from a marked increase in constitutive 5-HT_{2C}R activity in spinal cord injury patients. Future studies are still required to further untangle the complexities of 5-HT_{2C}R signalling, RNA editing and the neuronal mediators which regulate behaviour and physiology through this fascinating receptor that was first seen in the choroid plexus: “2C is to believe”.

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TABLE 1: Important preclinical and clinical developments in and around the 5-HT_{2C} receptor field.

1948	Synthesis of 5-HT	Rapport, 1948
1957	5-HT _M and _D receptors in guinea pig ileum	Gaddum and Picarelli, 1957
1978	Concept of neuroleptic receptor	Leysen et al. 1978
1979	Concept of 5-HT ₁ and 5-HT ₂ sites in brain	Peroutka and Snyder, 1979
1981	5-HT _{1A} and 5-HT _{1B} binding	Pedigo et al. 1981
1982-	8-OH-DPAT, a selective 5-HT _{1A} agonist and radioligand	HJjorth et al. 1982; Middlemiss and Fozard, 1983; Gozlan et al. 1983
1983	[³ H]Mesulergine, a dopaminergic ligand labels 5-HT ₂ sites	Closse, 1983
1984-	The choroid plexus receptor defined as 5-HT _{1C} receptor using [³ H]mesulergine, [³ H]5-HT, [¹²⁵ I]LSD and [¹²⁵ I]SCH23982	Pazos et al. 1984a; 1984b; Hoyer et al. 1985a; 1985b; Yagaloff and Hartig; 1985; 1986; Hoyer and Karpf, 1988
1985	Full characterization of 5-HT _{1A} , _{1B} , _{1C} receptors (species differences, no 5-HT _{1B} in pig brain), comparative distribution of 5-HT ₁ /5-HT ₂ sites in rodent brain	Hoyer et al. 1985a, 1985b; Pazos and Palacios, 1985; Pazos et al. 1985
1986-	Distribution of 5-HT ₁ and 5-HT ₂ receptors in the brain (species differences, no 5-HT _{1B} sites in human brain)	Hoyer et al. 1986a; 1986b
	Cloning of the beta ₂ adrenoceptor and 5-HT _{1A} receptor (the orphan G21)	Dixon et al. 1986; Fargin et al. 1988
	5-HT _{1C} couples to PLC activity, does not couple to cAMP	Conn et al. 1986; Palacios et al.

	production	1986, Hoyer et al. 1989
1987	Partial cloning of 5-HT _{1C} receptor	Lubbert et al. 1987
1988-	5-HT _{1C} and 5-HT ₂ receptors proposed to belong to same family based on pharmacological/operational and 2 nd messengers/transductional criteria	Hoyer 1988a, 1988b
	Full length cloning of 5-HT _{1C} and 5-HT ₂ receptors	Julius et al. 1988; Pritchett et al. 1988; Saltzmann et al. 1991; Xie et al. 1996
	5-HT _{1D} site identified in non-rodent brain	Hoyer et al. 1988; Waeber et al. 1988; Hoyer et al. 1988
1989-	Structural similarities between 5-HT _{2A} and 5-HT _{1C} receptors	Julius et al. 1989; Foguet et al. 1992b
	In situ hybridization of 5-HT _{1C} R mRNA in brain	Hofman and Mezey 1989; Mengod et al. 1990; Palacios et al. 1990; Pompeiano et al. 1994; Lopez-Gimenez et al. 2001; Serrats et al. 2005; Mengod et al. 2010
	5-HT _{1B} and 5-HT _{1D} receptors may be species homologues?	Hoyer and Middlemiss, 1989
1992	Structural similarities between the 5-HT _{2F} receptor (fundus) and 5-HT ₂ and 5-HT _{1C}	Foguet et al. 1992b; Lubbert et al. 1992
1993-	New nomenclature proposal for 5-HT receptors: 5-HT _{1C}	Humphrey et al. 1993

	becomes 5-HT _{2C} , 5-HT ₂ = 5-HT _{2A} , 5-HT _{2F} = 5-HT _{2B} , 7 families are recognised	
	Role of 5-HT _{2C} receptors in the amygdala / fear / aversion / anxiety / depression	Rocha et al. 1993; 1994; Cryan and Lucki, 2000; Millan, 2003; 2005; Rosenzweig Lipson et al. 2007b
1994	Official IUPHAR nomenclature 5-HT receptors	Hoyer et al. 1994
1995-	5-HT _{2C} R KO mice show feeding / metabolic defects, hyperphagia, late-onset obesity, insulin resistance, type 2 diabetes, epileptic seizures, an addiction phenotype, locomotor hyperactivity, neuroendocrine response to stress, anxiolytic phenotype.	Tecott et al. 1995; Brennan et al. 1997; Nonogaki et al. 1998; Vickers et al. 1999; Heisler and Tecott 2000; Tecott and Abdallah, 2003; Heisler et al., 2007a; 2007b; Wade et al. 2008; Tecott et al. 2005; Xu et al. 2008; 2010
	Synthesis of selective 5-HT _{2C} R antagonists, inverse agonists: SDZ SER082, SB 206553; SB-242084, RS-102221, SB2 43213, FR260010,	Nozulak et al. 1995; Kenneth et al. 1996; Bromidge et al. 1997; Bonhaus et al. 1997; Wood et al. 2001; Harada et al. 2006.
	Brain distribution of 5-HT _{2C} R using Antibodies	Abramowski et al. 1995
1996-	5-HT receptors aligned to human genome, 5-HT _{1D} alpha/beta become 5-HT _{1B} and 5-HT _{1D}	Hartig et al. 1996; Hoyer and Martin, 1997
1997-	5-HT _{2C} R is unique amongst GPCRs and subjected to multiple RNA editing. The unedited INI and the fully edited (VSV and VGV) isoforms show high and low constitutive activity.	Burns et al. 1997; Niswender et al. 1999; 2001; Rueter et al. 1999; Fitzgerald et al. 1999; see also Dracheva et al. 2003; 2008a; 2008b;

		2009; Camel et al. 2012; Du et al. 2006; 2007; Di Narzo et al 2014; 2015
1999-	Many antipsychotics are 5-HT _{2C} R inverse agonists/ antagonists. May explain obesity produced by antipsychotics.	Berg et al. 1999; Sullivan et al. 2015; Tsai et al. 2002; Templeman et al. 2005; Wallace et al. 2011
	The 5-HT _{2B} R is responsible for valvulopathies induced by agonists: fenfluramine, norfenfluramine, valproex, MDMA. 5-HT _{2B} R agonists are withdrawn from the market (fenfluramine, norfenfluramine, cabergoline, pergolide, valproex). Strict limitations for the development of 5-HT ₂ R agonists.	Rothmann et al. 2000; Setola et al. 2003; Roth, 2007; Huang et al. 2009; Rothmann and Baumann, 2009a, 2009b
2002-	5-HT _{2C} R agonism in nicotine, cocaine and alcohol addiction	Rocha et al. 2002; Filip and Cunningham, 2002; Tomkins et al. 2002; Bubar and Cunningham, 2006; 2007; 2008; Cunningham et al. 2011; 2013; 2014; Liu et al. 2011; 2012; Levin et al. 2011; Higgins et al. 2012; Rezvani et al. 2014; Anastasio et al. 2014, 2015
2003-	Agomelatine, the first 5-HT _{2C} R antagonist / melatonin R agonist in development for major depressive disorders	Millan et al. 2003; Millan, 2005; Millan et al. 2005;
2004-	5-HT _{2C} R Homomers, dimers; 5-HT _{2C} R/NMDAR heteromer; 5-HT _{2C} R /ghrelin receptor heteromer; 5-HT _{2C} R/melatonin MT ₂ R heteromer	Herrick-Davis et al. 2004, 2006, 2011, 2012, 2013; Bigford et al., 2012; Schellenkens et al. 2015; Kamal et al. 2015

2005-	Agomelatine: submission to EMEA for major depressive disorders; EMEA rejects agomelatine.	See EMEA/37021/2007
2005-	Discovery of 5-HT _{2C} R Agonists: WAY-163909; Vabicaserin (SCA136), Lorcaserin (APD356)	Dunlop et al. 2005; 2011; Thomsen et al. 2008
2007-	5-HT _{2C} R agonist vabicaserin (Pfizer); inverse agonists e.g. Sertindole; Development in schizophrenia	Siuciak et al. 2007; Dunlop et al. 2006; Rosenzweig-Lipson 2007a, 2012; Shen et al. 2014
2008-	Lorcaserin submitted to FDA for obesity	Thomsen et al. 2008; Smith et al. 2009; 2010; Higgs et al. 2016
2009	EMEA approves agomelatine as Valdoxan®, Melitor®, Thymanax® by Servier.	See EMA/633676/2014 (valdoxan), see EMA/695134/2016 (Thymanax)
2010-	5-HT _{2C} receptors in spinal cord injury, increased editing and constitutive activity, role in muscle spasms	Murray et al. 2010; Fouad et al. 2010; Murray et al. 2011; Husch et al. 2012
2012	FDA approves Lorcaserin for the treatment of certain forms of obesity as Belviq®, co-development between Arena and Eisai.	See FDA (2012)
2013-	Regular IUPHAR receptor Nomenclature updates in BJP	Alexander et al. 2013; 2015
	Crystal structure of 5-HT _{1B} and 5-HT _{2B} receptors reveals striking similarities in orthosteric binding sites, yet profound pharmacological differences.	Wacker et al. 2013; Wang et al. 2013; McCorvy and Roth, 2015

2014	Lorcaserin is active in nicotine addiction	See Eisai (2014)
	Development of vabicaserin in schizophrenia is stopped by Pfizer	See GovtTrials (2014)
2016	5-HT _{2C} R agonism effective in oxycodone abuse (rodents)	Cunningham et al. 2016