Kjell Fuxe

Publications 2012-2015 and 20 selected publications from complete list of published work with updates on especially significant publications from 2014-2015

A. Publications 2012 - 2015:

2012

1490. Marcellino D, Kehr J, Agnati LF, **Fuxe K.** 2012 Increased affinity of dopamine for D(2) -like versus D(1) -like receptors. Relevance for volume transmission in interpreting PET findings. Synapse. 66(3):196-203.

1491. Borroto-Escuela DO, Romero-Fernandez W, Mudó G, Pérez-Alea M, Ciruela F, Tarakanov AO, Narvaez M, Di Liberto V, Agnati LF, Belluardo N,**Fuxe K.** 2012 Fibroblast Growth Factor Receptor 1- 5-Hydroxytryptamine 1A Heteroreceptor Complexes and Their Enhancement of Hippocampal Plasticity. Biol Psychiatry. 71(1):84-91.

1492. Perez de la Mora MP, Gallegos-Cari A, Crespo-Ramirez M, Marcellino D, Hansson AC, **Fuxe K.** 2012 Distribution of dopamine D2-like receptors in the rat amygdala and their role in the modulation of unconditioned fear and anxiety. Neuroscience. 201:252-66.

1493. Guidolin D, Agnati LF, Albertin G, Tortorella C, **Fuxe K.** 2012 Bioinformatics aggregation predictors in the study of protein conformational diseases of the human nervous system. Electrophoresis. 33(24):3669-79.

1494. **Fuxe K,** Borroto-Escuela DO, Romero-Fernandez W, Tarakanov AO, Calvo F, Garriga P, Tena M, Narvaez M, Millón C, Parrado C, Ciruela F, Agnati LF, Narvaez JA, Díaz-Cabiale Z. 2012 On the existence and function of galanin receptor heteromers in the central nervous system. Front Endocrinol (Lausanne). 3:127.

1495. **Fuxe K,** Agnati LF, Mora F.2012 Brain integration: from networks to the cellular-molecular level. Brain Res. 1476:1-2.

1496. **Fuxe K,** Borroto-Escuela DO, Romero-Fernandez W, Diaz-Cabiale Z, Rivera A, Ferraro L, Tanganelli S, Tarakanov AO, Garriga P, Narváez JA, Ciruela F, Guescini M, Agnati LF. 2012 Extrasynaptic neurotransmission in the modulation of brain function. Focus on the striatal neuronal-glial networks. Front Physiol. 3:136.

1497. Agnati LF, Guidolin D, Guescini M, Battistin L, Stocchi V, De Caro R, Genedani S, **Fuxe K.** 2012 Aspects on the integrative actions of the brain from neural networks to "brain-body medicine". J Recept Signal Transduct Res. 32(4):163-80.

1498. Agnati LF, Barlow P, Ghidoni R, Borroto-Escuela DO, Guidolin D, **Fuxe K.**

2012 Possible genetic and epigenetic links between human inner speech, schizophrenia and altruism. Brain Res. 1476:38-57.

1499. Ferraro L, Frankowska M, Marcellino D, Zaniewska M, Beggiato S, Filip M, Tomasini MC, Antonelli T, Tanganelli S, **Fuxe K.** 2012 A novel mechanism of cocaine to enhance dopamine D2-like receptor mediated neurochemical and behavioral effects. An in vivo and in vitro study. Neuropsychopharmacology. 37(8):1856-66.

1500. **Fuxe K,** Borroto-Escuela DO, Romero-Fernandez W, Ciruela F, Manger P, Leo G, Díaz-Cabiale Z, Agnati LF. 2012 On the role of volume transmission and receptor-receptor interactions in social behaviour: focus on central catecholamine and oxytocin neurons. Brain Res. 1476:119-31.

1501. De-Miguel FF, **Fuxe K.** 2012 Extrasynaptic neurotransmission as a way of modulating neuronal functions. Front Physiol. 3:16.

1502. Agnati LF, Guidolin D, Cortelli P, Genedani S, Cela-Conde C, **Fuxe K.** 2012 Neuronal correlates to consciousness. The "Hall of Mirrors" metaphor describing consciousness as an epiphenomenon of multiple dynamic mosaics of cortical functional modules. Brain Res. 1476:3-21.

2013

1503. Romero-Fernandez W, Borroto-Escuela DO, Agnati LF, **Fuxe K.** 2013 Evidence for the existence of dopamine D2-oxytocin receptor heteromers in the ventral and dorsal striatum with facilitatory receptor-receptor interactions. Mol Psychiatry. 18(8):849-50.

1504. Frankowska M, Marcellino D, Adamczyk P, Filip M, **Fuxe K.** 2013 Effects of cocaine self-administration and extinction on D2 -like and A2A receptor recognition and D2 -like/Gi protein coupling in rat striatum. Addict Biol. 18(3):455-66.

1505. Borroto-Escuela DO, Romero-Fernandez W, Garriga P, Ciruela F, Narvaez M, Tarakanov AO, Palkovits M, Agnati LF, **Fuxe K.** 2013 G protein-coupled receptor heterodimerization in the brain. Methods Enzymol. 521:281-94.

1506. Agnati LF, Guidolin D, Woods AS, Ciruela F, Carone C, Vallelunga A, Escuela DO, Genedani S, **Fuxe K**. 2013 A new interpretative paradigm for Conformational Protein Diseases. Curr Protein Pept Sci. 14(2):141-60.

1507. Tarakanov AO, **Fuxe KG.** 2013 Integrin triplets of marine sponges in the murine and human MHCI-CD8 interface and in the interface of human neural receptor heteromers and subunits. Springerplus. 2(1):128.

1508. Borroto-Escuela DO, Ravani A, Tarakanov AO, Brito I, Narvaez M, Romero-Fernandez W, Corrales F, Agnati LF, Tanganelli S, Ferraro L, **Fuxe K.** 2013 Dopamine D2 receptor signaling dynamics of dopamine D2-neurotensin 1 receptor heteromers. Biochem Biophys Res Commun. 435(1): 140-6.

1509. **Fuxe K,** Borroto-Escuela DO, Romero-Fernandez W, Zhang WB, Agnati LF. 2013 Volume transmission and its different forms in the central nervous system. Chin J Integr Med. 19(5):323-9.

1510. Agnati LF, Guidolin D, Battistin L, Pagnoni G, **Fuxe K.** 2013 The neurobiology of imagination: possible role of interaction-dominant dynamics and default mode network. Front Psychol. 4:296.

1511. Borroto-Escuela DO, Romero-Fernandez W, Rivera A, Van Craenenbroeck K, Tarakanov AO, Agnati LF, **Fuxe K.** 2013 On the G-protein-coupled receptor heteromers and their allosteric receptor-receptor interactions in the central nervous system: focus on their role in pain modulation. Evid Based Complement Alternat Med. 2013:563716.

1512. **Fuxe K**, Borroto-Escuela DO, Romero-Fernandez W, Palkovits M, Tarakanov AO, Ciruela F, Agnati LF 2014 Moonlighting proteins and protein-protein interactions as neurotherapeutic targets in the G protein-coupled receptor field. Neuropsychopharmacology. 39(1):131-55.

1513. Borroto-Escuela DO, Flajolet M, Agnati LF, Greengard P, **Fuxe K.** 2013 Bioluminescence resonance energy transfer methods to study G protein-coupled receptor-receptor tyrosine kinase heteroreceptor complexes. Methods Cell Biol. 117:141-64.

1514. Borroto-Escuela DO, Corrales F, Narvaez M, Oflijan J, Agnati LF, Palkovits M, **Fuxe K.** 2013 Dynamic modulation of FGFR1-5-HT1A heteroreceptor complexes. Agonist treatment enhances participation of FGFR1 and 5-HT1A homodimers and recruitment of β-arrestin2. Biochem Biophys Res Commun. 441(2):387-92.

1515. Guidolin D, Agnati LF, Tortorella C, Marcoli M, Maura G, Albertin G, **Fuxe K.** 2014 Neuroglobin as a regulator of mitochondrial-dependent apoptosis: A bioinformatics analysis. Int J Mol Med. 33(1): 111-6.

1516. **Kjell Fuxe** , Dasiel O. Borroto-Escuela , Alexander Tarakanov , Wilber Romero Fernandez , Paul Manger , Alicia Rivera , Kathleen van Craenenbroeck , Kamila Skieterska , Zaida Diaz-Cabiale , Malgorzata Filip ,l, Luca Ferraro , Sergio Tanganelli, Diego Guidolin , Staffan Cullheim , Miguel Perez de la Mora , Luigi F. Agnati 2013 Understanding the balance and integration of volume and synaptic transmission. Relevance for psychiatry.Neurology,Psychiatry and Brain Research 19 : 141-158.

2014-2015

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1517. Sahlholm K, Marcellino D, Nilsson J, Ögren SO, **Fuxe K**, Århem P. Typical and atypical antipsychotics do not differ markedly in their reversibility of antagonism of the dopamine D2 receptor Int J Neuropsychopharmacol. 2014 Jan;17(1):149-55.

1518. Borroto-Escuela DO, Romero-Fernandez W, Narvaez M, Oflijan J, Agnati LF,

Fuxe K. 2014 Hallucinogenic 5-HT2AR agonists LSD and DOI enhance dopamine D2R protomer recognition and signaling of D2-5-HT2A heteroreceptor complexes. Biochem Biophys Res Commun. 443(1):278-84.

1519. Suárez-Boomgaard D, Gago B, Valderrama-Carvajal A, Roales-Buján R, Craenenbroeck KV, Duchou J, Borroto-Escuela DO, Medina-Luque J, de la Calle A, **Fuxe K,** Rivera A. Dopamine D_4 receptor counteracts morphine-induced changes in μ opioid receptor signaling in the striosomes of the rat caudate putamen.
Int J Mol Sci. 2014 Jan 21;15(1):1481-98.

1520. Beggiato S, Tanganelli S, **Fuxe K**, Antonelli T, Schwarcz R, Ferraro L. Endogenous kynurenic acid regulates extracellular GABA levels in the rat prefrontal cortex. Neuropharmacology. 2014 Jul;82:11-8.

1521. Edelstein L, **Fuxe K**, Smythies J. Life without glutamate: the epigenetic effects of glutamate deletion. Front Mol Neurosci. 2014 Feb 26;7:14.

1522**.** Jastrzębska J, Nowak E, Smaga I, Bystrowska B, Frankowska M, Bader M, Filip M, **Fuxe K.** Adenosine (A)(2A)receptor modulation of nicotine-induced locomotor sensitization. A pharmacological and transgenic approach. Neuropharmacology. 2014 Jun;81:318-26.

1523. Borroto-Escuela DO, Brito I, Romero-Fernandez W, Di Palma M, Oflijan J, Skieterska K, Duchou J, Van Craenenbroeck K, Suárez-Boomgaard D, Rivera A, Guidolin D, Agnati LF, **Fuxe K**. The G protein-coupled receptor heterodimer network (GPCR-HetNet) and its hub components. Int J Mol Sci. 2014 May 14;15(5):8570-90.

1524. Narváez M, Millón C, Borroto-Escuela D, Flores-Burgess A, Santín L, Parrado C, Gago B, Puigcerver A, **Fuxe K**, Narváez JA, Díaz-Cabiale Z. Galanin receptor 2-neuropeptide Y Y1 receptor interactions in the amygdala lead to increased anxiolytic actions. Brain Struct Funct. 2014 May 20.

1525. **Fuxe K,** Tarakanov A, Romero Fernandez W, Ferraro L, Tanganelli S, Filip M, Agnati LF, Garriga P, Diaz-Cabiale Z, Borroto-Escuela DO. Diversity and Bias through Receptor-Receptor Interactions in GPCR Heteroreceptor Complexes. Focus on Examples from Dopamine D2 Receptor Heteromerization.
Front Endocrinol (Lausanne). 2014 May 13;5:71.

1526. Agnati LF, Guidolin D, Maura G, Marcoli M, Leo G, Carone C, De Caro R, Genedani S, Borroto-Escuela DO, **Fuxe K.** Information handling by the brain: proposal of a new "paradigm" involving the roamer type of volume transmission and the tunneling nanotube type of wiring transmission. J Neural Transm. 2014 Dec;121(12):1431-49.

1527. **Fuxe K,** Agnati LF, Borroto-Escuela DO. The impact of receptor-receptor interactions in heteroreceptor complexes on brain plasticity. Expert Rev Neurother. 2014 Jul;14(7):719-21

1528. **Fuxe K,** Borroto-Escuela DO, Tarakanov AO, Romero-Fernandez W, Ferraro

L, Tanganelli S, Perez-Alea M, Di Palma M, Agnati LF. Dopamine D2 heteroreceptor complexes and their receptor-receptor interactions in ventral striatum: novel targets for antipsychotic drugs. Prog Brain Res. 2014;211:113-39.

1529. Agnati LF, **Fuxe K**. Extracellular-vesicle type of volume transmission and tunnelling-nanotube type of wiring transmission add a new dimension to brain neuro-glial networks. Philos Trans R Soc Lond B Biol Sci. 2014 Sep 26;369(1652)

1530. Patzke N, Bertelsen MF, **Fuxe K,** Manger PR. Nuclear organization of cholinergic, catecholaminergic, serotonergic and orexinergic systems in the brain of the Tasmanian devil (Sarcophilus harrisii). J Chem Neuroanat. 2014 Nov;61-62:94-106

1531. Borroto-Escuela DO, Narvaez M, Di Palma M, Calvo F, Rodriguez D, Millon C, Carlsson J, Agnati LF, Garriga P, Díaz-Cabiale Z, **Fuxe K**. Preferential activation by galanin 1-15 fragment of the GalR1 protomer of a GalR1-GalR2 heteroreceptor complex. Biochem Biophys Res Commun. 2014 Sep 26;452(3):347-53.

1532. Agnati LF, Guidolin D, Marcoli M, Genedani S, Borroto-Escuela D, Maura G, **Fuxe K.** "Neuro-semeiotics" and "free-energy minimization" suggest a unified perspective for integrative brain actions: focus on receptor heteromers and Roamer type of volume transmission. Curr Protein Pept Sci. 2014;15(7):703-18.

1533.Di Liberto V, Mudo G, **Fuxe K,** Belluardo N. Interactions between cholinergic and fibroblast growth factor receptors in brain trophism and plasticity
Curr Protein Pept Sci. 2014;15(7):691-702.

1536.Díaz-Cabiale Z, Flores-Burgess A, Parrado C, Narváez M, Millón C, Puigcerver A, Coveñas R, **Fuxe K**, Narváez JA. Galanin receptor/neuropeptide y receptor interactions in the central nervous system Curr Protein Pept Sci. 2014;15(7):666-72

1537. Van Craenenbroeck K, Borroto-Escuela DO, Skieterska K, Duchou J, Romero-Fernandez W, **Fuxe K.** Role of dimerization in dopamine D(4) receptor biogenesis. Curr Protein Pept Sci. 2014;15(7):659-65

1538. Ferraro L, Beggiato S, Borroto-Escuela DO, Ravani L, O'Connor WT, Tomasini MC, Borelli AC, Agnati LF, Antonelli T, Tanganelli S, **Fuxe K**. Neurotensin NTS1-dopamine D2 receptor-receptor interactions in putative receptor heteromers: relevance for Parkinson's disease and schizophrenia. Curr Protein Pept Sci. 2014;15(7):681-90

1539. Beggiato S, Antonelli T, Tomasini MC, Borelli AC, Agnati LF, Tanganelli S, **Fuxe K**, Ferraro L. Adenosine A2A-D2 receptor-receptor interactions in putative heteromers in the regulation of the striato-pallidal gaba pathway: possible relevance for parkinson's disease and its treatment. Curr Protein Pept Sci. 2014;15(7):673-80.

1540. Tena-Campos M, Ramon E, Rivera D, Borroto-Escuela DO, Romero-Fernandez W, **Fuxe K**, Garriga P. G-protein-coupled receptors oligomerization: emerging signaling units and new opportunities for drug design. Curr Protein Pept Sci. 2014;15(7):648-58.

1541. **Fuxe K,** Borroto-Escuela D, Fisone G, Agnati LF, Tanganelli S. Understanding the role of heteroreceptor complexes in the central nervous system. Curr Protein Pept Sci. 2014;15(7):647.

1542. Romero-Fernandez W, Borroto-Escuela DO, Vargas-Barroso V, Narváez M, Di Palma M, Agnati LF, Larriva Sahd J, **Fuxe K.** Dopamine D1 and D2 receptor immunoreactivities in the arcuate-median eminence complex and their link to the tubero-infundibular dopamine neurons. Eur J Histochem. 2014 Jul 18;58(3):2400.

1543. Navarro G, Borroto-Escuela DO, **Fuxe K**, Franco R. Potential of caveolae in the therapy of cardiovascular and neurological diseases. Front Physiol. 2014 Sep 30;5:370.

1544. Guidolin D, Agnati LF, Marcoli M, Borroto-Escuela DO, **Fuxe K**. G-protein-coupled receptor type A heteromers as an emerging therapeutic target. Expert Opin Ther Targets. 2015 Feb;19(2):265-83

1545**.** Wydra K, Suder A, Borroto-Escuela DO, Filip M, **Fuxe K.** On the role of A2A and D 2 receptors in control of cocaine and food-seeking behaviors in rats. Psychopharmacology (Berl). 2014 Nov 26. [Epub ahead of print]

1546**. Fuxe K**, Guidolin D, Agnati LF, Borroto-Escuela DO. Dopamine heteroreceptor complexes as therapeutic targets in Parkinson's disease.nExpert Opin Ther Targets. 2014 Dec 8:1-22.

1547**. Fuxe K,** Borroto-Escuela DO, Ciruela F, Guidolin D and Agnati LF. (2014) Receptor-receptor interactions in heteroreceptor complexes: a new principle in biology. Focus on their role in learning and memory. Neurosci Discov. 2014;2:6. http://dx.doi.org/10.7243/2052-6946-2-6

1548.Millón C, Flores-Burgess A, Narváez M, Borroto-Escuela DO, Santín L, Parrado C, Narváez JA, **Fuxe K**, Díaz-Cabiale Z. A Role For Galanin N-Terminal Fragment (1-15) in Anxiety- And Depression-Related Behaviours in Rats. Int J Neuropsychopharmacol. 2014 Oct 31.

1549.Borroto-Escuela DO, Narvaez M, Pérez-Alea M, Tarakanov AO, Jiménez-Beristain A, Mudó G, Agnati LF, Ciruela F, Belluardo N, **Fuxe K**. Evidence for the existence of FGFR1-5-HT1A heteroreceptor complexes in the midbrain raphe 5-HT system.
Biochem Biophys Res Commun. 2015 Jan 2;456(1):489-93.

1550.Wydra K, Gołembiowska K, Suder A, Kamińska K, **Fuxe K**, Filip M. On the role of adenosine (A)2A receptors in cocaine-induced reward: a pharmacological and neurochemical analysis in rats. Psychopharmacology (Berl). 2015 Jan;232(2):421-35.

1551. Carone C, Genedani S, Leo G, Filaferro M, **Fuxe K**, Agnati LF. In vitro effects of cocaine on tunneling nanotube formation and extracellular vesicle release in glioblastoma cell cultures. J Mol Neurosci. 2015 Jan;55(1):42-50.

1552. Leo G, Guescini M, Genedani S, Stocchi V, Carone C, Filaferro M, Sisti D, Marcoli M, Maura G, Cortelli P, Guidolin D, Fuxe K, Agnati LF. Acute isoproterenol induces anxiety-like behavior in rats and increases plasma content of extracellular vesicles. Physiol Behav. 2015 Apr 1;142:79-84

1553. Zhang WB, Wang GJ, **Fuxe K**. Classic and Modern Meridian Studies: A Review of Low Hydraulic Resistance Channels along Meridians and Their Relevance for Therapeutic Effects in Traditional Chinese Medicine. Evid Based Complement Alternat Med. 2015;2015:410979

B: 20 selected publications

The discovery of the central monoamine neurons

Dahlström, A., **Fuxe**, K., **1964** Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiol. Scand. 62, SUPPL 232:1-55. (part of Fuxe thesis 1965)

Fuxe K, Dahlström A, Höistad M, Marcellino D, Jansson A, Rivera A, Diaz-Cabiale Z, Jacobsen K, Tinner-Staines B, Hagman B, Leo G, Staines W, Guidolin D, Kehr J, Genedani S, Belluardo N, Agnati LF. **2007** From the Golgi-Cajal mapping to the transmitter-based characterization of the neuronal networks leading to two modes of brain communication: wiring and volume transmission.Brain Res Rev. 55(1),17-54.

Fuxe K, Dahlström A, Jonsson G, Marcellino D, Guescini M, Dam M, Manger P, Agnati L.**2010** The discovery of central monoamine neurons gave volume transmission to the wired brain. Prog Neurobiol. 90(2), 157-75.

The discovery of volume transmission as a novel major mode of cellular communication in the CNS

Agnati, L., **Fuxe**, K., Zoli, M., Zini, I., Toffano, G., Ferraguti, F., **1986** A correlation analysis of the regional distribution of central enkephalin and β -endorphin immunoreactive terminals and of opiate receptor in adult and old male rats. Evidence of the existence of two main types of communications in the central nervous system: The volume transmission and the wiring transmission. Acta Physiol. Scand. 128, 201-207.

Fuxe, K., Agnati, L.F. **1991** Two principle modes of electrochemical communicationin the brain: volume versus wiring transmission. In: **Fuxe**, K., Agnati, L.F.(Eds.), Volume Transmission in the Brain: Novel Mechanisms of Neuronal Transmission. Raven Press, New York, pp. 1–9.

Fuxe K and Agnati L F **2009** Cell–Cell Communication through the Extracellular Space. In: Squire LR (ed.) Encyclopedia of Neuroscience,volume 2, pp. 655-664. Oxford: Academic Press.

Marcellino D, Kehr J, Agnati LF, **Fuxe** K. **2011** Increased affinity of dopamine for D(2) -like versus D(1) -like receptors. Relevance for volume transmission in interpreting PET findings.Synapse. 2012 66(3):196-203

Fuxe K, Borroto-Escuela DO, Romero-Fernandez W, Diaz-Cabiale Z, Rivera A, Ferraro L, Tanganelli S, Tarakanov AO, Garriga P, Narváez JA, Ciruela F, Guescini M, Agnati LF. **2012** Extrasynaptic neurotransmission in the modulation of brain function. Focus on the striatal neuronal-glial networks. Front Physiol. 3:136.

Fuxe K , Dasiel O. Borroto-Escuela , Alexander Tarakanov ,Wilber Romero Fernandez , Paul Manger , Alicia Rivera , Kathleen van Craenenbroeck , Kamila Skieterska , Zaida Diaz-Cabiale , Malgorzata Filip ,l, Luca Ferraro , Sergio Tanganelli , Diego Guidolin , Staffan Cullheim , Miguel Perez de la Mora , Luigi F. Agnati **2013** Understanding the balance and integration of volume and synaptic transmission. Relevance for psychiatry. Neurology,Psychiatry and Brain Research 19 : 141-158.

Discoveries of receptor-receptor interactions in heteroreceptor complexes in the CNS and in neuropsychopharmacology

Fuxe, K., Agnati, L.F., Benfenati, F., Celani, M.F., Zini, I., Zoli, M., Mutt, V.**1983** Evidence for the existence of receptor- receptor interactions in the central nervous system. Studies on the regulation of monoamine receptors by neuropeptides. J. Neural Transm. 18, 165-179.

Fuxe, K., **1979.** Dopamine receptor agonists in brain research and as therapeutic agents. TINS 2, 1-4.

Tarakanov AO, **Fuxe** KG. **2010** Triplet puzzle: homologies of receptor heteromers., J Mol Neurosci. Jun;41(2),294-303.

Borroto-Escuela DO, Romero-Fernandez W, Tarakanov AO, Gómez-Soler M, Corrales F, Marcellino D, Narvaez M, Frankowska M, Flajolet M, Heintz N, Agnati LF, Ciruela F, **Fuxe** K., **2010.**Characterization of the A(2A)R-D(2)R interface: focus on the role of the C-terminal tail and the transmembrane helices. Biochem Biophys Res Commun. 402, 801-807.

Fuxe, K., D. Marcellino, G.Leo, LF.Agnati **2010** Molecular integration via allosteric interactions in receptor heteromers. A working hypothesis. Curr Opin Pharmacol 10(1): 14-22

Borroto-Escuela DO, Romero-Fernandez W, Tarakanov AO, Ciruela F, Agnati LF, **Fuxe** K. **2011** On the existence of a possible A2A-D2- β -Arrestin2 complex: A2A agonist modulation of D2 agonist-induced β -arrestin2 recruitment.J Mol Biol. 2011 Mar 11;406(5):687-99.

Borroto-Escuela DO, Romero-Fernandez W, Mudó G, Pérez-Alea M, Ciruela F, Tarakanov AO, Narvaez M, Di Liberto V, Agnati LF, Belluardo N, **Fuxe** K. **2012** Fibroblast Growth Factor Receptor 1- 5-Hydroxytryptamine 1A Heteroreceptor Complexes and Their Enhancement of Hippocampal Plasticity. Biol Psychiatry. 71(1): 84-91

Romero-Fernandez W, Borroto-Escuela DO, Agnati LF, **Fuxe** K. Evidence for the existence of dopamine D2-oxytocin receptor heteromers in the ventral and dorsal striatum with facilitatory receptor-receptor interactions. Mol Psychiatry. **2013** Aug;18(8):849-50.

Borroto-Escuela DO, Romero-Fernandez W, Narvaez M, Oflijan J, Agnati LF, **Fuxe** K. Hallucinogenic 5-HT2AR agonists LSD and DOI enhance dopamine D2R protomer recognition and signaling of D2-5-HT2A heteroreceptor complexes.Biochem Biophys Res Commun. **2014** 443(1):278-84.

Fuxe K, Borroto-Escuela DO, Romero-Fernandez W, Palkovits M, Tarakanov AO, Ciruela F, Agnati LF. **2014** Moonlighting proteins and protein-protein interactions as neurotherapeutic targets in the G protein-coupled receptor field. Neuropsychopharmacology. Jan;39(1):131-55.

Fuxe K, Borroto-Escuela DO, Ciruela F, Guidolin D and Agnati LF. (2014) Receptor-receptor interactions in heteroreceptor complexes: a new principle in biology. Focus on their role in learning and memory. Neurosci Discov. 2014;2:6. http://dx.doi.org/10.7243/2052-6946-2-6

D.Update based on publications of special significance from the last year

83.Fuxe K, Borroto-Escuela DO, Ciruela F, Guidolin D and Agnati LF. (2014) Receptor-receptor interactions in heteroreceptor complexes: a new principle in biology. Focus on their role in learning and memory. Neurosci Discov. 2014;2:6. http://dx.doi.org/10.7243/2052-6946-2-6

Summary

In this publication **83** we introduced a new hypothesis on the structure and operation of the **molecular engram**. The molecular basis of learning and memory is proposed to be based on novel heteroreceptor complxes formed and on the reorganization of homo- and heteroreceptor complexes in the postjunctional membrane of synapses. This takes place through **allosteric** receptor-receptor interactions in different types of homo-heteroreceptor complexes (built up of receptor-ion channel-adapter protein complexes). This leads also to changes in the **prejunctional** receptor complexes to facilitate the maintenance of the pattern of transmitter release to be learned through signals from the altered postjunctionl membrane.**Long-term memory** may be created by the transformation of parts of the heteroreceptor complexes into unique transcription factors which can lead to the formation of specific adapter proteins which can consolidate the homo and-heteroreceptor complexes into long-lived complexes with conserved allosteric receptor-receptor interactions. Thus, new types of **"barcodes"** can be formed based on reorganized homo and heterreceptor complexes and on novel receptor complexes formed in the **post and perisynaptic** membranes of synapses through **allosteric** mechanisms.

Hypothesis

Novel allosteric receptor-receptor interactions in sets of altered homo and heteroreceptor complexes in postsynaptic and perisynaptic membranes act as a molecular basis for learning and memory, the molecular engram

Learning A new temporal pattern of release of multiple transmitters in the

synapse is learnt through a transient reorganization of sets of homo- and heteroreceptor complexes (receptors, ion channels, adapter proteins) in the postsynaptic and adjacent perisynaptic membranes. This results in novel allosteric receptor-receptor interactions altering receptor protomer functions. In this way a short-term memory is created from the novel pattern of transmitter release to be learned leading to a **novel transient bar-code** representing a **molecular engram** of **short term memory.**

The novel pattern of transmitter release to be learned can be stabilized by **reorganization of pre-synaptic and associated perisynaptic homo-heteroreceptor complexes**. This can involve agonist dependent processes, release of soluble molecules like neuropeptides and trophic factors and exosomes from the post-perisynaptic membranes as a result of the new bar-code.

Long-term memory Consolidation of the reorganized homo-heteroreceptor complexes in the postjunctional membrane produces the **molecular engram of long-term memory**, a **permanent** barcode
1.Production of **unique transcription** factors from the new barcode;
2. Unique adapter proteins formed through trough these transcription factors Thus ,protein synthesis is needed
3. consolidation of the receptor complexes **themselves** and also to their link to the **cytoskeleton**.
4. **Volume transmission signals** from adjacent terminals of **emotional** pathways reaching the postjunctional membrane leads to life-long memories through **exceptional formation of special adapter proteins**

81. Wydra K, Suder A, Borroto-Escuela DO, Filip M, Fuxe K. On the role of A2A and D 2 receptors in control of cocaine and food-seeking behaviors in rats. Psychopharmacology (Berl). 2014 Nov 26. [Epub ahead of print]

86. Wydra K, Gołembiowska K, Suder A, Kamińska K, **Fuxe K**, Filip M. On the role of adenosine (A)2A receptors in cocaine-induced reward: a pharmacological and neurochemical analysis in rats. Psychopharmacology (Berl). 2015 Jan;232(2):421-35.

Strong support was obtained for our hypothesis that A2AR-D2R heteromers are critically involved in cocaine addiction based on two **psychopharmacology** papers **(81,86).** More specifically the activation of the A2AR protomer of the heteroreceptor complex inhibits the development of addictive behavior through antagonistic allosteric A2A-D2 receptor-receptor interactions in these complexes.This brings down the D2 protomer signaling of this complex in the ventral striato-pallidal GABA pathway which increases the activity of this pathway leading to antireward actions (punishment).***Targeting this receptor complex may lead to development of novel drugs against cocaine addiction.***

61. Borroto-Escuela DO, Brito I, Romero-Fernandez W, Di Palma M, Oflijan J, Skieterska K, Duchou J, Van Craenenbroeck K, Suárez-Boomgaard D, Rivera A,

Guidolin D, Agnati LF, **Fuxe K**. The G protein-coupled receptor heterodimer network (GPCR-HetNet) and its hub components. Int J Mol Sci. 2014 May 14;15(5):8570-90.

The overall architecture of the GPCR-GPCR heteroreceptor complexes is presented

The entire number of demonstrated GPCR heteroreceptor complexes was linked together and represented as a GPCR heterodimer network (GPCR-HetNet: *http://www.iiia.csic.es/~ismel/GPCR-Nets/*) (61). In this study static/non-dynamical human GPCR data were manually collected with a total of 187 different nodes/protomers (until August 2014) derived from 537 GPCR-GPCR edges/interaction studies in annotated databases and literature. This information was then integrated in a large scale graph, called the GPCR heterodimer network (GPCR-HetNet), where the nodes are the receptor protomers and the edges are their relationships. The results from the GPCR-HetNet indicate a scale free model in which only a few of the protomers dominate the connectivity and hold the network together. Two different hub criteria show that the dopamine D2 receptor, the beta-2 adrenergic receptor, the growth hormone secretagogue receptor type 1, the mu-type opioid receptor, the secretin receptor, the delta-type opioid receptor and the Cannabinoid receptor 1 are the hubs in the network. Other highly connected protomers are also identified and described in this study, as well as the emergence of potential allosteric interaction avenues and of higher order heteroreceptor complexes. In this study the overall architecture of the GPCR-GPCR heteroreceptor complexes is for the first time presented, which provides relevant insight into receptor-receptor interaction connectivity, topology and organization. This may help researchers to better understand the complexity of GPCR heteroreceptor systems.

82. Fuxe K, Guidolin D, Agnati LF, Borroto-Escuela DO. Dopamine heteroreceptor complexes as therapeutic targets in Parkinson's disease.Expert Opin Ther Targets. 2014 Dec 8:1-22.

The hypothesis is introduced that the molecular mechanism for development of l-DOPA-induced dyskinesias involve a reorganization of the D1R and D2R heteroreceptor complexes in the direct and indirect efferent pathways respectively and a disbalance of the signaling of dopamine receptor homomers versus non-DA receptor homomers in these pathways. It gives a novel understanding of the mechanism for the antidyskinetic actions of several drugs.
The hypothesis also states that combined blockade of mGluR5 and A2AR receptors in early PD in homomers and in A2AR-D2R-mGluR5 heterotrimeric complexes would restore the balance of A2AR/mGluR5 and D2R signaling and remove the brake on D2R protomer signaling in this heteroreceptor complex. Therefore, combined treatment with these antagonists early in PD and later on with l-DOPA or dopamine receptor agonists as PD progresses is an exciting novel strategy for restoring motor function in early and late PD and for preventing motor complication to develop like dyskinesias.