**Supplementary Table S2:** Age-related alterations in the protein density and affinity to ligands (or other compounds) of brain Gi/Go-coupled GPCRs. Information on alterations in mRNA levels, in Binding potential and in Affinity of ligand binding were also included when available. Binding potential is the *Bmax* to *KD* ratio, with *Bmax* being the total density (a measure of concentration) of receptors in a sample of tissue, and *KD* the equilibrium dissociation constant of the radioligand. Affinity of ligand binding is the inverse of *KD*. RT-PCR - Reverse Transcription Polymerase Chain Reaction; qPCR – quantitative (‘real-time’) PCR.

|  |  |  |  | **Age-associated alterations in:** |  |
| --- | --- | --- | --- | --- | --- |
| **Receptors Classes** | **Brain Region** | **Animal** | **Method; receptor subtype analyzed** | **Protein Density** | **Affinity to ligand / other** | **Others, including** **Binding Potential** | **Reference** |
| Adrenoceptors | Hindbrain (Rhombencephalon) | Male New Zealand White Rabbits (1 month-3 years) | [3H]clonidine binding; **α2** | Decreased | Increased |  | (Hamilton et al., 1984) |
| Cerebellum – Stratum granulare | Human *(postmortem)* (20-70 years) | [3H]UK-14304 binding (Autoradiography); **α2** | No alteration |  |  | (Pascual et al., 1991) |
| Lateral periaqueductal area | No alteration |  |  | (Pascual et al., 1991) |
| Interpeduncular nucleus | No alteration |  |  | (Pascual et al., 1991) |
| Forebrain (Prosencephalon) | Male New Zealand White Rabbits (1 month-3 years) | [3H]clonidine binding; **α2** | Decreased |  |  | (Hamilton et al., 1984) |
| Hypothalamus – Ventromedial nucleus | Human *(postmortem)* (20-70 years) | [3H]UK-14304 binding (Autoradiography); **α2** | No alteration |  |  | (Pascual et al., 1991) |
| Hippocampus – CornuAmmonis area 1 | No alteration |  |  | (Pascual et al., 1991) |
| Amygdala – Nucleus medialis and basalis accesorius | No alteration |  |  | (Pascual et al., 1991) |
| Claustrum | Decreased |  |  | (Pascual et al., 1991) |
| Basal Ganglia – Striatum – Caudate and Putamen | Decreased |  |  | (Pascual et al., 1991) |
| Basal Ganglia – Nucleus basalis of Meynert | Decreased |  |  | (Pascual et al., 1991) |
| Cerebral cortex | Wistar rats (70 days and 2 years) | [3H]clonidine binding; **α2** | No alteration | No alteration |  | (Nomura et al., 1986) |
| Cerebral cortex – Frontal cortex – Layer I | Human *(postmortem)* (20-70 years) | [3H]UK-14304 binding (Autoradiography); **α2** | Decreased |  |  | (Pascual et al., 1991) |
| Cerebral cortex – Frontal cortex – Prefrontal cortex | Rhesus monkeys *(Macaca mulatta)* (3-10 years and >20 years) | [3H]clonidine binding (Autoradiography); **α2** | Decreased (Layer I) | No alteration |  | (Bigham and Lidow, 1995) |
| Human *(postmortem)* (1-88 years) | UK14304 stimulated [35S]GTPγS binding; **α2** |  |  | Decreased agonist (UK14304) stimulated [35S]GTPγS binding | (González-Maeso et al., 2002) |
| Cerebral cortex - Frontal cortex – Primary motor cortex - Layer I-V | Rhesus monkeys *(Macaca mulatta)* (3-10 years and >20 years) | [3H]clonidine binding (Autoradiography); **α2** | Decreased | No alteration |  | (Bigham and Lidow, 1995) |
| Cerebral cortex - Parietal cortex – Somatosensorycortex – Layer I-V | Decreased | No alteration |  | (Bigham and Lidow, 1995) |
| Cerebral cortex -Temporal cortex-Layer I | Human *(postmortem)* (20-70 years) | [3H]UK-14304 binding (Autoradiography); **α2** | Decreased |  |  | (Pascual et al., 1991) |
| Cerebral cortex – Occipital cortex - Primary visual cortex | Decreased (Layer III) |  |  | (Pascual et al., 1991) |
| Rhesus monkeys *(Macaca mulatta)* (3-10 years and >20 years) | [3H]clonidine binding (Autoradiography); **α2** | No alteration | No alteration |  | (Bigham and Lidow, 1995) |
| Brainstem -Trigeminal nucleus  | Human *(postmortem)* (20-70 years) | [3H]UK-14304 binding (Autoradiography); **α2** | No alteration |  |  | (Pascual et al., 1991) |
| Dopamine Receptors | Cerebellum | Male Fischer 344 rats (6 and 24 months) | [3H]spiperone binding (Autoradiography); **D2**[3H]nemonapride binding (Autoradiography); **D2** | No alteration |  |  | (Araki et al., 1997) |
| Male Wistar rats (3,12 and 24 months) | [3H]spiroperidol binding (Autoradiography); **D2-like** (probably D3) | Decreased | No alteration |  | (Ricci et al., 1996) |
| Corpora quadrigemina – Inferior Colliculus | Fischer 344 rats (3 and 24 months) | [35S]-labelled mRNA hybridization and Northern blot; **D2** |  |  | Decreased D2 mRNA levels | (Weiss et al., 1992) |
| Substantia nigra | Male Fischer 344 rats (6 and 24 months) | [3H]spiperone binding (Autoradiography); **D2**[3H]nemonapride binding (Autoradiography); **D2** | No alteration |  |  | (Araki et al., 1997) |
| Male Wistar-Kyoto rats (6 and 24 months) | RT-PCR (mRNA); **D2** |  |  | Decreased D2 mRNA levels | (Valerio et al., 1994) |
| Human (18-73 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D3** |  |  | No alteration in nondisplaceable binding potential of an agonist | (Nakajima et al., 2015) |
| Human *(postmortem)* (0-20 and >65 years years) | [3H]spiroperidol binding; **D2** | Decreased | No alteration |  | (Rinne, 1987) |
| Male Sprague-Dawleyrats (10 weeks and 18-20 months) | qPCR (mRNA); **D2**Western Blot; **D2** | Decreased |  | Decreased D2 mRNA levels | (Villar-Cheda et al., 2014) |
| Substantia nigra - Ventral Tegmental area | Human (19-55 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D3** |  |  | No alteration in binding potential of an agonist | (Matuskey et al., 2016) |
| [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (Whole-brain voxel-wise analysis); **D3** |  |  | Increased binding potential of an agonist | (Matuskey et al., 2016) |
| Forebrain - Anterior Limbic cortex | New Zealand White Rabbits (5 month and 5.5 years) | [3H]spiroperidol binding; **Dopamine receptors** | Decreased | No alteration |  | (Thal et al., 1980) |
| Thalamus | Human (21-82 years) | [11C]FLB 457 binding (PET); **D2** |  |  | Decreased binding potential of an antagonist | (Inoue et al., 2001) |
| Human (19-55 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D2/3** |  |  | No alteration in binding potential of an agonist | (Matuskey et al., 2016) |
| Thalamus – Medial and Lateral Nuclear group | Human (19-74 years) | [11C]FLB 457 binding (PET); **D2; D3** |  |  | Decreased binding potential of an antagonist | (Kaasinen et al., 2000) |
| Hypothalamus | Human (18-73 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D3** |  |  | No alteration in nondisplaceable binding potential of an agonist | (Nakajima et al., 2015) |
| Human (19-55 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D3** |  |  | No alteration in binding potential of an agonist | (Matuskey et al., 2016) |
| [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (Whole-brain voxel-wise analysis); **D3** |  |  | No alteration in binding potential of an agonist | (Matuskey et al., 2016) |
| Anterior Pituitary  | Male Wistar-Kyoto rats (6 and 24 months) | RT-PCR (mRNA); **D2** |  |  | Increased D2 mRNA levels | (Valerio et al., 1994) |
| RT-PCR (mRNA); **D4** |  |  | No alteration in D4 mRNA levels | (Valerio et al., 1994) |
| Pituitary Gland – Anterior and intermediate lobes | Fischer 344 rats (3 and 24 months) | [35S]-mRNA hybridization and Northern blot; **D2** |  |  | Increased D2 mRNA levels | (Weiss et al., 1992) |
| Hippocampus  | Male Wistar-Kyoto rats (6 and 24 months) | RT-PCR (mRNA); **D2** |  |  | No alteration in D2 mRNA levels | (Valerio et al., 1994) |
| Human (21-82 years) | [11C]FLB 457 binding (PET); **D2** |  |  | Decreased binding potential of an antagonist | (Inoue et al., 2001) |
| Human (19-74 years) | [11C]FLB 457 binding (PET)**; D2; D3** |  |  | Decreased binding potential of an antagonist | (Kaasinen et al., 2000) |
| Hippocampus – CornuAmmonis area 1 | Male Fischer 344 rats (6 and 24 months) | [3H]spiperone binding (Autoradiography); **D2**[3H]nemonapride binding (Autoradiography); **D2** | No alteration |  |  | (Araki et al., 1997) |
| Amygdala | Human (19-74 years) | [11C]FLB 457 binding (PET); **D2; D3** |  |  | Decreased binding potential of an antagonist | (Kaasinen et al., 2000) |
| Human (19-55 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D2/3** |  |  | No alteration in binding potential of an agonist | (Matuskey et al., 2016) |
| Basal Ganglia - Striatum | Male Sprague-Dawley rats (4 and 22 months) | [3H]spiperone binding; **D2** | Decreased | No alteration |  | (O’Boyle and Waddington, 1984) |
| Male Wistar rats (3, 12, and 24 months) | Decreased | No alteration |  | (Henry et al., 1986) |
| Male Wistar rats (3-6 and24-26 months) | [3H]spiperone binding (Autoradiography); **D2** | Decreased |  |  | (Han et al., 1989) |
| Male Wistar rats (6 months and 24-25 months) | [35S]-labelled D2 cDNA hybridization (mRNA); **D2** |  |  | Decreased D2 mRNA levels | (Mesco et al., 1991) |
| Male Fischer 344 rats (6 and 24 months) | [3H]spiperone binding (Autoradiography); **D2**[3H]nemonapride binding (Autoradiography); **D2** | No alteration |  |  | (Araki et al., 1997) |
| Fischer 344 rats (3 and 24 months) | [35S]-labelled mRNA hybridization and Northern blot; **D2** |  |  | Decreased D2 mRNA levels | (Weiss et al., 1992) |
| Male Wistar-Kyoto rats (6 and 24 months) | RT-PCR (mRNA); **D2** |  |  | Decreased D2 mRNA levels | (Valerio et al., 1994) |
| RT-PCR (mRNA); **D3** |  |  | No alteration in D3 of mRNA levels | (Valerio et al., 1994) |
| New Zealand White Rabbits (5 month and 5.5 years) | [3H]spiroperidol binding; **Dopamine receptors** | Decreased | No alteration |  | (Thal et al., 1980) |
| Male Fischer 344 x Brown-Norway rats (F1) (4 and 37 months) | [3H](+)-7-hydroxy-2-(*N, N*-di-*n*-propylamino)tetralin; **D3** | Increased |  |  | (Wallace and Booze, 1996) |
| Human (20-81 years) | [11C]raclopride binding (PET); **D2** | Decreased | No alteration |  | (Rinne et al., 1993) |
| Human (19-82 years) | [11C]raclopride binding (PET); **D2** | Decreased | No alteration (right striatum);Decreased (women’s left striatum) | Decreased binding potential of an antagonist | (Pohjalainen et al., 1998) |
| Male Human (21-49 years) | F-18-N-methylspiperone (PET); **D2** | Decreased |  |  | (Wang et al., 1995) |
| Human (*postmortem*) (19-88 years) | [3H]spiperone binding; **D2** | No alteration | No alteration |  | (De Keyser et al., 1990) |
| Human (*postmortem*) (7-104 years) | Decreased (men);No alteration (women) |  |  | (Seeman et al., 1987) |
| Male Sprague-Dawleyrats (10 weeks and 18-20 months) | qPCR (mRNA); **D2**Western Blot; **D2** | Decreased |  | Decreased D2 mRNA levels | (Villar-Cheda et al., 2014) |
| Basal Ganglia – Striatum – Caudate and Putamen | Fischer 344 rats (5-6 and 26-28 months) | [3H]spiroperidol binding (Autoradiography); **D2** | Decreased | No alteration |  | (Joyce et al., 1986) |
| Rhesus Monkeys *(Macaca mulatta)* (2-22 years) | [3H]spiroperidol binding; **D2** | Decreased | No alteration |  | (Lai et al., 1987) |
| Human (18-73 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol and [11C]raclopride binding (PET); **D2** |  |  | Decreased nondisplaceable binding potential by [11C]raclopride (antagonist) (putamen and caudate); Decreased nondisplaceable binding potential by [11C]-(+)-PHNO (agonist) (caudate) and no alteration (putamen) | (Nakajima et al., 2015) |
| Human (21-68 years) | [11C]raclopride binding (PET); **D2** | Decreased |  |  | (Antonini A et al., 1993) |
| Human (19-73 years) | [11C]3-N-methylspiperone binding (PET); **D2** | Decreased |  |  | (Wong et al., 1984) |
| Human (21-74 years) | [11C]raclopride binding (PET); **D2-like** | Decreased |  | Decreased uptake ratio index and binding potential of an antagonist | (Ishibashi et al., 2009) |
| Human (*postmortem*) (0-20 and >65 years years) | [3H]spiroperidol binding; **D2** | Decreased | No alteration |  | (Rinne, 1987) |
| Human (*postmortem*) (6-93 years) | Decreased | No alteration |  | (Rinne et al., 1990) |
| Human (*postmortem*) (<40 and >70 years) | [3H]fluphenazine binding; **D2** | Decreased (caudate);No alteration (putamen) | No alteration |  | (Morgan et al., 1987) |
| Human (19-55 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D2** |  |  | Decreased binding potential of an agonist | (Matuskey et al., 2016) |
| [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (Whole-brain voxel-wise analysis); **D2** |  |  | Decreased binding potential of an agonist | (Matuskey et al., 2016) |
| Basal Ganglia – Striatum – Ventral Striatum | Human (18-73 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol and [11C]raclopride binding (PET); **D2; D3** |  |  | Decreased nondisplaceable binding potential by [11C]raclopride (antagonist);No alteration with [11C]-(+)-PHNO (agonist) | (Nakajima et al., 2015) |
| Human (19-55 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D2/3** |  |  | No alteration in binding potential of an agonist | (Matuskey et al., 2016) |
| Basal Ganglia – Striatum - Caudate,Putamen and Ventral striatum | Female Human (23-80 years) | [18F]fallypride binding (PET); **D2** |  |  | Decreased binding potential of an antagonist | (Dang et al., 2017) |
| Human (18-81 years) | [18F]fallypride binding (PET); **D2; D3** |  |  | Decreased binding potential of an antagonist | (Dang et al., 2017) |
| Basal Ganglia – Striatum – Nucleus accumbens | Male Fischer 344 rats (6 and 24 months) | [3H]spiperone binding (Autoradiography); **D2**[3H]nemonapride binding (Autoradiography); **D2** | No alteration |  |  | (Araki et al., 1997) |
| Male Fischer 344 x Brown-Norway rats (F1) (4 and 37 months) | [3H](+)-7-hydroxy-2-(*N, N*-di-*n*-propylamino)tetralin; **D3** | Increased |  |  | (Wallace and Booze, 1996) |
| Basal Ganglia – Striatum – Olfactory tubercle | Fischer 344 rats (3 and 24 months) | [35S]-labelled mRNA hybridization and Northern blot; **D2** |  |  | Decreased D2 mRNA levels | (Weiss et al., 1992) |
| Male Wistar-Kyoto rats (6 and 24 months) | RT-PCR (mRNA); **D2** |  |  | No alteration in D2 mRNA levels | (Valerio et al., 1994) |
| RT-PCR (mRNA); **D3** |  |  | Decreased D3 mRNA levels | (Valerio et al., 1994) |
| Basal Ganglia – Globus pallidus | Human (18-73 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol and [11C]raclopride binding (PET); **D2; D3** |  |  | No alteration in nondisplaceable binding potentialby [11C]raclopride (antagonist) and [11C]-(+)-PHNO (agonist) | (Nakajima et al., 2015) |
| Basal Ganglia - Pallidum | Human (*postmortem*) (0-20 and >65 years years) | [3H]spiroperidol binding; **D2** | Decreased | No alteration |  | (Rinne, 1987) |
| Human (19-55 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D2/3** |  |  | No alteration in binding potential of an agonist | (Matuskey et al., 2016) |
| Basal Ganglia - Ventral Pallidum | Human (18-73 years) | [11C]-(+)4-Propyl- 3,4,4a,5,6,10b-hexahydro-*2H*-naphtho[1,2-b][1,4]oxazin-9-ol binding (PET); **D2; D3** |  |  | No alteration in nondisplaceable binding potential of an agonist | (Nakajima et al., 2015) |
| Female Human(23-80 years) | [18F]fallypride binding (PET); **D2** |  |  | Decreased binding potential of an antagonist | (Dang et al., 2017) |
| Human (18-81 years) | [18F]fallypride binding (PET); **D2; D3** |  |  | Decreased binding potential of an antagonist | (Dang et al., 2016) |
| Cerebral cortex - Frontal cortex | Male Fischer 344 rats (6 and 24 months) | [3H]spiperone binding (Autoradiography); **D2**[3H]nemonapride binding (Autoradiography); **D2** | No alteration |  |  | (Araki et al., 1997) |
| Male Wistar-Kyoto rats (6 and 24 months) | RT-PCR (mRNA); **D2** |  |  | Decreased D2 mRNA levels | (Valerio et al., 1994) |
| New Zealand White Rabbits (5 mth & 5.5 yrs) | [3H]spiroperidol binding; **Dopamine receptors** | Decreased | No alteration |  | (Thal et al., 1980) |
| Human (19-73 years) | [11C]3-N-methylspiperone binding (PET); **D2** | Decreased |  |  | (Wong et al., 1984) |
| Human (21-82 years) | [11C]FLB 457 binding (PET; **D2** |  |  | Decreased binding potential of an antagonist | (Inoue et al., 2001) |
| Human (19-74 years) | [11C]FLB 457 binding (PET); **D2; D3** |  |  | Decreased binding potential of an antagonist | (Kaasinen et al., 2000) |
| Cerebral cortex - Parietal cortex | Male Fischer 344 rats (6 and 24 months) | [3H]spiperone binding (Autoradiography); **D2**[3H]nemonapride binding (Autoradiography); **D2** | No alteration |  |  | (Araki et al., 1997) |
| Human (21-82 years) | [11C]FLB 457 binding (PET); **D2** |  |  | Decreased binding potential of an antagonist | (Inoue et al., 2001) |
| Cerebral cortex -Occipital cortex |  |  | Decreased binding potential of an antagonist | (Inoue et al., 2001) |
| Cerebral cortex -Temporal cortex |  |  | Decreased binding potential of an antagonist | (Inoue et al., 2001) |
| Cerebral cortex – Lateral and medial Temporal cortex | Human (19-74 years) | [11C]FLB 457 binding (PET); **D2; D3** |  |  | Decreased binding potential of an antagonist | (Kaasinen et al., 2000) |
| Anterior Cingulate cortex |  |  | Decreased binding potential of an antagonist | (Kaasinen et al., 2000) |
| Acetylcholine receptors | Cerebellum – Granular and molecular layer | Fischer 344 rats (6 and 22 months) | Silver grain (Autoradiography); **M2** | No alteration |  |  | (Tayebati et al., 2001) |
| Silver grain (Autoradiography); **M4** | Increased |  |  | (Tayebati et al., 2001) |
| Thalamus | Human (*postmortem*) (7-80 years) | [3H]-quinuclidinyl benzilate binding; **M2** | Increased |  |  | (Nordberg et al., 1992) |
| Thalamus – Lateral and Medial Nuclear group | Male Wistar rats (5-6 and 24-25 months) | [3H]-quinuclidinyl benzilate binding (Autoradiography); **Acetylcholine receptors** | Decreased (lateral);No alteration (medial) |  |  | (Blake et al., 1991) |
| Hypothalamus | No alteration |  |  | (Blake et al., 1991) |
| Hippocampus | Human (*postmortem*) (0-20 and >65 years years) | [3H]1quinuclidinyl(phenyl)-4-benzilate binding; **M2** | Decreased | No alteration |  | (Rinne, 1987) |
| Hippocampus – Dentate gyrus | Male Wistar rats (5-6 and 24-25 months) | [3H]-quinuclidinyl benzilate binding (Autoradiography); **Acetylcholine receptors** | No alteration |  |  | (Blake et al., 1991) |
| Hippocampus – Dentate gyrus – Granular and molecular layer | Male Fischer 344 rats (6 and 22 months) | [3H]N-methyl-scopolamine binding; **M2** | Decreased |  |  | (Tayebati et al., 2001) |
| [3H]N-methyl-scopolamine binding; **M4** | No alteration |  |  | (Tayebati et al., 2001) |
| Hippocampus – CornuAmmonis area 1 and 3 – Radial layer | Male Fischer 344 rats (6 and 22 months) | [3H]N-methyl-scopolamine binding; **M2** | Decreased |  |  | (Tayebati et al., 2001) |
| [3H]N-methyl-scopolamine binding;**M4** | No alteration |  |  | (Tayebati et al., 2001) |
| Hippocampus – CornuAmmonis area 1, 2 and 3 | Male Wistar rats (5-6 and 24-25 months) | [3H]-quinuclidinyl benzilate binding (Autoradiography); **Acetylcholine receptors**[35S]-labeled mRNA hybridization; **M4** | No alteration |  | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Amygdala | No alteration |  | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Basal Ganglia - Striatum | Fischer 344 rats (6 or 15 and 22 months) | [3H]N-methyl-scopolamine binding; **M2** | No alteration |  |  | (Tayebati et al., 2004) |
| [3H]N-methyl-scopolamine binding; **M4** | Decreased |  |  | (Tayebati et al., 2004) |
| Basal Ganglia - Neostriatum | Male Fischer 344 x Brown-Norway rats (3 and 33 months) | Northern Blot (mRNA); **M2** |  |  | No alteration in M2 mRNA levels | (Lee et al., 1994) |
| Northern Blot (mRNA); **M4** |  |  | Decreased M4 mRNA levels | (Lee et al., 1994) |
| Basal Ganglia – Striatum – Dorsolateral and dorsomedial striatum | Male Fischer 344 x Brown-Norway rats (F1) (6, 18 and 24 months) | Oxotremorine-M stimulated [35S]GTPγS binding (Autoradiography); **M2/M4**[3H]AFDX-384 binding (Autoradiography); **M2/M4** | No alteration |  | Decreased agonist (oxotremorine-M) stimulated [35S]GTPγS binding (dorsomedial striatum); No alteration (dorsolateral striatum) | (Nieves-Martinez et al., 2012) |
| Basal Ganglia – Striatum – Caudate and Putamen | Male Wistar rats (5-6 and 24-25 months) | [3H]-quinuclidinyl benzilate binding (Autoradiography); **Acetylcholine receptors**[35S]-labeled hybridization (mRNA); **M4** | Decreased | No alteration | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Human (*postmortem*) (0-20 and >65 years years) | [3H]1-quinuclidinyl(phenyl)-4-benzilate binding; **M2** | Decreased | No alteration |  | (Rinne, 1987) |
| Basal Ganglia – Striatum – Nucleus accumbens | Male Wistar rats (5-6 and 24-25 months) | [3H]-quinuclidinyl benzilate binding (Autoradiography); **Acetylcholine receptors**[35S]-labeled hybridization (mRNA); **M4** | Decreased |  | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Basal Ganglia – Striatum – Olfactory tubercle | Decreased |  | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Rhinencephalon – Piriform cortex | Decreased |  | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Cerebral cortex - Frontal cortex | Decreased |  | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Human (*postmortem*) (0-20 and >65 years years) | [3H]1-quinuclidinyl(phenyl)-4-benzilate binding; **M2** | Decreased | No alteration |  | (Rinne, 1987) |
| Human (*postmortem*) (7-80 years) | [3H]-quinuclidinyl benzilate binding; **M2** | Decreased |  |  | (Nordberg et al., 1992) |
| Cingulate cortex | Male Wistar rats (5-6 and 24-25 months) | [3H]-quinuclidinyl benzilate binding (Autoradiography); **Acetylcholine receptors**[35S]-labeled hybridization (mRNA); **M4** | Decreased |  | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Cingulate cortex – Retrosplenial cortex | Decreased |  | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Parieto-frontal cortex | No alteration |  | No alteration in M4 mRNA levels | (Blake et al., 1991) |
| Reunions nucleus | No alteration |  |  | (Blake et al., 1991) |
| Serotonin receptors | Pons - Locus Coeruleus | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | Decreased (men);No alteration (women) |  |  | (Dillon et al., 1991) |
| Cerebellum – Granular and molecular layer | ICR Mouse (3 and 12 months) | Immunocytochemistry;**5-HT1A** | Decreased |  |  | (Yew et al., 2009) |
| Human (57-78 and 82-91 years) | Decreased |  |  | (Yew et al., 2009) |
| Dorsal and median Raphe nucleus | Male Syrian Hamsters (Harlan Sprague Dawley, SYR- HSD) (3-4 and 17-19 months) | [3H]4-(2´-Methoxy)-phenyl-1-[2´-(N-2”-pyridinyl)-p-fluorobenzamido]ethyl-piperzin binding (Autoradiography); **5-HT1A**8-OH-DPAT stimulated [35S]GTPγS binding (Autoradiography); **5-HT1A** | No alteration |  | No alteration in agonist (8-OH-DPAT) stimulated [35S]GTPγS binding | (Duncan and Hensler, 2002) |
| Raphe nucleus | Human (22-53 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | No alteration in binding potential of an antagonist | (Tauscher et al., 2001) |
| Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | Decreased (men’s dorsal);No alteration (men’s median and obscurus; women’s brain) |  |  | (Dillon et al., 1991) |
| Dorsal Raphe | Human (24-56 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | No alteration in binding potential of an antagonist | (Parsey et al., 2002) |
| Thalamus | Human (21-80 years) |  |  | No alteration in binding potential of an antagonist | (Meltzer et al., 2001) |
| Human (18-61 years) | [11C]P943 binding (PET); **5-HT1B** |  |  | No alteration in binding potential of an antagonist | (Matuskey et al., 2012) |
| Thalamus - Medial nuclear group | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | No alteration (men and women) |  |  | (Dillon et al., 1991) |
| Hypothalamus  | Human (18-61 years) | [11C]P943 binding (PET); **5-HT1B** |  |  | Decreased binding potential of an antagonist | (Matuskey et al., 2012) |
| White matter | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | No alteration (men and women) |  |  | (Dillon et al., 1991) |
| Hippocampus | Human (24-56 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | No alteration in binding potential of an antagonist | (Parsey et al., 2002) |
| Human (21-80 years) |  |  | Decreased binding potential of an antagonist (men); No alteration (women) | (Meltzer et al., 2001) |
| Human (18-61 years) | [11C]P943 binding (PET); **5-HT1B** |  |  | No alteration in binding potential of an antagonist | (Matuskey et al., 2012) |
| Human (*postmortem*) (30-83 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding; **5-HT1A** | No alteration (men);Decreased (women) | No alteration |  | (Palego et al., 1997) |
| Hippocampus – Dentate gyrus | Male Syrian Hamsters (Harlan Sprague Dawley, SYR- HSD) (3-4 and 17-19 months) | [3H]4-(2´-Methoxy)-phenyl-1-[2´-(N-2”-pyridinyl)-p-fluorobenzamido]ethyl-piperzin binding (Autoradiography); **5-HT1A**8-OH-DPAT stimulated [35S]GTPγS binding (Autoradiography); **5-HT1A** | Decreased |  | No alteration in agonist (8-OH-DPAT) stimulated [35S]GTPγS binding | (Duncan and Hensler, 2002) |
| Human *(postmortem)* (45-84 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A**RT-PCR mRNA; **5-HT1A** | Decreased |  | No alteration in 5-HT1A mRNA levels | (Burnet et al., 1994) |
| Hippocampus – Dentate gyrus – Granular layer, Molecular layer and hilus | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | Decreased (men); Increased (women’s granular layer); No alteration (women’s molecular layer and hilus) |  |  | (Dillon et al., 1991) |
| Hippocampus – CornuAmmonis area – Pyramidal and molecular layer | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | No alteration (men and women) |  |  | (Dillon et al., 1991) |
| Hippocampus – CornuAmmonis area 1 | Male Syrian Hamsters (Harlan Sprague Dawley, SYR- HSD) (3-4 and 17-19 months) | [3H]4-(2´-Methoxy)-phenyl-1-[2´-(N-2”-pyridinyl)-p-fluorobenzamido]ethyl-piperzin binding (Autoradiography); **5-HT1A**8-OH-DPAT stimulated [35S]GTPγS binding (Autoradiography); **5-HT1A** | No alteration |  | Increased agonist (8-OH-DPAT) stimulated [35S]GTPγS binding | (Duncan and Hensler, 2002) |
| Human *(postmortem)* (45-84 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A**RT-PCR (mRNA); **5-HT1A** | Decreased |  | No alteration in 5-HT1A mRNA levels | (Burnet et al., 1994) |
| Hippocampus –Subiculum | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | Decreased (men);No alteration (women) |  |  | (Dillon et al., 1991) |
| Parahippocampal gyrus | Human *(postmortem)* (45-84 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A**RT-PCR (mRNA); **5-HT1A** | Decreased |  | No alteration in 5-HT1A mRNA levels | (Burnet et al., 1994) |
| Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | Decreased (men’s external band);No alteration (women and in men’s middle and internal band) |  |  | (Dillon et al., 1991) |
| Amygdala | Human (24-56 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | No alteration in binding potential of an antagonist | (Parsey et al., 2002) |
| Human (18-61 years) | [11C]P943 binding (PET); **5-HT1B** |  |  | No alteration in binding potential of an antagonist | (Matuskey et al., 2012) |
| Claustrum | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | No alteration (men and women) |  |  | (Dillon et al., 1991) |
| Basal Ganglia | Human (21-80 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | No alteration in binding potential of an antagonist | (Meltzer et al., 2001) |
| Basal Ganglia – Striatum – Caudate and Putamen | Human (18-61 years) | [11C]P943 binding (PET); **5-HT1B** |  |  | Increased binding potential of an antagonist (putamen);No alteration (caudate)  | (Matuskey et al., 2012) |
| Basal Ganglia -Pallidum |  |  | Increased binding potential of an antagonist | (Matuskey et al., 2012) |
| Cerebral cortex | Male Wistar rats (4 and 24 months) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding; **5-HT1A** | Decreased | No alteration |  | (Huguet et al., 1994) |
| Cerebral cortex - Frontal cortex | Human *(postmortem)* (16-75 years) | No alteration | No alteration |  | (Arranz et al., 1993) |
| [3H]5-hydroxytryptamine binding; **5-HT1D** | Decreased | No alteration |  | (Arranz et al., 1993) |
| Human (18-61 years) | [11C]P943 binding (PET); **5-HT1B** |  |  | Decreased binding potential of an antagonist | (Matuskey et al., 2012) |
| Cerebral cortex - Frontal cortex – Superior frontal gyrus | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | Decreased (men’s prefrontal, and external and internal band of frontal parietal level);No alteration (men’s middle band of frontal parietal level);No alteration (women) |  |  | (Dillon et al., 1991) |
| Cerebral cortex - Frontal cortex – Middle and inferior frontal gyrus | Human (*postmortem*) (15-81 years) | No alteration (men and women) |  |  | (Dillon et al., 1991) |
| Cerebral cortex - Frontal cortex – Orbitofrontal cortex | Human (22-53 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | Decreased binding potential of an antagonist | (Tauscher et al., 2001) |
| Cerebral cortex - Frontal cortex – Lateral Orbitofrontal cortex | Human (21-80 years) |  |  | Decreased binding potential of an antagonist (men); No alteration (women) | (Meltzer et al., 2001) |
| Cerebral cortex - Frontal cortex – Precentral gyrus | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography) **5-HT1A** | Decreased (men);No alteration (women) |  |  | (Dillon et al., 1991) |
| Cerebral cortex - Frontal cortex – Prefrontal cortex | Rhesus monkeys *(Macaca mulatta)* (3-10 years and >20 years) | [3H]5-hydroxytrytamine binding (Autoradiography); **Serotonin receptors** | No alteration | No alteration |  | (Bigham and Lidow, 1995) |
| Human *(postmortem)* (1-88 years) | 8-OH-DPAT stimulated [35S]GTPγS binding; **5-HT1A** |  |  | Decreased agonist (8-OH-DPAT) stimulated [35S]GTPγS binding | (Araki et al., 1997) |
| Human (*postmortem*) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding; **5-HT1A** | No alteration | No alteration |  | (Palego et al., 1997) |
| Cerebral cortex - Frontal cortex – Dorsolateral prefrontal cortex | Human (22-53 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | Decreased binding potential of an antagonist | (Tauscher et al., 2001) |
| Cerebral cortex - Frontal cortex – Medial prefrontal cortex | Human (24-56 years) |  |  | No alteration in binding potential of an antagonist | (Parsey et al., 2002) |
| Cerebral cortex - Frontal cortex – Orbital prefrontal cortex |  |  | No alteration in binding potential of an antagonist |
| Cerebral cortex - Frontal cortex – Primary motor cortex | Rhesus monkeys *(Macaca mulatta)* (3-10 years and >20 years) | [3H]5-hydroxytrytamine binding (Autoradiography); **Serotonin receptors** | No alteration | Decreased (I-IIIa);No alteration (IIIb-VI) |  | (Bigham and Lidow, 1995) |
| Cerebral cortex - Parietal cortex | Human (22-53 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | Decreased binding potential of an antagonist | (Tauscher et al., 2001) |
| Human (18-61 years) | [11C]P943 binding (PET); **5-HT1B** |  |  | Decreased binding potential of an antagonist | (Matuskey et al., 2012) |
| Human (*postmortem*) (30-83 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding; **5-HT1A** | Unalterated in men; Decreased in women | No alteration |  | (Palego et al., 1997) |
| Cerebral cortex - Parietal cortex – Somatosensory cortex | Rhesus monkeys *(Macaca mulatta)* (3-10 years and >20 years) | [3H]5-hydroxytrytamine binding (Autoradiography); **Serotonin receptors** | Decreased (Layer I-V);No alteration (Layer VI) | Decreased (I-V); No alteration (VI) |  | (Bigham and Lidow, 1995) |
| Cerebral cortex - Parietal cortex – Inferior parietal lobe | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | Decreased (men);No alteration (women) |  |  | (Dillon et al., 1991) |
| Cerebral cortex - Parietal cortex – Postcentral gyrus | Decreased (men);No alteration (women) |  |  |
| Cerebral cortex -Occipital cortex | Human (22-53 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | Decreased binding potential of an antagonist | (Tauscher et al., 2001) |
| Human (21-80 years) |  |  | Decreased binding potential of an antagonist (men); No alteration (women)  | (Meltzer et al., 2001) |
| Human (18-61 years) | [11C]P943 binding (PET); **5-HT1B** |  |  | Decreased binding potential of an antagonist | (Matuskey et al., 2012) |
| Human (*postmortem*) (30-83 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding; **5-HT1A** | No alteration (men);Increased (women) | Increased (men);No alteration (women) |  | (Palego et al., 1997) |
| Cerebral cortex -Occipital cortex – Primary visual cortex | Rhesus monkeys *(Macaca mulatta)* (3-10 years and >20 years) | [3H]5-hydroxytrytamine binding (Autoradiography); **Serotonin receptors** | No alteration | No alteration |  | (Bigham and Lidow, 1995) |
| Cerebral cortex -Temporal cortex | Human (18-61 years) | [11C]P943 binding (PET); **5-HT1B** |  |  | Decreased binding potential of an antagonist | (Matuskey et al., 2012) |
| Human (*postmortem*) (30-83 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding; **5-HT1A** | No alteration | No alteration |  | (Palego et al., 1997) |
| Cerebral cortex -Temporal cortex – Transverse temporal gyrus | Human (*postmortem*) (15-81 years) | Decreased (men’s middle and internal band);No alteration (women; men’s external band) |  |  | (Dillon et al., 1991) |
| Cerebral cortex -Temporal cortex – Superior/Medial/Inferior temporal gyrus | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin bind (Autoradiography); **5-HT1A** | Decreased (men); No alteration (women) |  |  | (Dillon et al., 1991) |
| Cerebral cortex -Temporal cortex – Mediotemporal cortex | Human (22-53 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | No alteration in binding potential of an antagonist | (Tauscher et al., 2001) |
| Cerebral cortex -Temporal cortex – Mesial temporal cortex | Human (21-80 years) |  |  | Decreased binding potential of an antagonist (men); No alteration (women) | (Meltzer et al., 2001) |
| Cerebral cortex -Temporal cortex – Lateral temporal cortex | Human (22-53 years) |  |  | Decreased binding potencial of an antagonist | (Tauscher et al., 2001) |
| Cerebral cortex - Cingulate body | Human (24-56 years) |  |  | No alteration in binding potential of an antagonist | (Parsey et al., 2002) |
| Cingulate cortex | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | No alteration (men’s pre-frontal cortex);Decreased (men’s frontal parietal);No alteration (women) |  |  | (Dillon et al., 1991) |
| Anterior Cingulate cortex | Human (22-53 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | Decreased binding potential of an antagonist | (Tauscher et al., 2001) |
| Human (24-56 years) |  |  | No alteration in binding potential of an antagonist | (Parsey et al., 2002) |
| Cingulate cortex – Subgenual Cingulate | Human (21-80 years) |  |  | Decreased binding potential of an antagonist (men); No alteration (women) | (Meltzer et al., 2001) |
| Cingulate cortex – Pregenual Cingulate |  |  | Decreased binding potential of an antagonist (men); No alteration (women) |
| Insular cortex | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | Decreased (men);No alteration (women) |  |  | (Dillon et al., 1991) |
| Brainstem - Brainstrem raphe | Human (21-80 years) | *Carbonyl*-[11C]-N-[2-[4-(2-methoxyphenyl)-1-piper- azinyl]ethyl]-N-(2-pyridinyl)cyclohexane carboxamide binding (PET); **5-HT1A** |  |  | Decreased binding potential of an antagonist (men); No alteration (women) | (Meltzer et al., 2001) |
| Lateral Occipitotemporal gyrus | Human (*postmortem*) (15-81 years) | [3H]8-hydroxy-2-(di*-N*-propylamino)tetralin binding (Autoradiography); **5-HT1A** | Decreased (men’s external and internal band);No alteration (men’s middle band);No alteration (women) |  |  | (Dillon et al., 1991) |
| Orbital gyrus | No alteration (men and women) |  |  |
| Gyrus rectus |  |  |
| Purinoceptors | ------------------------------------ |
| Opioid Receptors | Mindbrain (Mesencephalon) | Male Fischer 344 rats (5 and 26 months) | [3H]dihydromorphine binding; **Opioid receptors** | No alteration | No alteration |  | (Messing et al., 1981) |
| Male Sprague-Dawley rats (2 and 19 months) | 3H-bremazocine binding; **κ** | No alteration | No alteration |  | (Maggi et al., 1989) |
| Substantia nigra | Male Hartley Guinea-pigs (1 and 36 months) | [3H]bremazocine binding (Autoradiography); **κ** | Decreased |  |  | (Hiller et al., 1992) |
| Thalamus | Male Fischer 344 rats (5 and 26 months) | [3H]dihydromorphine binding; **Opioid receptors** | No alteration | No alteration |  | (Messing et al., 1981) |
| Male Sprague-Dawley rats (2 and 19 months) | 3H-bremazocine binding; **κ** | Increased | No alteration |  | (Maggi et al., 1989) |
| Hypothalamus | Male Sprague-Dawley rats (2 and 19 months) | 3H-bremazocine binding; **κ** | No alteration | No alteration |  | (Maggi et al., 1989) |
| Male Sprague-Dawley rats (2 and 22 months) | 3H-dihydromorphine binding; **µ** | Decreased | No alteration |  | (Piva et al., 1987) |
| Hippocampus  | Male Wistar rats (2-3, 6-12 and 24 months) | 3H-etorphine binding; **Opioid receptors** | Decreased | No alteration |  | (Hess et al., 1981) |
| Male Sprague-Dawley rats (2 and 19 months) | 3H-bremazocine binding; **κ** | No alteration | No alteration |  | (Maggi et al., 1989) |
| Amygdala | Male Fischer 344 rats (5 and 26 months) | [3H]dihydromorphine binding; **Opioid receptors** | No alteration | No alteration |  | (Messing et al., 1981) |
| Male Wistar rats (2-3, 6-12 and 24 months) | 3H-etorphine binding; **Opioid receptors** | No alteration | No alteration |  | (Hess et al., 1981) |
| Male Sprague-Dawley rats (2 and 19 months) | 3H-bremazocine binding; **κ** | Increased | No alteration |  | (Maggi et al., 1989) |
| Basal Ganglia - Striatum | Male Fischer 344 rats (5 and 26 months) | [3H]dihydromorphine binding; **Opioid receptors** | Decreased | No alteration |  | (Messing et al., 1981) |
| Male Wistar rats (2-3, 6-12 and 24 months) | 3H-etorphine binding; **Opioid receptors** | Decreased | No alteration |  | (Hess et al., 1981) |
| Male Sprague-Dawley rats (2 and 19 months) | 3H-bremazocine binding; **κ** | No alteration | No alteration |  | (Maggi et al., 1989) |
| Basal Ganglia – Striatum – Caudate and Putamen | Male Hartley Guinea-pigs (1 and 36 months) | [3H]bremazocine binding (Autoradiography); **κ** | Decreased |  |  | (Hiller et al., 1992) |
| Basal Ganglia – Globus Pallidus | Male Hartley Guinea-pigs (1 and 36 months) | [3H]bremazocine binding (Autoradiography); **κ** | No alteration |  |  | (Hiller et al., 1992) |
| Cerebral cortex - Frontal cortex – Prefrontal cortex | Human *(postmortem)* (1-88 years) | DAMGO stimulated [35S]GTPγS binding; **µ** |  |  | Increased agonist (DAMGO) stimulated [35S]GTPγS binding | (González-Maeso et al., 2002) |
| Cerebral cortex - Frontal cortex - Lateral Agranular Field | Male Hartley Guinea-pigs (1 and 36 months) | [3H]bremazocine binding (Autoradiography); **κ** | Decreased |  |  | (Hiller et al., 1992) |
| Cerebral cortex – Parietal cortex – Primary and Supplementary Somatosensory cortex | Male Hartley Guinea-pigs (1 and 36 months) | [3H]bremazocine binding (Autoradiography); **κ** | Decreased |  |  | (Hiller et al., 1992) |
| Cerebral cortex -Occipital cortex | Decreased |  |  |
| Cerebral cortex -Temporal cortex | Decreased |  |  |
| Cerebral cortex -Anterior cortex | Male Fischer 344 rats (5 and 26 months) | [3H]dihydromorphine binding; **Opioid receptors** | Decreased | No alteration |  | (Messing et al., 1981) |
| Male Sprague-Dawley rats (2 and 19 months) | 3H-bremazocine binding; **κ** | No alteration | No alteration |  | (Maggi et al., 1989) |
| Male Wistar rats (2-3, 6-12 and 24 months) | 3H-etorphine binding; **Opioid receptors** | No alteration | No alteration |  | (Hess et al., 1981) |
| Cerebral cortex - Posterior cortex | Male Sprague-Dawley rats (2 and 19 months) | 3H-bremazocine binding; **κ** | No alteration | No alteration |  | (Maggi et al., 1989) |
| Cerebral cortex – Frontal Lobe - Frontal poles | Male Fischer 344 rats (5 and 26 months) | [3H]dihydromorphine binding; **Opioid receptors** | Decreased | Increased |  | (Messing et al., 1981) |
| Male Wistar rats (2-3, 6-12 and 24 months) | 3H-etorphine binding; **Opioid receptors** | Decreased | No alteration |  | (Hiller et al., 1992) |
| Male Sprague-Dawley rats (2 and 19 months) | 3H-bremazocine binding; **κ** | No alteration | No alteration |  | (Maggi et al., 1989) |
| Medialprefrontal cortex | Male Wistar rats (60–150 days) | nor-binaltorphimine stimulated [35S] GTPγS binding; **κ** |  |  | Decreased antagonist (nor-binaltorphimine) stimulated [35S]GTPγS binding | (Sirohi and Walker, 2015) |
| Cingulate cortex - Retrosplenial cortex | Male Hartley Guinea-pigs (1 and 36 months) | [3H]bremazocine binding (Autoradiography); **κ** | No alteration |  |  | (Hiller et al., 1992) |
| Agranular Insular cortex – Dorsal part | Decreased |  |  |
| Somatostatin Receptors | Cerebellum – Granular and molecular layer | Human (*postmortem*) (28-86 years) | [125I-Try0, DTrp8]S14 binding, Autoradiography; **Somatostatin receptors** | No alteration |  |  | (Laquerriere et al., 1994) |
| Hypothalamus | Male Wistar rats (*Rattus norvegicus)* (1 and 18 months) | 125I-TyrI-somatostatin binding; **Somatostatin receptors** |  | No alteration |  | (Sirvio et al., 1987) |
| Pituitary gland | Male Fischer 344 rats (6 and 24 months) | RT-PCR (mRNA); **SSTR2; SSTR5** |  |  | Decreased SSTR2 and SSTR5 mRNA levels | (Shimokawa et al., 2000) |
| Sprague-Dawley rats (2 days and 1 year) | cRNA labeled with [32P]-UTP (mRNA); **SSTR2** |  |  | Increased SSTR2 mRNA levels | (Reed et al., 1999) |
| cRNA labeled with [32P]-UTP ( qPCR - mRNA); **SSTR1; SSTR3; SSTR4; SSTR5** |  |  | No alteration in SSTR1, SSTR3, SSTR4, SSTR5 mRNA levels | (Villar-Cheda et al., 2012) |
| Hippocampus | Male Wistar rats (*Rattus norvegicus)* (1 and 18 months) | 125I-TyrI-somatostatin binding; **Somatostatin receptors** |  | Decreased |  | (Sirvio et al., 1987) |
| Basal Ganglia - Striatum |  | Decreased |  |
| Cerebral cortex - Frontal cortex |  | Decreased |  |
| Angiotensin Receptors | Substantia nigra | Male Sprague-Dawley rats (10 weeks and 24 months) | qPCR (mRNA); **AT1**Western blot; **AT1** | Increased |  | Increased AT1 mRNA levels | (Villar-Cheda et al., 2012) |
| Male Sprague-Dawley rats (10 weeks & 18-20 months) | qPCR (mRNA); **AT1**Western Blot; **AT1** | Increased |  | Increased AT1 mRNA levels | (Villar-Cheda et al., 2014) |
| Striatum | Male Sprague-Dawley rats (10 weeks & 18-20 months) | qPCR (mRNA); **AT1**Western Blot; **AT1** | Increased |  | Increased AT1 mRNA levels | (Villar-Cheda et al., 2014) |
| Cannabinoid Receptors | Cerebellum | Human (18-45 and 45-70 years) | N-[2-(3-cyano-phenyl)-3-(4-(2-[18F]fluor-ethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2- methylproponamide binding (PET); **CB1** |  | Increased (women);No alteration (men) |  | (Van Laere et al., 2008) |
| Substantia nigra | Male Wistar rats (3 months and >2 years) | [3H]-WIN 55,212-2 binding (Autoradiography); **Cannabinoid receptors**WIN 55,212-2 stimulated [35S]GTPγS binding (Autoradiography); **Cannabinoid receptors** | Decreased (pars reticulata) |  | Decreased agonist (WIN 55,212-2) stimulated [35S]GTPγS binding | (Romero et al., 1998) |
| Thalamus | Human (18-45 and 45-70 years) | N-[2-(3-cyano-phenyl)-3-(4-(2-[18F]fluor-ethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2- methylproponamide binding (PET); **CB1** |  | Increased (women);No alteration (men) |  | (Van Laere et al., 2008) |
| Hippocampus | Male Wistar rats (2 and 24 months) | Western Blot; **CB1** | Decreased |  |  | (Canas et al., 2009) |
| Human (18-45 and 45-70 years) | N-[2-(3-cyano-phenyl)-3-(4-(2-[18F]fluor-ethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2- methylproponamide binding (PET); **CB1** |  | Increased (women);No alteration (men) |  | (Van Laere et al., 2008) |
| Mice (6 and 15 months) | [18F]FMPEP-*d2* binding (PET); **CB1** |  | Increased |  | (Takkinen et al., 2018) |
| Hippocampus – Dentate gyrus | Male Wistar rats (3 months and >2 years) | [3H]-WIN 55,212-2 binding (Autoradiography); **Cannabinoid receptors** | Increased |  |  | (Romero et al., 1998) |
| Hippocampus – CornuAmmonis area 1 | No alteration |  |  |
| Amygdala | Human (18-45 and 45-70 years) | N-[2-(3-cyano-phenyl)-3-(4-(2-[18F]fluor-ethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2- methylproponamide binding (PET); **CB1** |  | Increased (women);No alteration (men) |  | (Van Laere et al., 2008) |
| Basal Ganglia – Striatum – Caudate and Putamen | Male Wistar rats (3 and 24 months) | [3H]CP55,940 binding (Radioautography); **Cannabinoid receptors**α-[35S]dATP radiolabed hybridization (mRNA); **Cannabinoid receptors** | Decreased |  | Decreased cannabinoid receptors mRNA levels | (Mailleux and Vanderhaeghen, 1992) |
| Male Wistar rats (3 months and >2 years) | [3H]-WIN 55,212-2 binding (Autoradiography); **Cannabinoid receptors**[3H]-WIN 55,212-2 stimulated [35S]GTPγS binding (Autoradiography); **Cannabinoid receptors**[35S]dATP labelled hybridization (mRNA); **Cannabinoid receptors** | Decreased (lateral caudate-putamen);No alteration (medial caudate-putamen) |  | No alteration in agonist (WIN 55,212-2) stimulated [35S]GTPγS binding (lateral caudate-putamen); Decreased cannabinoid receptors mRNA levels (lateral and medial caudate-putamen) | (Romero et al., 1998) |
| Human (18-45 and 45-70 years) | N-[2-(3-cyano-phenyl)-3-(4-(2-[18F]fluor-ethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2- methylproponamide binding (PET); **CB1** |  | Increased (women’s putamen);No alteration (men’s putamen) |  | (Van Laere et al., 2008) |
| Male Human (21-56 years) | [11C]OMAR binding (PET); **CB1** |  |  | No alteration in binding of an antagonist (putamen) | (Wong et al., 2010) |
| Basal Ganglia - Globus Pallidus | Male Wistar rats (3 months and >2 years) | [3H]-WIN 55,212-2 binding (Autoradiography); **Cannabinoid receptors**[3H]-WIN 55,212-2 stimulated [35S]GTPγS binding (Autoradiography); **Cannabinoid receptors** | No alteration |  | No alteration in agonist (WIN 55,212-2) stimulated [35S]GTPγS binding | (Romero et al., 1998) |
| Male Human (21-56 years) | [11C]OMAR binding (PET); **CB1** |  |  | Decreased binding of an antagonist | (Wong et al., 2010) |
| Basal Ganglia -Entopeduncular nucleus | Male Wistar rats (3 months and >2 years) | [3H]-WIN 55,212-2 binding (Autoradiography); **Cannabinoid receptors** | Decreased |  |  | (Romero et al., 1998) |
| Cortex | Male Human (21-56 years) | [11C]OMAR binding (PET); **CB1** |  |  | No alteration in binding of an antagonist | (Wong et al., 2010) |
| Cerebral cortex | Male Wistar rats (3 months and >2 years) | [3H]-WIN 55,212-2 binding (Autoradiography); **Cannabinoid receptors**[35S]dATP labelled hybridization (mRNA); **Cannabinoid receptors** | Decreased (deep layer VI);No alteration (superficial layer I) |  | No alteration in cannabinoid receptors mRNA levels | (Romero et al., 1998) |
| Cerebral cortex - Frontal cortex | Human (*postmortem*) (22-73 years) | [3H]CP55940 binding (Autoradiography); **CB1**([3H]CP55940) stimulated [35S]GTPγS binding; **CB1** | Decreased |  | Decreased basal [35S]GTPγS binding;No alteration in agonist ([3H] CP55940) stimulated [35S]GTPγS binding | (Mato and Pazos, 2004) |
| Cerebral cortex - Frontal cortex – Orbitofrontal cortex | Human (18-45 and 45-70 years) | N-[2-(3-cyano-phenyl)-3-(4-(2-[18F]fluor-ethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2- methylproponamide binding (PET); **CB1** |  | Increased (women); No alteration (men) |  | (Van Laere et al., 2008) |
| Cerebral cortex - Frontal cortex – Lower lateral prefrontal cortex |  |  |
| Cerebral cortex -Occipital cortex |  |  |
| Cerebral cortex – Middle and inferior temporal cortex |  |  |
| Cerebral cortex – Temporal lobe - Entorhinal cortex |  |  |
| Anterior cingulate cortex |  |  |
| Parietotemporal cortex | Mice (6 and 15 months) | ([3R,5R]-5-((3-([18F]fluoromethoxy-d2)phenyl)-3-((R)-1-phenyl-ethylamino)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one) binding (PET); **CB1** |  | Increased |  | (Takkinen et al., 2018) |
| Leukotriene Receptors | -------------------------- |
| Metabotropic GABA Receptors | Cerebellum - Molecular layer | Fischer 344 rats (3 and 26 months) | [3H]GABA (Autoradiography); **GABAB**  |  |  | No alteration in GABAB receptor binding | (Milbrandt et al., 1994) |
| Corpora Quadrigemina – Inferior Colliculus |  | Decreased |  |
| Hippocampus  | Male Fischer 344 rats (6-22 months) | Western Blot; **GABABR2** | No alteration |  |  | (McQuail et al., 2012) |
| Cerebral cortex - Frontal cortex | Decreased |  |  |
| Sensory cortex | Human (*postmortem*) (34-89 years) | Western Blot; **GABABR2** | No alteration |  |  | (Pandya et al., 2019) |
| Motor cortex | Human (*postmortem*) (34-89 years) | Western Blot; **GABABR2** | No alteration |  |  | (Pandya et al., 2019) |
| Cerebellum | Human (*postmortem*) (34-89 years) | Western Blot; **GABABR2** | No alteration |  |  | (Pandya et al., 2019) |
| Cerebral cortex -Temporal cortex - Inferior temporal gyrus | Human (*postmortem*) (34-89 years) | Western Blot; **GABABR2** | No alteration |  |  | (Pandya et al., 2019) |
| Cerebral cortex -Temporal cortex - Medial temporal gyrus | Human (*postmortem*) (34-89 years) | Western Blot; **GABABR2** | No alteration |  |  | (Pandya et al., 2019) |
| Cerebral cortex -Temporal cortex - Superior temporal gyrus | Human (*postmortem*) (34-89 years) | Western Blot; **GABABR2** | No alteration |  |  | (Pandya et al., 2019) |
| Primary visual cortex | Rhesus Monkeys *(Macaca mulatta)* (8-15 years and 23-26 years) | qPCR (mRNA); **GABABR2** |  |  | Increased GABAB2 mRNA levels | (Liao et al., 2016) |
| Cerebral cortex - Frontal cortex – Prefrontal cortex | Human *(postmortem)* | Baclofen stimulated [35S]GTPγS binding; **GABAB** |  |  | Decreased in agonist (baclofen) stimulated [35S]GTPγS binding | (González-Maeso et al., 2002) |
| Metabotropic Glutamate Receptors | Cerebellum | Male Fischer 344 rats (3-25 months) | Western blot; **mGluR2/3**35S-dATP labeled hybridization (mRNA); **mGluR2; mGluR3** | Increased |  | No alteration in mGluR2 mRNA levels; Increased mGluR3 mRNA levels | (Simonyi et al., 2005) |
| Immunohistochemistry; **mGluR2/3** | No alteration |  |  | (Simonyi et al., 2005) |
| Thalamus – Lateral dorsal nucleus | Male Fischer 344 rats (3-25 months) | Immunohistochemistry; **mGluR2/3** | Increased |  |  | (Simonyi et al., 2005) |
| 35S-dATP labeled hybridization (mRNA); **mGluR7** |  |  | Decreased mGluR7 mRNA levels | (Simonyi et al., 2000) |
| Thalamus – Ventral posterior lateral nucleus |  |  | No alteration in mGluR7 mRNA levels |
| Immunohistochemistry; **mGluR2/3** | Increased |  |  | (Simonyi et al., 2005) |
| Thalamus – Thalamic reticular nucleus | Immunohistochemistry; **mGluR2/3**. 35S-dATP labeled hybridization (mRNA); **mGluR3** | Increased |  | Increased mGluR3 mRNA levels | (Simonyi et al., 2005) |
| White matter – Internal capsule | 35S-dATP labeled hybridization (mRNA); **mGluR3** |  |  | Increased mGluR3 mRNA levels |
| Hippocampus | Western blot; **mGluR2/3** | Increased |  |  |
| Hippocampus – Dentate gyrus | 35S-dATP labeled hybridization (mRNA); **mGluR2** |  |  | Decreased mGluR2 mRNA levels (upper blade); No alteration (lower blade) |
| 35S-dATP labeled hybridization (mRNA); **mGluR3** |  |  | No alteration mGluR3 mRNA levels (upper blade); Increased (lower blade) |
| 35S-dATP labeled hybridization (mRNA); **mGluR7** |  |  | No alteration mGluR7mRNA levels (upper blade); Decreased (lower blade) | (Simonyi et al., 2000) |
| Hippocampus – CornuAmmonis area 1 and 3 | Increased (CA3) |  | Decreased mGluR7mRNA levels (CA1); No alteration (CA3) |
| Immunohistochemistry; **mGluR2/3** | No alteration (CA1) |  |  | (Simonyi et al., 2005) |
| Basal Ganglia – Striatum – Caudate and Putamen | Male Fischer 344 rats (3-25 months) | Western blot; Immunohistochemistry; **mGluR2/3**35S-dATP labeled hybridization (mRNA); **mGluR2; mGluR3** | Increased |  | Increased mGluR2 mRNA levels; No alteration in mGluR3 mRNA levels | (Simonyi et al., 2005) |
| 35S-dATP labeled hybridization (mRNA); **mGluR7** |  |  | No alteration in mGluR7 mRNA levels | (Simonyi et al., 2000) |
| Basal Ganglia – Striatum – Nucleus accumbens | 35S-dATP labeled hybridization (mRNA); **mGluR3** |  |  | Increased mGluR3 mRNA levels (core); No alteration (shell) | (Simonyi et al., 2005) |
| 35S-dATP labeled hybridization (mRNA); **mGluR7** |  |  | No alteration in mGluR7 mRNA levels | (Simonyi et al., 2000) |
| Piriform cortex |  |  | Decreased mGluR7 mRNA levels |
| Cerebral cortex | Western blot; **mGluR2/3** | Increased |  |  | (Simonyi et al., 2005) |
| Cerebral cortex - Frontal cortex | Immunohistochemistry; **mGluR2/3** 35S-dATP labeled hybridization (mRNA); **mGluR2; mGluR3** | Increased |  | No alteration in mGluR2 and mGluR3 mRNA levels |
| 35S-dATP labeled hybridization (mRNA); **mGluR7** |  |  | Decreased mGluR7 mRNA levels | (Simonyi et al., 2000) |
| Cerebral cortex - Parietal cortex |  |  | Decreased mGluR7 mRNA levels |
| 35S-dATP labeled hybridization (mRNA); **mGluR2; mGluR3** |  |  | No alteration in mGluR2 and mGluR3 mRNA levels | (Simonyi et al., 2005) |
| Cerebral cortex -Occipital cortex | Male Fischer 344 rats (3-25 months) | 35S-dATP labeled hybridization (mRNA); **mGluR2; mGluR3** |  |  | No alteration in mGluR2 mRNA levels; Increased mGluR3 mRNA levels | (Simonyi et al., 2005) |
| 35S-dATP labeled hybridization (mRNA); **mGluR7** |  |  | Decreased mGluR7 mRNA levels | (Simonyi et al., 2000) |
| Cerebral cortex -Temporal cortex | Male Fischer 344 rats (3-25 months) |  |  | Decreased mGluR7 mRNA levels |
| 35S-dATP labeled hybridization (mRNA); **mGluR2; mGluR3** |  |  | No alteration in mGluR2 and mGluR3 mRNA levels | (Simonyi et al., 2005) |
| Cerebral cortex – Temporal lobe - Entorhinal cortex |  |  | No alteration in mGluR2 and mGluR3 mRNA levels |
| 35S-dATP labeled hybridization (mRNA); **mGluR7** |  |  | No alteration in mGluR7 mRNA levels | (Simonyi et al., 2000) |
| Corpus callosum | Immunohistochemistry; **mGluR2/3**35S-dATP labeled hybridization (mRNA); **mGluR3** | Increased |  | Increased mGluR3 mRNA levels | (Simonyi et al., 2005) |
| Periaqueductal area - Central gray  | Increased |  | Increased mGluR3 mRNA levels |
| 35S-dATP labeled hybridization (mRNA); **mGluR7** |  |  | No alteration in mGluR7 mRNA levels | (Simonyi et al., 2000) |

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