

GABA_A Receptors

Key References

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Overview

GABA_A receptors are responsible for the majority of neuronal inhibition in the mammalian CNS. Agonist activation results in the opening of their integral anion channel, generally leading to hyperpolarization of the cell membrane and thus inhibition. Electron microscopic studies of the native receptors have shown that they are composed of five subunits arranged pseudo-symmetrically around the ion channel, which passes through the cell membrane. Viewed from the cell exterior, the receptor appears as a 'doughnut' with an external diameter of around 8 nm; the 3 nm central cavity representing the channel vestibule opening.

GABA_A receptors are hetero-oligomers whose subunits are selected from four principle families named α , β , γ and δ , although others, including ρ , π , θ and ϵ , have been identified. In the human brain, molecular cloning studies have so far isolated six α , three β and three γ subunit isoforms while only a single δ subunit is currently known. A single gene encodes each of the subunit isoforms, although additional heterogeneity is introduced by alternative splicing in a number of cases. This plethora of subunits may suggest that there exist a vast array of GABA_A receptor subtypes, but preferred assemblies clearly exist with most estimates proposing the presence of tens rather than hundreds of receptor subtypes. It is currently believed that 70-80% of GABA_A receptors contain a benzodiazepine binding site and are composed of β , $\gamma 2$ and either an $\alpha 1$, $\alpha 2$, $\alpha 3$ or $\alpha 5$ subunit, the most abundant of which is the $\alpha 1$ subtype.

Although the precise subunit composition of the receptor subtype determines its pharmacological and biophysical characteristics, additional functional diversity is introduced

by a number of additional factors, including its cellular location and phosphorylation status. Certain receptor subtypes appear to be localized to the subsynaptic membrane where they are exposed, for brief periods, to high concentrations of released GABA, producing the phasic transmission associated with inhibitory postsynaptic currents. However, it is becoming increasingly clear that other receptor subtypes are found extrasynaptically; these are sensitive to significantly lower concentrations of the transmitter present at these sites where they mediate a tonic, slowly desensitizing current the importance of which is now becoming recognized.

The GABA_A receptor family is the target for a number of psychoactive drugs, notably benzodiazepines, barbiturates, neurosteroids and general anaesthetics, each class interacting with unique allosteric sites on the receptor. Agents with positive efficacy facilitate agonist-induced receptor activation that may produce sedation/hypnosis, anxiolysis, anticonvulsant activity, muscle relaxation, anterograde amnesia and loss of consciousness. However, inverse agonists exhibit diametrically opposed effects, decreasing the effects of agonist activation; subtype-selective inverse agonists may have potential as promnesic agents.

Each GABA_A receptor subunit isoform exhibits a distinct topographical distribution in the brain, suggesting that they mediate specific physiological functions, a conclusion that has gained support from recent advances with the 'knock-in' technology. The subunit isoform distribution pattern is not static, however, and changes not only developmentally, but also as a consequence of normal physiological cycles and pharmacological intervention with agents that are

known to produce their effects by interaction with these receptors. Indeed, aberrant expression of certain receptor subtypes may be of pathophysiological importance. Significant progress has been made in the identification of specific amino acids, within the subunit sequences, which underpin the recognition properties of the distinct GABA_A receptor subtypes. This, together with the realization that ligands may exhibit distinct intrinsic efficacies at individual subtypes, has led to a renewed interest in the potential of the GABA_A receptor family for the development of new therapeutics with a more limited pharmacodynamic profile. These receptors of the mammalian CNS have proved to be an important drug target over many years and recent developments hold much promise for the future.

GABA_A Receptors

CURRENTLY ACCEPTED TERMINOLOGY	Transmitter Recognition Site	Allosteric Modulatory Sites
AGONISTS	Isoguvacine (G002), Muscimol (G019 , M1523), THIP (Gaboxadol) (T101), Piperidine-4-sulphonic acid (P9159), Isonipecotic acid	Not applicable
ANTAGONISTS	Bicuculline (B6889 , B9130), SR 95531 (Gabazine) (S106)	Ro 15-1788 (Flumazenil) (F6300), ZK 93426
INDIRECT AGONIST	γ -Vinyl GABA (V8261)	Not applicable
POSITIVE MODULATORS	Not known	Allopregnanolone (P0666), Barbiturates (Phenobarbital (P5178), Pentobarbital (P3761), Thiopental (T1019)), Flunitrazepam (F9261), Diazepam (D0899), Alprazolam (A8800), Zolpidem (Z103) [α_1 subunit selective], Zaleplon [α_1 subunit selective], Zopiclone (Z4900), Abecarnil, L-838,417 [$\alpha_2 \alpha_3 \alpha_5$ selective]
NEGATIVE MODULATORS	Not known	Pregnenolone sulfate (P9129), DMCM (E007), FG 7142 (E006), Ro 19-4603, L-655,708 (L9787) [α_5 subunit selective]
PARTIAL MODULATORS	Not known	Bretazenil (B6434), Imidazenil
CHANNEL BLOCKERS	TBPS (B104), Picrotoxin (P1675)	Not relevant
SIGNAL TRANSDUCTION MECHANISMS	Cl ⁻ influx	Cl ⁻ influx, modulation of GABA gating
RADIOLIGANDS OF CHOICE	[³ H]-Muscimol, [³ H]-SR 95531	[³ H]-Flunitrazepam, [³ H]-Zolpidem, [³ H]-Ro 15-1788, [³⁵ S]-TBPS, [³ H]-Ro 15-4513
TISSUE EXPRESSION	Central nervous system	Central nervous system
PHYSIOLOGICAL FUNCTION	Neuronal inhibition	Modulation of neuronal inhibition
DISEASE RELEVANCE	Sleep disorders, convulsive disorders, schizophrenia	Sleep disorders, convulsive disorders, muscle tone, memory, anxiety disorders

Abbreviations

DMCM: Methyl 6,7-dimethoxy-4-ethyl- β -carboline-3-carboxylate

FG 7142: N-Methyl- β -carboline-3-carboxamide

L-655,708: Ethyl(s)-(11,12,13,13a-tetrahydro-7-methoxy-9-oxo)-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate

L-838,417: 7-tert-Butyl-(2,5-difluoro-phenyl)-6-(2-methyl-2H-[1,2,4]triazolo[4,3-b]pyridazine

Ro 15-4513: Methyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate

Ro 19-4603: Imidazo[1,5a]-1,4-thienodiazepinone

SR 95531: 2-(3'-Carboxy-2'-propyl)-3-amino-6-(4-methoxyphenyl)-pyridazinium bromide

TBPS: t-Butylbicyclophosphorothionate

THIP: 4,5,6,7-Tetrahydroisoxazolo[5,4-c]pyridin-3-ol

ZK 93426: 5-Isopropyl-4-methyl- β -carboline-3-carboxylate ethyl ester