

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 pseudosymmetrically around the ion channel pathway which passes through the cell membrane, and the receptor appears as a 'doughnut' with a diameter of around 8 nm when viewed from the cell exterior.

The receptors are generally hetero-oligomers, the subunits being selected from four principle families α , β , γ and δ , although others including π , θ and ϵ have been identified. In the human brain, molecular cloning studies have so far isolated six α subunit isoforms, three β and three γ while only a single δ isoform is currently known. Each of the subunit isoforms are encoded by a single gene, 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 this does not appear to be the case. There are perhaps four principle receptor subtypes in the brain accounting for 70-80% of the total receptor population, but these are supplemented with fewer than 10 less common subtypes. The most common GABA_A receptor of the mammalian CNS appears to comprise two α 1, two β 2 and a single γ 2 subunit. However, it is clear that the precise subunit composition of the receptor subtype determines its pharmacological and gating characteristics.

The GABA_A receptor family is the target for a number of psychoactive drugs; namely benzodiazepines, barbiturates, neurosteroids and the general anesthetics with each class interacting with unique allosteric sites on the receptor. The spectrum of pharmacological activity is wide with positive efficacy of agents producing sedation/hypnosis, anxiolysis, anti-convulsant activity, muscle relaxation and anterograde amnesia. However, it is now also clear that certain ligands may also exhibit negative efficacy. The benzodiazepine site has been particularly well studied in this regard; negative allosteric ligands at this site producing both anxiogenic, proconvulsant and promnesic effects.

Each of the GABA_A receptor subunit isoforms exhibits a distinct distribution in the brain, suggesting that they mediate specific physiological functions. This distribution pattern is not immutable and changes, not only developmentally, but also as a consequence of pharmacological intervention with agents which are known to produce their effects by interaction with these receptors. Indeed such experiments suggest that aberrant expression of certain receptor subtypes may underlie several clinical conditions. Recent advances with 'knock-in' technology suggest that particular GABA_A receptor subtypes are principally responsible for specific aspects of the pharmacological profile of these compounds. This, coupled with the design of subtype specific ligands has led to the renewed interest of the pharmaceutical industry in drug targeting of this receptor family as evidenced from the patent literature.

The benzodiazepine site has been the focus for the majority of studies to date, although similar exploration of the other allosteric sites of the GABA_A receptor family will undoubtedly occur in due course. Progress in the identification of specific amino acids within the subunit sequences which underpin the selectivity of the distinct GABA_A receptor subtypes will contribute further to the armory of the medicinal chemist in their quest to develop novel ligands with greater pharmacological specificity. Whether these will also limit the development of tolerance and withdrawal which have plagued the public image of these agents in recent years, remains to be seen.

GABA_A Receptors

CURRENTLY ACCEPTED TERMINOLOGY	Transmitter Recognition Site	Allosteric Modulatory Sites
AGONISTS	Isoguvacine (G-002) Muscimol (G-019 , M 1523) THIP (Gaboxadol) (T-101) Piperidine-4-sulphonic acid (P 9159)	—
ANTAGONISTS	Bicuculline (B 6889 , B 9130) SR 95531 (Gabazine) (S-106)	Ro 15-1788 (Flumazenil) (F 6300) ZK 93426
INDIRECT AGONIST	γ -Vinyl GABA (V 8261)	—
POSITIVE MODULATORS	—	Allopregnanolone (P 0666) Barbiturates (Phenobarbital (P 5178), Pentobarbital (P 3761), Thiopental (T 1019)) Flunitrazepam (F 9261) Zolpidem (Z-103) Abecarnil
NEGATIVE MODULATORS	—	Pregnenolone sulfate (P 9129) DMCM (E-007) Ro 19-4603 Ro 05-3663 TBPS (B-104) Picrotoxin (P 1675)
PARTIAL MODULATORS	—	Bretazenil Imidazenil
SIGNAL TRANSDUCTION MECHANISMS	Cl ⁻ influx	Cl ⁻ influx, modulation 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

ABBREVIATIONS

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

Ro 05-3663: 5-Methyl-1,4-benzodiazepin-2(3H)-one

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

SR 95531: 2-(3-Carboxypropyl)-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