Review Article

Perspectives of Presynaptic Autoreceptors and Presynaptic Heteroreceptors in the Mechanism of Neurotransmission

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ABSTRACT

The presynaptic autoreceptors and / or presynaptic heteroreceptors of the principal neurotransmitters involved in the release mechanism of neurotransmission have been identified employing various experimental models, based on receptor types / receptor subtypes and it's stimulatory or inhibitory functions. The pharmacological, neurophysiological, neurobiochemical *in vivo* or *in vitro* insect, animal or human prototype experimental models were selected from the exhaustive search of literature published in standard journals using, Google search engine, to identify the presynaptic autoreceptors or presynaptic heteroreceptors. The complexity of neuronal function in nervous system is based on the expression of presynaptic autoreceptors controlling / regulating the release and that of presynaptic heteroreceptors activated by the neurotransmitter / modulator released from other axon terminal communicated inter/ intraneuronally. In the present review, eight types of prominent presynaptic auto or heteroreceptors of seven neurotransmitters of central and peripheral nervous system namely cholinergic muscarinic, cholinergic nicotinic, adrenergic, serotonergic, dopaminergic, histaminergic, glutaminergic and GABArgic and their subtypes were classified according to stimulatory or inhibitory functions and explained on the basis of prototype experimental *in vitro / in vivo* tissue models.

Key words: Presynaptic, Autoreceptors, Heteroreceptors, Neurotransmitter, Tissue models, Neuronal functions.

INTRODUCTION

The central mechanism of neurotransmission is via complex collection of billions of various types of nerve cells. The pattern of neuronal network formed by the individual neuron, identified from the neurotransmitter released via auto or heteroreceptor activation that determines its function for the regulation of flow of information. The autoreceptors are release regulating receptors localized externally on presynaptic axon terminal.[1] Receptors controlling the release following depolarization are suggested to be presynaptic autoreceptors[2] whereas heteroreceptors are coexisting with autoreceptors which are activated by the neurotransmitters or modulators, released from the other inter/ intra neuronal axon terminal.[3] In the present review, research perspectives on neurotransmission via presynaptic autoreceptors and presynaptic heteroreceptors such as cholinergic, adrenergic, dopaminergic, serotonergic, histaminergic, glutaminergic and GABArgic using prototype pharmacological, neurophysiological and neurobiochemical experimental techniques of *in vivo* and *in vitro* cellular system from live species which include insect (e.g. cockroach), animals (e.g. mice, rats, guinea pigs, rabbits, feline etc.) and human have been described. The data were collected from extensive search of literature via search engines Google, and papers published in the national and international journals.

RESULTS

The presynaptic autoreceptors / heteroreceptors for the seven types of principal neurotransmitters were classified into eight classes (Class I – Class VIII) as

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Table 1: Classification of Presynaptic Autoreceptors / Heteroreceptors.		
Class No.	**Sub-Class**	**Receptor sub-type**
I		**Presynaptic cholinergic muscarinic autoreceptors / heteroreceptors**
	I-(a)$_{(1)}$	Presynaptic cholinergic muscarinic autoreceptors
	I-(a)$_{(1)}$	Presynaptic cholinergic muscarinic inhibitory M_2/ M_4 autoreceptors
	I-(b)	Presynaptic cholinergic muscarinic heteroreceptors
	I -(a)$_{(1)}$	Presynaptic cholinergic muscarinic M_4 heteroreceptors
II		**Presynaptic cholinergic nicotinic autoreceptors / heteroreceptors**
	II-(a)	Presynaptic cholinergic nicotinic autoreceptors
	II -(a)(1)	Presynaptic cholinergic nicotinic stimulatory autoreceptors
	II-(a)(2)	Presynaptic cholinergic nicotinic stimulatory autoreceptors at skeletal NMJ.
	II- (b)	Presynaptic cholinergic nicotinic heteroreceptors
	II-(b)(1)	Presynaptic cholinergic nicotinic (glutaminergic) heteroreceptors
III		**Presynaptic adrenergic autoreceptors / heteroreceptors**
	III- (a)	Presynaptic adrenergic autoreceptors
	III-(a)$_{(1)}$	Presynaptic adrenergic α_2 inhibitory autoreceptors
	III- (b)	Presynaptic adrenergic heteroreceptors
	III- (b)$_{(1)}$	Presynaptic adrenergic α_2 heteroreceptors
IV		**Presynaptic serotonergic autoreceptors / heteroreceptors**
	IV-(a)	Presynaptic serotonergic autoreceptors
	IV-(a)$_{(1)}$	Presynaptic serotonergic 5 HT_{1A} autoreceptors
	IV-(a)$_{(2)}$	Presynaptic serotonergic 5 HT_{1B} autoreceptors
	IV-(a)$_{(3)}$	Presynaptic serotonergic 5 HT_{1D}autoreceptors
	IV-(b)	Presynaptic serotonergic heteroreceptors
	IV (b)$_{(1)}$	**Presynaptic serotonergic 5 HT_{2A} heteroreceptors**
V		**Presynaptic dopaminergic autoreceptors / heteroreceptors**
	V-(a)	Presynaptic dopaminergic autoreceptors
	V-(a)$_{(1)}$	Presynaptic dopaminergic D_2 inhibitory autoreceptors
	V-(a)$_{(2)}$)	Presynaptic dopaminergic D_3 inhibitory autoreceptors
	V-(b)	Presynaptic dopaminergic heteroreceptors
	V-(b)$_{(1)}$	Presynaptic dopaminergic D_1 like (nACh-R) stimulatory heteroreceptors
	V-(b)$_{(2)}$	Presynaptic dopaminergic (mAChR) stimulatory heteroreceptors
	V-(b)$_{(3)}$	Presynaptic dopaminergic (ACh-R) inhibitory heteroreceptors
	V-(b)$_{(4)}$	Presynaptic dopaminergic (mGlu-R) inhibitory heteroreceptors
	V-(b)$_{(5)}$	Presynaptic dopaminergic ($GABA_B$ -R) inhibitory heteroreceptors
VI		**Presynaptic histaminergic autoreceptors / heteroreceptors**
	VI -(a)	Presynaptic histaminergic autoreceptors
	VI-(a)$_{(1)}$	Presynaptic histaminergic (H_3) inhibitory autoreceptors
	VI $_{(b)}$	Presynaptic histaminergic heteroreceptors
	VI (b)$_{(1)}$	Presynaptic histaminergic (H_3-GABAB) inhibitory heteroreceptors
VII		**Presynaptic glutaminergic autoreceptors / heteroreceptors**
	VII -(a)	Presynaptic glutaminergic autoreceptors
	VII -(a)$_{(1)}$	Presynaptic glutaminergic inhibitory autoreceptors
	VII -(b)	Presynaptic glutaminergic heteroreceptors
	VII -(b)$_{(1)}$	Presynaptic glutaminergic (GABA) inhibitory heteroreceptors
	VII.-(b)$_{(2)}$	Presynaptic glutaminergic (nACh) stimulatory heteroreceptors
VIII		**Presynaptic GABArgic autoreceptors / heteroreceptors**
	VIII- (a)	Presynaptic GABArgic autoreceptors
	VIII- (a)$_{(1)}$	Presynaptic GABArgic (GABA-B) inhibitory autoreceptors
	VIII- (b)	Presynaptic GABArgic heteroreceptors
	VIII-(b)$_{(1)}$	Presynaptic GABArgic (GABA-B) (Glu-R) inhibitory heteroreceptors

Table 2: List of Abbreviations from the text.		
Sl. No.	**Abbreviation**	**Long form of Abbreviation**
01	GABA	Gamma Amino Butyric Acid
02	Oxo-M	Oxotremorine
03	EEG	Electro Encephalogram
04	mPRF	Medial pentane reticular formation
05	LAL	Levator auris longus
06	DA	Dopamine
07	Cre / loxp	Causes recombination / locus of crossing (x) over P1
08	WT	Wild type
09	PAM	Positive allosteric modulator
10	LFHSN	Lateral fusiform hair sensory nerve
11	CA-1	Comu Ammonis
12	d-TC	d-tubocurarine
13	^{3}HMCC	[^{3}H] methylcarbamylcholine
14	f-PTP	facilitating post tetanic potentiation
15	NE	Nor-epinephrine
16	EKC	Ethylketocyclazocine
17	Dbh	Dopamine β hydroxylase
18	cAMP	Cyclic Adenosine Mono Phosphate
19	FSCV	Fast scan cyclic voltammetry
20	8-OH-DPAT	8-hydroxy-2-di-n-propylamino tetralin
21	WAY- 100135	N-tert-butyl-3,4-(2-methoxyphenyl) piperazin-lyl-2-phenyl propranamide dihydrochloride
22	SERT	Serotonin transporter
23	PKd	Equilibrium dissociation constant
24	TOF	Train of four
25	D_2S	DA D_2 short
26	G (i) PCR	G (inhibitory) protein coupled receptor
27	AC	Adenylyl cyclase
28	m-Glu-R	Metabotropic glutamate receptor
29	SNPc	Substantia nigra par compacta
30	GIRK	G protein activated inwardly rectifying potassium channel
31	mACh R	Muscarinic Acetylcholine receptor
32	NAC	Nucleus accubens
33	APET	Areclaidine propargyl ester tosylate
34	TEA	Tetra ethyl ammonium
35	[I (KM)]	Muscarinic regulated current
36	VTA	Ventral tegumnetal area
37	TTX	Tetrodotoxin
38	KCNQ2	Potassium voltage gated channel subfamily Q member 2
39	RAMH	R-alfa-methyl histamine
40	uIPSCs	Unitary inhibitory postsynaptic currents
41	uEPSCs	Unitary excitatory postsynaptic currents
42	Mf-CA3	Mossy fiber at CA3 pyramidal cells
43	KARS	Kainate receptors
44	ACPD	1 amino cyclopentane -1,3-dicarboxylic acid
45	f- EPSP	Field excitatory postsynaptic potential
46	MCCG	2-methyl-2 (carboxy-cyclopropyl) glycine
47	DCG –IV	[(dicarboxy cyclo-propyl) glycine] –IV
48	m-EPSC	miniature Excitatory postsynaptic current
49	3-5-DHPG	[(RS)-3,5,-Dihydroxyphenylglycine]
50	DASP	d-aspartate
51	MPEP	2 methyl -6-(phenylethynyl) pyridine
52	CPCCOEt	(cyclopropa (b) chromen-la-carboxylate-ethyl-ester
53	SCN	Supra chiasmatic nucleus
54	IPSC	Inhibitory post synaptic current
55	PTX	Pertussis toxin

Table 3: List of Abbreviations for Auto / Heteroreceptors in the Summary Chart.			
Reno.	**Class of Receptor type**	**Name of Auto / Heteroreceptors**	**Abbreviations**
01	**Class – I**	Presynaptic cholinergic (muscarinic) Autoreceptors / Heteroreceptors	**[P.c.(m).A/H]**
02	**Class-I-(a)**	Presynaptic cholinergic (muscarinic) autoreceptors	**[P.c. (m).A]**
03	**Class- I-(a)$_{(1)}$**	Presynaptic cholinergic (muscarinic) inhibitory M_2 /M_4 Autoreceptors	**[P.c.(m) i M_2/M_4.A]**
04	**Class-I-(b)**	Presynaptic cholinergic (muscarinic) heteroreceptors	**[P.c.(m).H]**
05	**Class-I-(b)$_{(1)}$**	Presynaptic cholinergic (muscarinic) M_4 (DA-D_1-R) heteroreceptors	**[P.c.(m) M_4 (DA-D_1.H]**
06	**Class-II**	Presynaptic cholinergic (nicotinic) autoreceptors /heteroreceptors	**[P.c.(n) A/H]**
07	**Class-II-(a)**	Presynaptic cholinergic (nicotinic) autoreceptors	**[P.c.(n).A]**
08	**Class –II-(a)$_{(1)}$**	Presynaptic cholinergic (nicotinic) stimulatory autoreceptors	**[P.c.(n).s.A]**
09	**Class-II-(a)$_{(2)}$**	Presynaptic cholinergic (nicotinic) stimulatory autoreceptors at neuro-muscular junction	**[P.c.(n).s.Anmj]**
10	**Class-II-(b)**	Presynaptic cholinergic (nicotinic) heteroreceptors	**[P.c.(n).H]**
11	**Class-II-(b)$_{(1)}$**	Presynaptic cholinergic (nicotinic) (glutaminergic) heteroreceptors	**[P.c.(n).gl.H]**
12	**Class-III**	Presynaptic adrenergic α_2 inhibitory autoreceptors/ heteroreceptors	**[P.a. (α_2).i.A/H]**
13	**Class-III-(a)**	Presynaptic adrenergic autoreceptors	**[P.a.A]**
14	**Class-III-(a)$_{(1)}$**	Presynaptic adrenergic α_2 inhibitory autoreceptors	**[P.a. (α_2).i.A]**
15	**Class-III-(b)**	Presynaptic adrenergic heteroreceptors	**[P.a.H]**
16	**Class-III-(b)$_{(1)}$**	Presynaptic adrenergic α_2 inhibitory (kappa, Opioid) heteroreceptors	**[P.a. (α_2).i.H]**
18	**Class-IV**	Presynaptic serotonergic Autoreceptors / Heteroreceptors	**[P.s.(5HT).A/H]**
19	**Class-IV-(a)**	Presynaptic serotonergic autoreceptors	**[P.s.(5HT).A]**
20	**Class-IV-(a)$_{(1)}$**	Presynaptic serotonergic $5HT_{1A}$ inhibitory autoreceptors	**[P.s.($5HT_{1A}$).i.A]**
21	**Class-IV-(a)$_{(2)}$**	Presynaptic serotonergic $5HT_{1B}$ inhibitory autoreceptors	**[P.s.($5HT_{1B}$).i.A]**
22	**Class-IV-(a)$_{(3)}$**	Presynaptic serotonergic $5HT_{1D}$ inhibitory autoreceptors	**[P.s.($5HT_{1C}$).i.A]**
23	**Class-IV-(b)**	Presynaptic serotonergic heteroreceptors	**[P.s.(5HT).H]**
24	**Class-IV-(b)$_{(1)}$**	Presynaptic serotonergic $5HT_{2A}$ heteroreceptors	**[P.s.($5HT_{2A}$).H]**
25	**Class-V**	Presynaptic dopaminergic autoreceptors /heteroreceptors	**[P.DA.A / H]**
26	**Class-V-(a)**	Presynaptic dopaminergic autoreceptors	**[P.DA. A]**
27	**Class-V-(a)$_{(1)}$**	Presynaptic dopaminergic D_2 inhibitory autoreceptors	**[P.DA.(D_2).i.A]**
28	**Class-V-(a)$_{(2)}$**	Presynaptic dopaminergic D_3 inhibitory autoreceptors	**[P.DA.(D_3).i.A]**
29	**Class-V-(b)**	Presynaptic dopaminergic heteroreceptors	**[P.DA.H]**
30	**Class-V-(b)$_{(1)}$**	Presynaptic dopaminergic (nACh-R) stimulatory heteroreceptors	**[P.DA.(nACh-R).s.H]**
31	**Class-V-(b)$_{(2)}$**	Presynaptic dopaminergic (mACh) stimulatory heteroreceptors	**[P.DA.(mACh-R).s.H]**
32	**Class-V-(b)$_{(3)}$**	Presynaptic dopaminergic (mACh) inhibitory heteroreceptors	**[P.DA.(mACh-R).i.H]**
33	**Class-V-(b)$_{(4)}$**	Presynaptic dopaminergic (mGlu-R) inhibitory heteroreceptors	**[P.DA.(mGlu-R).i.H]**
34	**Class-V-(b)$_{(5)}$**	Presynaptic dopaminergic (GABA-R) inhibitory heteroreceptors	**[P.DA.(GABA-R).i.H]**
35	**Class-VI**	Presynaptic histaminergic H_3 autoreceptors / heteroreceptors	**[P.H_3.A/H]**
36	**Class-VI-(a)**	Presynaptic histaminergic H_3 autoreceptors	**[P.H_3.A]**
37	**Class-VI-(a)$_{(1)}$**	Presynaptic histaminergic H_3 inhibitory autoreceptors	**[P.H_3.i.A]**
38	**Class -VI-(b)**	Presynaptic histaminergic H_3 heteroreceptors	**[P.H_3.H]**
39	**Class-VI-(b)$_{(1)}$**	Presynaptic histaminergic (H_3-R) ($GABA_B$) inhibitory heteroreceptors	**[P(H_3-R) ($GABA_B$) i.H]**
40	**Class- VII**	Presynaptic glutaminergic Autoreceptors / Heteroreceptors	**[P. (gl). A / H]**
41	**Class VII-(a)**	Presynaptic glutaminergic autoreceptors	**[P.(gl).A]**
42	**Class VII-(a)$_{(1)}$**	Presynaptic glutaminergic inhibitory autoreceptors	**[P.(gl) .i.A]**
43	**Class VII-(b)**	Presynaptic glutaminergic (GABA) heteroreceptors	**[P.(gl).(GABA).H]**
44	**Class VII-(b)$_{(1)}$**	Presynaptic glutaminergic (GABA) inhibitory heteroreceptors	**[P.(gl).(GABA).i.H]**
45	**Class VII-(b)$_{(2)}$**	Presynaptic glutaminergic (nACh R) stimulatory heteroreceptors	**[P.(gl).(nACh-R).s.H]**
46	**Class VIII**	Presynaptic GABA autoreceptors /heteroreceptors	**[P.(ga).A/H]**
47	**Class VIII-(a)**	Presynaptic gabargic autoreceptors	**[P.(ga).A]**
48	**Class VIII-(a)$_{(1)}$**	Presynaptic gabargic ($GABA_B$) inhibitory autoreceptors	**[P.(ga) ($GABA_B$).i.A]**
49	**Class VIII-(b)**	Presynaptic Gabargic heteroreceptors	**[P.(ga).H]**
50	**Class VIII-(b)$_{(1)}$**	Presynaptic Gabargic ($GABA_B$)(Glu) inhibitory heteroceptors	**[P.(ga).($GABA_B$) (Glu-R).i.H**

shown in Table 1 and were described in brief on the basis of the tissue model system used for the identification.

CLASS I

PRESYNAPTIC CHOLINERGIC MUSCARINIC AUTORECEPTORS / HETERORECEPTORS

I-(a) Presynaptic cholinergic (muscarinic) autoreceptors

I- $(a)_{(1)}$.1

Presynaptic cholinergic muscarinic inhibitory M_2 / M_4 autoreceptors

I- $(a)_{(1)}$.1

Human cerebral cortex and scopolamine induced amnesia in knock out (KO) mice

It was shown that acetylcholine (ACh) released from parasympathetic neuron by interacting with M_2 and M_4 muscarinic auto receptor located on human cerebral cortex, inhibited further neurally released ACh. It was observed that scopolamine - induced amnesia was considerably reduced in M_2 and M_4 single KO mice. The abnormal regulation of cholinergic function in the hippocampus, may be due to altered autoreceptor function that resulted into cognitive deficit as evidenced from the impaired passive avoidance in M_2 and M_2/ M_4-KO but not M_4 -KO mice.[4]

I- $(a)_{(1)}$.2

Mouse hippocampal, cortical and striatal brain slice preparation

Potassium stimulated [^{3}H] ACh release measurements were performed in superfused brain slices prepared from mutant mice lacking M_2 receptor KO, M_4receptor KO and M_2-M_4 receptor double KO mice labeled with [^{3}H] choline in the presence or absence of nonselective muscarinic agonist oxotremorine (Oxo-M) or antagonist atropine. Oxo-M (0.1-10 μM) inhibited K^+ -stimulated ACh release measurements of [^{3}H] choline by about 80 % in hippocampal, cortical or striatal brain slices from wild type mice. On the other hand in the presence of atropine (2 μM), inhibition of K^+ -induced ACh release measurements of [^{3}H] choline caused by Oxo-M was completely abolished confirming the existence of presynaptic autoreceptor as muscarinic type. From studies on M_2 single KO mice and M_2-M_4 double KO mice in hippocampal and cortical slice preparation, it was suggested that inhibition of K^+ -stimulated ACh release is primarily mediated by M_2 subtype whereas that of M_4 single KO mice, in striatal slice preparation is predominantly mediated by M_4 subtype of presynaptic muscarinic inhibitory autoreceptors.[5]

I- $(a)_{(1)}$.3

Prefrontal cortex of C57BL /6J mouse

The role of cholinergic muscarinic M_2 autoreceptor in modulating ACh release in prefrontal cortex of C57BL/ 6J mouse has been evaluated on cortical EEG by micro dialysis delivery of muscarinic antagonist AF-DX116 (3 nM). It was observed that the mean ACh release in prefrontal cortex was significantly increased by AF-DX116.[6]

I- $(a)_{(1)}$.4

Feline medial pentane reticular formation

The micro dialysis delivery of cholinergic muscarinic receptor antagonist to the feline medial pentane reticular formation (mPRF) and simultaneous measurements of endogenously released ACh was performed. From the minimum ACh releasing concentration by cholinergic muscarinic antagonists scopolamine (1 nM), AF-DX 116 (3 nM) and pirenzepine (300 nM), it was concluded that in mPRF of feline, ACh release was regulated by presynaptic muscarinic M_2 subtype of inhibitory autoreceptor.[7]

I- $(a)_{(1)}$.5

Confocal microscopy and quantitative morphological analysis on transgenic mouse motor endplate

The individual presynaptic muscarinic autoreceptor subtypes M_1, M_2 and M_4 allow direct competitive interaction between nerve terminals through differential activity-dependent ACh release in the synaptic cleft during neonatal neural development. The muscarinic subtypes, mACh-R M_1, M_2 and M_4 were identified by counting brightly fluorescent axon per end plate in p7, p 9 and p15 transgenic mice using confocal microscopy and quantitative morphological analysis. Involvement of mACh-R M_1, M_2 and M_4 subtypes individually studied by *in vivo* subcutaneous injections of mACh-R agonist Oxo-M and selective mACh-R subtypes antagonist M_1 (pirenzepine), M_2 (methoctramine) and M_4 (muscarinic toxin 3) over the external surface of LAL (Levator auris longus) muscle, in controlling axonal elimination after removal of the LAL muscle.[8]

I- (b)

Presynaptic cholinergic (muscarinic) heteroreceptors

I- $(b)_{(1)}$

Presynaptic cholinergic muscarinic M_4 (DA-D_1-R) heteroreceptors

The M_4 muscarinic receptor is a Gi/o protein coupled receptor. Activation of M_4 heteroreceptors in the striatum inhibited D_1 induced locomotor stimulation in mice.

I- $(b)_{(1)}$.1

Effects on locomotor activity in WT and M_4 deficient KO mice

Regulation of locomotor activity was studied using KO mice deficient in M_4 receptor. Activation of Dopamine (DA) D_1 receptor increased basal locomotor activity and in comparison with wild type, greatly enhanced locomotor response, indicating hetero-inhibitory control on DA D_1 receptor mediated locomotor stimulation at the striatal projection neuron.[9]

I- $(b)_{(1)}$.2

Behavioral effects on M_4-ACh-R deficient mutant mice

In a specific subset of striatal projection neurons muscarinic M_4 ACh-R are co-expressed with DA D_1receptor. Mutant mice lacking M_4-ACh-R were generated in DA D_1 receptor expressing cells in striatal projection neuron using cre / loxp Technology, which displayed enhanced behavioral sensitization.[10]

I– $(b)_{(1)}$.3

Effects on locomotor activity in rats and wild type (WT) and KO mice

Highly selective M_4 positive allosteric modulator (PAM), VUO152100 dose-dependently reversed the amphetamine induced enhancement in locomotor activity in rats, WT mice and KO mice deficient of M_4–ACh-R subtype. In microdialysis, it was revealed that PAM VUO152100 also reversed the amphetamine induced increases in extracellular DA levels in nucleus accumbens and caudate–putamen indicating hetero-inhibitory control of the muscarinic M_4 subtype over DA level.[11]

CLASS -II.

PRESYNAPTIC CHOLINERGIC NICOTINIC AUTORECEPTORS /HETERORECEPTOR

II- (a)

Presynaptic cholinergic (nicotinic) autoreceptors

II – $(a)_{(1)}$

Presynaptic cholinergic nicotinic stimulatory autoreceptors

II – $(a)_{(1)}$.1

Rat cerebro-cortical slice preparation

The tritiated ACh release evoked at 0.1 and 3 Hz from rat cerebro cortex slices; was inhibited by the muscarinic cholinergic agonist, Oxo-M and stimulated by the muscarinic cholinergic antagonist, atropine. The [^{3}H] ACh release induced at 0.1 Hz and not at 3 Hz; was stimulated by the nicotine which was inhibited by the nicotinic antagonist, mechamylamine. The [^{3}H] ACh release induced at 3Hz and not at 0.1Hz, was decreased by the anticholinesterase, neostigmine whereas in the presence of atropine, neostigmine potentiated ACh release. Potassium (15 mM) evoked synaptosomal [^{3}H] ACh release was inhibited by ACh, whereas [^{3}H] ACh was enhanced, by ACh when external calcium concentration was decreased (0.1 mM Ca^{2+}). It was suggested that, nicotinic autoreceptors become responsive under the conditions that mimic impairment of ACh release, giving clues of the effective adjunct in the therapy of cholinesterase inhibitors and nicotinic agonists for the Alzheimer's disease.[12]

II - $(a)_{(1)}$.2

Human and rat striatal synaptosome preparation

The [^{3}H]-D-aspartate or [^{3}H]-ACh release from human neocortex and rat striatal synaptosome preparation was used to evaluate the existence of functional presynaptic nicotinic hetero and autoreceptors. It was shown that presynaptic nicotinic autoreceptors of α4β2 type localized at cholinergic nerve terminals and presynaptic nicotinic heteroreceptors of α7* type localized at glutaminergic nerve terminal. Activation of these presynaptic auto and heteroreceptors mediated enhancement in the ACh and glutamate release respectively.[13]

II – $(a)_{(1)}$.3

Rat hippocampal synaptosome preparation

The (-) nicotine and the nicotinic agonists such as (+) epibatidine, (+) anatoxin-a, cystine, isoare-colone evoked concentration dependent increase in [^{3}H] ACh release as shown by a "bell shaped" concentration- response curve, from superfused rat hippocampal synaptosomal preparation that was abolished by the nicotinic antagonist dihydro-β-erythroidine, mechamylamine and pempidine.

However the α 7 selective antagonist methyllycaconitine did not abolish nicotine-induced [^{3}H]

ACh release. At the same time KCl-induced [^{3}H] ACh release remain unaffected indicating the existence of nicotinic autoreceptor in the rat hippocampal synaptosome preparation.[14]

II – $(a)_{(1)}.4$

Somato-dendritic interneuron in the CA1 field

Patch clamp studies were performed to record responses from interneurons. The existence of functional α7 and α4β2 like nACh -R was shown on somatodendritic region and preterminal /terminal region of interneuron in the CA1 field. It was observed that the presynaptic heteroreceptor α7 nACh-R was desensitized faster than α4β2 nACh-R. On the other hand desensitization of α7 nACh-R induced by the non-selective agonist, ACh, lasts longer than that of α7 nACh-R induced by the selective agonist, choline, Indicating the involvement of nACh-R in cognitive function and certain neurological disorders such as Alzheimer's disease and schizophrenia.[15]

II – $(a)_{(1).}5$

Cockroach LFHSN cholinergic nerve terminals

From intracellular microelectrode recordings and micro-iontophoretic application, existence of presynaptic nicotinic ACh-R has been shown in the axonal membrane of the cholinergic nerve terminal of the lateral fusiform hair sensory nerve (LFHSN). The endogenously released ACh from cholinergic nerve terminal at the synapse following normal and evoked spike burst, depolarized the LFHSN suggesting that the nicotinic ACh-R acts as a presynaptic cholinergic nicotinic autoreceptor.[16]

II –$(a)_{(2)}$

Presynaptic cholinergic nicotinic stimulatory autoreceptors at the skeletal neuromuscular junction (NMJ).

II-$(a)_{(2)}.1$

Tritiated efflux measurements of ACh using radiolabelled technique at rat left hemidiaphragm preparation

The existence of facilitatory nicotinic autoreceptors was shown from the maximum inhibition of tritiated efflux using radiolabelled technique. The effect of snake venom neurotoxins, β-bungarotoxin, ϰ-bungarotoxin, α cobra-neurotoxin, erabutoxin-b and plant neurotoxin d-tubocurarine (d-TC) following incubation of rat left hemidiaphragm with [^{3}H] choline, was evaluated on evoked release of newly synthecised [^{3}H] ACh. It was observed that d-TC reduced the evoked [^{3}H] ACh release to about 50% by blocking presynaptic nicotinic autoreceptors at the motor endplates.[17] The evoked release of newly synthecised [^{3}H] ACh following incubation of rat left hemidiaphragm with [^{3}H] choline was investigated in the absence of anticholinesterase. It has been shown that, α -bungarotoxin, α-cobra toxin and erabutoxin-b did not affect nerve evoked release of newly synthecised [^{3}H] ACh in the absence of anti-AChE following incubation of rat left hemidiaphragm preparation with [^{3}H] choline. Under identical condition d-TC reduced evoked release of [^{3}H] ACh by about 50%. The α-bungarotoxin, α-cobratoxin, ϰ-bungarotoxin except erabutoxin–b enhanced basal tritium efflux immediately when applied to the end plate preparation.[18] Chronic administration of nicotine to the rat, caused a brain region specific up-regulation of [^{3}H] methylcarbamylcholine (^{3}HMCC) sites, increased binding in the frontal cortex, parietal cortex, striatum and hippocampus. Nicotine effect was selective to the nicotinic binding site as both muscarinic binding site M_1 [^{3}H] pirenzepine and M_2 [^{3}H] ACh remain unaffected. Nicotine agonist methylcarbamylcholine increased ACh release from frontal cortex and hippocampus by calcium-dependent mechanism, which was not observed in rats treated with nicotine. Chronically treated rats with nicotine showed partial recovery of nicotinic autoreceptor function of ACh release when allowed to recover for 4 days, however, density of nicotine binding sites remain increased in comparison to the control.[19]

II– $(a)_{(2)}.2$

Effects of nicotinic antagonists on high frequency twitch responses and [^{3}H] ACh release:

The subtype specific nACh-R antagonist, depressed nerve evoked contraction and [^{3}H] ACh release in rat phrenic nerve hemidiaphragm. During high frequency train (50 Hz-5sec.), muscle tension was transiently increased. The nACh-R antagonist d-TC, mechamylamine and hexamethonium in addition to reduction in the muscle tension, also caused tetanic fade. It was inferred that blockade of presynaptic nicotinic facilitatory autoreceptor consisting of α3β2 subunits, produced tetanic fade which may be due to blocking nicotinic auto-facilitation of ACh release.[20]

II-$(a)_{(2)}.3$

Effects of d-TC on rat phrenic nerve hemidiaphragm preparation

The existence of presynaptic stimulatory autoreceptor was reported using d-TC on mammalian neuromuscular junction subjected to tetanic stimulation. It was shown that d-TC blocks the prejunctional nicotinic ACh receptors thereby reduced the ACh output during high frequency stimulation with consequent transformation of sustained tetanus to a tetanic fade. These prejunctional nicotinic receptors controlling the vesicular release of ACh during high frequency stimulation are termed as presynaptic nicotinic

stimulatory autoreceptors at the rat neuromuscular junction.[21,22]

II –(a)$_{(2).}$4

Effects of enhydrotoxin-a / *E.schistosa* antivenin treatment on rat phrenic nerve diaphragm preparation

Using model studies of principal sea snake neurotoxin enhydrotoxin-a (61-4)[23] and monovalent *E. schistosa* horse antivenin[24] treatment and 100% washout at the mammalian neuro-muscular junction subjected to high frequency stimulation, it has been possible to unravel the existence of presynaptic site of action in predominant postsynaptically acting enhydrotoxin-a, as transformation of sustained tetanus to an exaggerated twitch response when neuro-muscular transmission was restored to a Normal twitch response following single indirect electrical stimulation.[25] The antibodies of principal neurotoxin enhydrotoxin-a present in the sea snake antivenin, while displacing enhydrotoxin-a from the postsynaptic nicotinic cholinoceptive sites, able to restore the normal twitch response. However, sustained response to the high frequency stimulation was lost, as prolonged exposure of the antibodies at the postsynaptic nicotinic receptors, altered it's conformational state, required to elicit the normal sustained tetanic response when neuro-muscular preparation was subjected to the high frequency stimulation. In the context of nonavailability of the postsynaptic cholinoceptive sites, the accumulated ACh elicited exaggerated twitch response as the facilitating PTP (f-PTP) by interaction with nicotinic cholinoceptors expressed to elicit facilitatory twitch response, known as presynaptic nicotinic stimulatory type of autoreceptors.[26] The AChE inhibitor, physostigmine pretreatment restored the sustained form of tetanus in the toxin-antivenin-treated neuromuscular preparation when hydrolysis of ACh was prevented and sufficient ACh was available at the post- synaptic cholinoceptive sites to restore the altered conformation of the post synaptic nicotinic receptors for the normal sustained form of tetanus.[25]

II–(b)

Presynaptic nicotinic (glutaminergic) heteroreceptors

II –(b)$_{(1)}$.1

Human neocortex and rat striatal synaptosomal preparation

The basal release of [^{3}H] d- aspartate from the superfused human neocortex and the rat striatal synaptosomes was not affected by nACh-R agonist such as anatoxin-a, epibatidine, nicotine or ACh plus atropine, however, K^+-evoked Ca^{2+}-dependent exocytotic release of [^{3}H] d-aspartate was enhanced. The enhancement in [^{3}H] ACh release by ACh plus atropine on human cortical synaptosome however, was insensitive to the nicotinic antagonist α-bungarotoxin. The enhancement in [^{3}H] ACh release was completely blocked by the ganglion blocker mechamylamine, indicating the existence of α-7* nicotinic heteroreceptors mediating enhancement in glutamate release on glutaminergic axon terminals in human neocortex and in the rat striatum.[13]

CLASS - III

PRESYNAPTIC ADRENERGIC α_2 INHIBITORY AUTORECEPTORS / HETERO-RECEPTORS

III-(a)

Presynaptic adrenergic autoreceptors

III –(a)$_{(1)}$

Presynaptic adrenergic α_2 inhibitory autoreceptors

III-(a)$_{(1).}$1

Pig brain cortex slice preparation

Pig brain cortex slices were preincubated with [^{3}H] norepinephrine (NE) followed by super fusion and stimulation electrically at 6 pulses / 100 Hz. The pKd values of thirteen α_2 antagonists were determined against α_2 agonist UK 14304 .The pKd values of all antagonists, except one showed excellent correlation with the values reported earlier for α_{2A}type but not for other types α_{2B}, α_{2C} & α_{2D} and showed parallel shift of concentration response curve of UK 14304 to the right. It was inferred that α_2 autoreceptors in pig brain cortex are of α_{2A}subtype.[27]

III –(a)$_{(1)}$.2

Rabbit caudate nucleus slice preparation

The α_2 agonist modulates the endogenously released DA in rabbit head caudate nucleus slice preparation. Endogenously released DA was measured by fast cyclic voltammetry from oxidation potential on voltammogram. Stimulation of the caudate nucleus slice by 6 pulses / 100 Hz, increased extracellular concentration of DA. Selective $\alpha_2$agonist UK 14304 reduced the endogenously released DA from the slices stimulated by 6 pulses / 100 Hz, whereas α_2 antagonist, did not affect the DA release from slices stimulated by 6 pulses / 100 Hz. The DA antagonist sulpiride however, increased release of DA, when caudate nucleus slice was stimulated by 10 pulses /1 Hz, indicative of the existence of the release inhibiting α_{2A}autoreceptor on dopaminergic axon.[28]

III–(a)$_{(1)}$.3

Microdialysis studies on rat brain

Microdialysis studies on the antidepressant drugs NE reuptake inhibitor, desipramine; mixed 5 HT/ NE reuptake inhibitor, sibutramine and NE / DA reuptake inhibitor, aminotine by decreasing the function of presynaptic adrenergic α_2 autoreceptor enhanced the extracellular NE level in the various regions of the rat brain. The chronic administration of antidepressant contributes to the enhancement in the therapeutic effect by desensitization of presynaptic adrenergic α_2 autoreceptors. Therapeutic effect of the antidepressants was further enhanced when α_2 adrenergic antagonist, yohimbine was co-administered with antidepressants.[29]

III-(b)

Presynaptic adrenergic heteroreceptors

III –(b)$_{(1)}$

Presynaptic α_2 adrenergic (kappa, opioid) heteroreceptors

III-(b)$_{(1)}$.1

Rabbit Hippocampus slice preparation

The [^{3}H] NA release evoked by electrical field stimulation (360 pulses / 3 Hz) was inhibited by the kappa receptor agonist, ethylketocyclazocine (EKC) via activation of presynaptic kappa opioid ($\alpha_2$adrenergic) heteroreceptors. The [^{3}H] NA release was enhanced in the presence of α_2 antagonist Yohimbine (0.1 to 1 μM) when α_2 autoinhibitory control was antagonized. On the other hand, removal of Yohimbine treatment, [^{3}H] NA release was completely inhibited.[28]

CLASS-IV

PRESYNAPTIC SEROTONERGIC AUTORECEPTORS / HETERORECEPTORS

IV-(A)

Presynaptic serotonergic autoreceptors

The somato-dendritic release of serotonin from raphe cells, by action on presynaptic inhibitory 5 HT_{1A} autoreceptors, was decreased as evidenced from the decrease in firing rate of raphe cells whereas presynaptic 5 HT_{1D} / 5 HT_{1B} inhibitory autoreceptors at the axon terminals in fore brain, were involved in the modulation of release of 5 HT. These receptors are G (i) PCR, which inhibited adenylyl cyclase. Additionally $5HT_{1A}$, $5HT_{1B}$ and $5HT_{1D}$ activated receptor operated K^+ channel and inhibited voltage gated Ca^{2+}channel. Antimigraine effect of $5HT_{1D}$ /$_{1B}$ agonist, Sumatriptan was by modulation via G (i)-AC-Ca^{2+} pathway, restored the carotid artery flow.[30]

IV-(a)$_{(1)}$

Presynaptic serotonergic $5HT_{1A}$ inhibitory autoreceptors

IV-(a)$_{(1)}$.1

Rat dorsal raphe and median raphe nuclei in hippocampus

The presynaptic $5HT_{1A}$ –R is a Gi/o protein coupled metabotropic inhibitory autoreceptor, involved in regulation of 5 HT neuronal activity. It is exclusively localized on the cell bodies and dendrites of serotonergic neuron in the dorsal and median raphe nuclei in hippocampus. Activation of presynaptic $5HT_{1A}$-R reduced 5HT release involved in pro-cognitive effects of passive avoidance retention. Agent antagonizing $5HT_{1A}$-R via $5HT_7$-R activation, facilitated memory retention. $5HT_{1A}$-R by activation via pertussis toxin sensitive Gi /o protein resulted into hyperpolarization, decreased cAMP formation, inhibited neuronal firing via activation of G protein coupled inwardly rectifying potassium channel and inhibition of Ca^{2+} channel.[31]

IV-(a)$_{(1)}$.2

Guinea pig dorsal raphe nucleus slice preparation

5HT release measurements were performed by FSCV (Fast Scan Cyclic Voltammetry). $5HT_{1A}$ agonist, 8OH DPAT [(8 hydroxy -2-di-n-propylamino) tetralin] produced concentration dependent inhibition of 5 HT release evoked by repeated single 0.1 msec pulses of electrical stimulation which was competitively antagonized by the selective $5HT_{1A}$ receptor antagonist, ± WAY 100135 (N-tert-butyl 3-4-(2- methoxyphenyl) piperazin –lyl-2-phenylpropanamide dihydrochloride) . The ± WAY 100135 increased 5 HT release, evoked by train of 5 pulses at 1 Hz suggesting the existence of 5 HT_{1A} autoreceptor in guinea pig dorsal raphe nucleus.[32]

IV-(a)$_{(2)}$

Presynaptic serotonergic $5HT_{1B}$ inhibitory autoreceptors

IV-(a)$_{(2)}$.1

Rat hippocampal synaptosome preparation

The rotating disk electrode voltammetry on synaptosomal preparation was used for the determination of regulation of serotonin transporter (SERT) mediated reuptake of 5HT via $5HT_{1B}$ presynaptic inhibitory autoreceptor. In the presence of selective 5 HT_B antagonist SB 224289, reuptake of 5HT by SERT was decreased whereas, SERT activity mediated reuptake

of 5HT was enhanced by selective $5HT_{1B}$ agonist, CP 94253 indicating the regulatory role of $5HT_{1B}$ inhibitory autoreceptor in SERT mediated 5HT reuptake at the rat hippocampal synaptosome preparation.[33]

IV-(a)$_{(3)}$

Presynaptic serotonergic $5HT_{1D}$ inhibitory autoreceptors

IV–(a)$_{(3)}$.1

Guinea pig cerebral cortex slice preparation

In the presence of $5HT_{1D}$ presynaptic auto receptor preferring antagonists LY 367642, LY 456219 and LY 456220, LY 310762, [^{3}H] 5 HT release from guinea pig cortex slice was potentiated whereas in the presence of selective 5 HT_{1D} receptor agonist L-772405, inhibited [^{3}H] 5 HT release. In microdialysis studies, intraperitoneal administration of $5HT_{1D}$ preferring antagonist LY- 310762 at the concentration 10 mg / kg potentiated extracellular concentration of 5 HT that was produced by maximal effective concentration of 20 mg / kg a standard selective serotonin inhibitor, fluoxetine. On the other hand [^{3}H] 5 HT release, in the presence of 5 HT_{1D} antagonist and 5 HT transport inhibitor LY-367642, was potentiated to a greater extent in comparison with the [^{3}H] 5 HT release by standard fluoxetine indicating the existence of 5 HT_{1D} as a presynaptic inhibitory autoreceptor at guinea pig cortical slices.[34]

IV-(a)$_{(3)}$.2

Guinea pig dorsal raphe nucleus slice preparation

The 5HT release measurements were performed by FSCV. $5HT_{1D}$ agonist, sumatriptan produced concentration-dependent inhibition of 5 HT release evoked by repeated single 0.1 msec pulses of electrical stimulation, which was competitively antagonised by the selective $5HT_{1D}$ receptor antagonist, GR 127935. The GR 127935 increased 5 HT release evoked by the train of 5 pulses at 1 Hz suggesting the existence of 5 HT_{1D} autoreceptor in guinea pig dorsal raphe nucleus.[32]

IV-(b)

Presynaptic serotonergic heteroreceptors

IV-(b)$_{(1)}$

Presynaptic serotonergic $5HT_{2A}$ heteroreceptors

IV-(b)$_{(1)}$.1

Serotonergic $5HT_{2A}$ (mGlu-R) heteroreceptor in post-partum human brain

Antipsychotic drugs with high affinity for presynaptic serotonergic $5HT_{2A}$ heteroreceptors were used to treat schizophrenia. The drugs interacting with mGlu also have been used to treat schizophrenia. The interaction of mGlu with 5 HT_{2A}-R form a functional complex in brain cortex. Hallucinogenic drugs target the $5HT_{2A}$-R-mGluR$_2$ complex. Activation of mGlu-R**2** of the complex eliminated hallucinogen specific responses. Studies on $5HT_{2A}$-R of the complex in post-partum human brain of untreated schizophrenic patients showed up-regulation of $5HT_{2A}$ receptor of the functional complex whereas mGlu-R$_2$ of the complex was down-regulated.[35]

CLASS -V

PRESYNAPTIC DOPAMINERGIC AUTORECEPTORS / HETERORECEPTORS

Dopaminergic system in the brain, play a critical role in neuronal function of cognition, locomotion, reward processing and neuroendocrine functions, primarily via DA heteroreceptors and secondarily via DA autoreceptors. The DA autoreceptors by providing feedback inhibition, control cell firing, synthesis, release and uptake of dopamine. The DA D_1 like (D_1 and D_5) are stimulatory heteroreceptors, located on non-dopaminergic neuron whereas the DAD_1 like (D_2, D_3 and D_4) are inhibitory heteroreceptors also located on non-dopaminergic neuron.[36,37]

V-(a)

Presynaptic dopaminergic Autoreceptors

V-(a)$_{(1)}$

Presynaptic dopaminergic (D_2) inhibitory autoreceptors

V-(a)$_{(1)}$.1

Presynaptic dopaminergic D_2 inhibitory autoreceptors

The DA autoreceptor present on dopaminergic neuron play an important role in regulating DA synthesis, release and uptake of DA. The DA autoreceptor of D_2 subtypes are located on the soma and dendrites of midbrain DA neurons in the ventral tegumental area (VTA), substantia nigra par compacta (SNPc) and in the projection area of axon terminals. The D_2S (DA D_2 short) variant is primarily expressed presynaptically which is involved in controlling the DA release by inhibiting cAMP formation via Gi /o coupling. The DA D_2 inhibitory autoreceptor modulate activity directly through the activation of potassium conductance and indirectly modulate dopaminergic transmission

by expression of tyrosine hydroxylase and plasma membrane DA transporter.[38-40]

V-(a)$_{(1)}$.2

Effects on locomotor response and operant conditioning in mice

The mice were examined for the locomotor activity and spatial reversal learning on operant conditioning. In comparison with wild type mice and with deficient D_2 autoreceptor i.e. Auto Drd2-KO-mice, it was revealed that auto Drd2-KO mice showed enhanced sensitivity to locomotor stimulating effect of cocaine (10 mg/kg, I.P.) whereas auto Drd2-KO mice revealed slower response in the spatial reversal learning and cause impairment in sustaining a prolonged nose porking response.[41]

V-(a)$_{(1)}$.3

Autoreceptor mediated action of isoform D_2L- KO mice

The two isoforms of DA receptor D_2S (short) and D_2L (long) differ by 29 amino acid residues in 3rd intracellular loop. In D_2L -KO mice, D_2S receptor expression was up-regulated. These mice also exhibited increase in the consumption of both sugar, water and ethanol which may be due to the imbalance in the ratio of D_2S and D_2L**.** The D_2L-KO mice also exhibited autoreceptor mediated action i.e. hyperpolarization at the DA soma and inhibition of DA release at the dopaminergic presynaptic nerve terminal.[42]

V-(a)$_{(1)}$.4

Brain slice preparation of C57BL / 6J mice

The effect of cocaine was evaluated on brain slices containing nucleus accumbens core from C57BL/6J mice. Cocaine by interaction between DA transporter and D_2/ D_3 autoreceptor modulate it's effect to cause inhibition of DA uptake through DA transporters on pre-synaptic dopaminergic nerve terminals. The nonselective D_2/ D_3 autoreceptor antagonist raclopride, enhanced inhibition of DA uptake. It was shown that selective D_3 autoreceptor antagonist, SB-277011-A, was responsible for Increased potency of cocaine whereas selective D_2 agonist sumanirole, decreased the inhibition of DA uptake and selective D_3 agonist, PD 128907, was devoid of inhibitory effect on DA uptake via DA transporters. Chronic administration of D_2 agonist, quinpirole, decreased number of dopaminergic axon terminals with consequent decrease in DA release, mediated through the inhibition of protein kinase A. It was suggested that chronic administration of D_2 agonist, activated D_2 autoreceptor that inhibited synaptogenesis by the translational regulation of protein synthesis involved in the synapse formation.[43]

V-(a)$_{(2)}$

Presynaptic Dopaminergic (D_3) inhibitory autoreceptors

V-(a)$_{(2)}$.1

Micro dialysis and effects on freely moving rats

Dopamine D_3 presynaptic autoreceptors control synthesis and release of DA in the nucleus acumens, olfactory tubercles, striatum and frontal cortex. It was shown that D_3/ D_2 receptor agonist (+) 7-OH DPAT (7-hydroxy-N, N-dipropyl-2-aminotetralin) dose-dependently decreased synthesis of DA. The inhibitory action was mimicked by highly potent D_3 agonist CGS-15855 A (-) quinpirole, quinelorane and N-0434. In freely moving rats, dialysate concentration of DA was dose-dependently reduced by (+) 7-OH DPAT in the nucleus accumbens and contralateral striatum on the other hand, haloperidol blocked completely the action of (+)-7-OH DPAT.[44]

V-(b)

Presynaptic dopaminergic heteroreceptors

The DA D_1 like (D_1 and D_5) are stimulatory DA heteroreceptors, which via Gα(s) / olf GTP system increases excitability and promotes transition to the upstate in NMDA receptor, increases in L-type of calcium channel and Na^+ channel currents. On the other hand, DA D_2 like (D_2,D_3 and D_4) are DA inhibitory type of heteroreceptors which via Gαi/o GTP system activate inwardly rectifying potassium channels (GIRK) and plays important role in regulation of locomotion, cognition and motivation.[36,45,46]

V-(b)$_{(1)}$

Presynaptic dopaminergic D_1 like (nACh-R) stimulatory heteroreceptors

V_(b)$_{(1).}$1

Mouse cortical slice preparation

The presynaptic nACh-R having structure consisting of β_2 subunits that is expressed on DA nerve terminals. From microdialysis studies, nicotine application enhanced extracellular release of DA.

From FCV studies in cortical slice preparation, nicotine inhibited evoked DA release. However, nicotine antagonist application by nACh-R blockade of presynaptic dopaminergic (nACh-R) heteroreceptors or due to desensitization, decreased DA release

and subsequently facilitated DA release during high frequency stimulation.[47,48]

V-(b)$_{(1)}$.2

Rat striatal slice and synaptosome preparation

Presynaptic dopaminergic (nACh-R) heteroreceptors located on dopaminergic nerve terminal are β_2 subunits containing nACh-R involved in the release of DA. The nACh-R agonists, nicotine, anatoxin-a induced [^{3}H] DA release from striatal slice and synaptosome preparation of rat. In the presence of ganglion blocker, mechamylamine [^{3}H] DA release, induced by high concentration of nACh-R, agonist was higher from cortical slice. The additional increase in [^{3}H] DA release was by indirect activation of non β_2 subunits containing nicotinic ACh receptor.[49]

V–(b)$_{(1)}$.3

Mouse striatal slice preparation

Extracellular DA concentration was monitored using FSCV from mouse striatal slice containing both nucleus accumbens (NAc) and caudate putamen (CPu). Application of mACh-R agonist Oxo-M and APET (Areclaidine propargyl ester tosylate) decreased DA release induced by low frequency stimulation (1-10 Hz, 4 pulses) whereas DA release, was increased by high frequency stimulation (> 25 Hz, 4 pulses).The frequency dependent biphasic effect on DA release was based on the availability of ACh for activation of striatal presynaptic dopaminergic (nACh-R) heteroreceptors on dopaminergic axon.[50]

V-(b)$_{(2)}$

Presynaptic dopaminergic (mAChR) stimulatory heteroreceptors

V–(b)$_{(2)}$.1

Rat striatal synaptosome preparation

Presynaptic dopaminergic (mACh) M_5 muscarinic ACh subtype localized at SNPc is a release facilitating M_5 muscarinic DA heteroreceptors localized on dopaminergic nerve terminal. Muscarine regulated current [I (KM)] in high extracellular K^+ induced [^{3}H] DA release from rat striatal synaptosome, was inhibited by I (KM) activator, retigabine. The [I (KM)] blocker, Tetraethyl ammonium (TEA), enhanced high K^+ induced [^{3}H] DA release**.**The cholinergic agonist Oxo-M potentiated high K^+ induced [^{3}H] DA release which was inhibited competitively by pirenzepine however, remain unaffected by retigabine and abolished by anti-KCNQ2 antibodies.[51]

V-(b)$_{(3)}$

Presynaptic dopaminergic (ACh-R) inhibitory heteroreceptors

V-(b)$_{(3)}$.1

Rat striatal slice preparation

From FSCV measurements in rat striatal slices, activation of dopaminergic (mACh-R) heteroreceptors produced inhibition of DA release. The concentration-dependent decrease of DA release and it's reversal were observed with ACh E inhibitor eserine. The inhibitory response was mimicked by cholinergic agonist (muscarine and nicotine) and blocked by specific cholinergic antagonists atropine, dihydro-β-erythroidine respectively.[52]

V-(b$_{)(3)}$.2

Striatal slice preparation in KO mice

In striatal slice preparation from M_1-M_5 mACh-R KO mice, it was shown that M_3 mACh-R KO inhibited K^+ induced [^{3}H] DA release whereas M_4 and M_5 mACh-R KO, facilitated K^+ induced DA release. The FCV measurements in mACh-R KO mice striatal slice preparation showed decrease in the evoked DA release, whereas inhibition of evoked DA release, caused by mACh-R agonist, Oxo-M was enhanced. The inhibitory effect of Oxo-M may be due to higher affinity of ACh for nACh-R than that of mACh-R.[53]

V_ (b)$_{(4)}$

Presynaptic dopaminergic (mGlu-R) inhibitory heteroreceptors

V-(b)$_{(4)}$.1

Mouse striatal slice preparation

Dopamine release was monitored using FCV measurements from striatal slices. The release of DA was induced by DA uptake inhibitor or by high frequency stimulation. Glutamate spillover induced either by glutamate uptake blockade or high frequency stimulation, by inhibitory modulation depressed DA release via activation of dopaminergic (mGlu-R) inhibitory heteroreceptors.[53]

V-(b)$_{(5)}$

Presynaptic dopaminergic ($GABA_B$ -R) inhibitory heteroreceptors

V–(b)$_{(5)}$.1

Striatum of intact and kainic acid lesioned rats

Administration of $GABA_B$ receptor agonist, Baclofen in the striatum of intact and kainic acid lesioned rats decreased level of extracellular DA whereas administration of $GABA_B$ receptor antagonist's phaclofen and bicuculline, elevated level of extracellular DA which was completely suppressed by Tetrodotoxin

(TTX) indicating the presynaptic dopaminergic $GABA_B$ inhibitory heteroreceptors activation in the mechanism of DA release.[54]

CLASS -VI

PRESYNAPTIC HISTAMINERGIC H_3 AUTORECEPTORS / HETERORECEPTOR

VI-(a)

Presynaptic histaminergic autoreceptors

VI-$(a)_{(1)}$

Presynaptic histaminergic H_3 inhibitory autoreceptors

VI-$(a)_{(1)}$.1

Cerebral cortical slice preparation

In cerebral cortex slice preparation labeled with [^{3}H] histidine, the high K^+ induced depolarization enhanced [^{3}H] histamine by about 2 fold and to a lesser extent in rat cerebral cortex synaptosome preparation. With increasing concentration of exogenous histamine, the high K^+ induced depolarization was decreased progressively which was reversed competitively by specific H_3 antagonist's burimamide, impromidine whereas it remained almost unaffected by specific H_1 and H_2 antagonist mepyramine and tiotidine respectively. In the absence of exogenous histamine, H_3 antagonist enhanced high K^+ induced depolarization and also involved in stimulation of [^{3}H] histamine synthesis. Histamine H_3 is an autoreceptor that control the release and synthesis of histamine at the histaminergic nerve terminals and perikarya.[55]

VI–$(a)_{(1)}$.2

Mouse brain cortical slice preparation

Presynaptic H_3 autoreceptors coupled to Go / Gi protein is located on histaminergic neuron of CNS. Activation of $\alpha_2$autoreceptors by endogenous NE in mouse brain slice preparation, decreased the H_3 autoreceptors mediated effect whereas blockade of α_2 autoreceptors, increased the H_3 autoreceptors mediated effect. The K^+ channel blocker, TEA attenuated H_3 autoreceptors mediated inhibition of NE release. The effect of TEA on H_3 autoreceptors mediated inhibition was abolished by lowering Ca^{2+} concentration.[56]

VI-(b)

Presynaptic histaminergic heteroreceptors

VI –$(b)_{(1)}$

Presynaptic histaminergic (H_3-R) ($GABA_B$) inhibitory heteroreceptors

VI –$(b)_{(1)}$.1

Rat cerebro-cortical slice preparation

The paired whole cell patch clamp studies were performed on rat cerebro-cortical slice preparation to record unitary excitatory and inhibitory postsynaptic currents (uEPSCs and uIPSCs). The H_3 receptor agonist, R-α -methyl-histamine (RAMH) reduced amplitude of both uEPSCs and uIPSCs in GABArgic interneuron. On the other hand H_3 receptor antagonists JNJ 5207852 dihydrochloride or thioperamide, inhibited RAMH induced suppression of uEPSCs and uIPSCs indicating presynaptic histaminergic ($GABA_B$-R) inter-neuronal inhibitory heteroreceptor activation at the rat cerebrocortical slice preparation.[57]

CLASS -VII

Presynaptic Glutaminergic Autoreceptors / Heteroreceptors

VII-(a)

Presynaptic glutaminergic autoreceptors

VII–$(a)_{(1)}$

Presynaptic glutaminergic inhibitory autoreceptors

Presynaptic glutaminergic inhibitory autoreceptors by binding to G protein, decrease excitability in presynaptic terminal via activation of K^+ conductance and decrease calcium influx into presynaptic terminal via inhibition of voltage gated calcium channel . Glutamate autoreceptors also act directly on transmitter containing vesicles.[58]

VII –$(a)_{(1)}$.1

Hippocampal slice preparation from Wistar rats and C57 BL mice

Mossy fiber at CA3 pyramidal cell (mf-CA3) synapse, is a prominent hippocampal synapse modulated by both facilitatory and inhibitory glutamate autoreceptors. Two types of glutamate autoreceptors, release suppressing metabotropic glutamate receptors (mGlu-R) and release facilitating kainate receptors (KARS) were identified at the mf-CA3 synapse, based on suppression and augmentation of glutamate transmitter release. Mossy fibers stimulation at low frequency, suppressed transmitter release by the action on presynaptic mGlu-R which provide predominant role of short term plasticity in glutaminergic autoregulation at mf-CA3 whereas facilitation of transmitter release at mf-CA3, was KARS independent. Under similar experimental conditions, kainate receptors were insufficient to facilitate transmitter release.[59]

VII –(a)$_{(1)}$.2

Human Hippocampal slice preparation

Metabotropic glutamate receptor (mGlu-R) by expressing glutamate inhibitory autoreceptors control the release of excitatory neurotransmission. The mGlu-R agonist ACPD (1- amino cyclo-pentane-1, 3-dicarboxylic acid) reduced reversibly field EPSPs (f-EPSPs), whereas this effect of inhibition was blocked by the mGlu antagonist, MCCG [2-methyl-2-(carboxy - cyclopropyl) glycine]. The inhibition of f- EPSP was mimicked by DCG-IV [(dicarboxycyclo-propyl) glycine- IV]. In whole cell recordings from granule cells of human dentate gyrus, miniature EPSC reduced significantly without affecting mean amplitude of mEPSCs.[60]

VII –(a)$_{(1)}$.3

Mouse cortical synaptosome preparation

The mGlu 1 /mGlu 5 receptor agonist 3, 5–DHPG [(RS)-3, 5-Dihydroxyphenylglycine] concentration-dependently (0.1 -100) potentiated K^+ (12 mM) induced release of [^{3}H] DASP (d-aspartate) with biphasic pattern of transmitter release. The 1st phase of potentiation was at 0.3 μM and after decline, 2nd phase of potentiation was at 30-100 μM of 3, 5 –DHPG which was abolished by selective mGlu5 receptor antagonist MPEP [2 methyl-6-(phenylethynyl) pyridine] hydrochloride. However remain unaffected by selective mGlu1 antagonist 7-hydroxyimino CPCCOEt (cyclo propa (b) chromen-la –carboxylate-ethyl ester). The 3, 5-DHPG revealed high binding site for mGlu5 and low binding site of mGlu1.[61]

VII-(b)

Presynaptic Glutaminergic Heteroreceptors

VII-(b)$_{(1)}$

Presynaptic glutaminergic (GABA) inhibitory heteroreceptors

VII –(b)$_{(1)}$.1

Guinea pig hippocampus slice preparation

The whole cell recording from CA1 stratum radiatum in the neuron was performed. Modulation of GABA release by group III metabotropic glutamate or kianate receptors in the interneuron of hippocampus using selective glutamate agonist and antagonist. The group III mGlu-R agonist L-AP-4, attenuated monosynaptic GABArgic signals in interneuron as shown by depression of excitatory post synaptic currents (EPSCs) by activation of glutaminergic ($GABA_B$) inhibitory heteroreceptors in the interneuron but not in pyramidal Neuron whereas kainite enhanced frequency and amplitude of spontaneous GABArgic signals in the interneuron of hippocampus.

Glutamate released from the excitatory glutaminergic neuron escape from synaptic cleft and activate preferentially presynaptic metabotropic glutaminergic ($GABA_B$) heteroreceptors on adjacent interneuron, Inhibited GABA release by modulating inhibitory GABArgic neurotransmission.[62]

VII-(b)$_{(2)}$

Presynaptic glutaminergic (nACh-R) stimulating heteroreceptors

VII–(b)$_{(2)}$.1

Rat hippocampus slice preparation

The intracellular recordings from Mossy fiber CA-3 glutaminergic synapse in hippocampus of rat revealed that in the presence of TTX, presynaptic action potential was eliminated. On the other hand, nicotine application activated neuronal nicotinic heteroreceptors thereby enhanced frequency of spontaneous miniature excitatory postsynaptic currents (sEPSCs), without affecting EPSC amplitude. Increasing extracellular Ca^{2+} concentration, increased the amount of neurotransmitter released by nicotine stimulation.[63] Nanomolar concentration of nicotine activated presynaptic α-7 subunit of nACh-R, thereby increased presynaptic intracellular Ca^{2+} concentration.[64]

CLASS -VIII

PRESYNAPTIC GABA AUTORECEPTORS / HETERORECEPTORS

GABA, a mono carboxylic amino acid, mediating inhibitory neurotransmission in central nervous system, exist in high concentration in the brain. The inhibitory actions of GABA are through three different types of GABA receptors. (i) $GABA_A$ receptor is an inotropic ligand gated Cl^- ion channel. (ii) $GABA_B$, (ii) $GABA_C$, receptor subtype is a metabotropic GPCR mediate inhibitory action by inhibiting adenylyl cyclase, activating K^+ channel and reducing Ca^{2+} conductance whereas $GABA_C$ receptor subtype is a transmitter gated Cl^- ion channel. It is less widely distributed however GABA, is more potent on $GABA_C$ than $GABA_A$. $GABA_B$ is a presynaptic autoreceptor mediating inhibition of GABA release. $GABA_B$ is a heterodimer which consists of two sub-types, $GABA_{B\,(1)}$ and $GABA_{B\,(2)}$, whereas $GABA_{B\,(1)}$ consists of two isoforms, $GABA_{B\,(1a)}$ and $GABA_{B\,(1b)}$.[65]

VIII-(a)

Presynaptic GABArgic autoreceptor

VIII-(a)$_{(1)}$

Presynaptic GABArgic ($GABA_B$) inhibitory autoreceptors

VIII-$(a)_{(1).}$1

Cortical slice preparation in KO mice

The KO mice were generated for two subtypes of $GABA_B$ receptor, $GABA_{B(1)}$ and $GABA_{B(2)}$and for two isoforms of $GABA_{B(1)}$i.e. $GABA_{B\,(1a)}$ and $GABA_{B\,(1b)}$. In cortical slice preparation from KO mice, it was revealed that $GABA_B$ autoreceptors located in GABArgic nerve terminals, inhibited GABA release. GABA agonist Baclofen and selective antagonist CGP55645 did not affect the GABA release from cortical slices from $GABA_{B\,(1)-/-}$ mice. The [^{3}H] GABA released per pulse from cortical slices of $GABA_{B\,(1)-/-}$ and $GABA_{B\,(2)-/-}$ by stimulation frequency remain unaffected indicating the loss of presynaptic $GABA_B$ autoreceptor function in KO mice.[65]

VIII-$(a)_{(1)}$.2

Rat brain supra chiasmatic nucleus neuron preparation

The whole –cell patch clamp, voltage clamp and current clamp recordings were performed on rat brain supra chiasmatic nucleus (SCN) neuron preparation. $GABA_B$ receptor agonist Baclofen caused concentration dependent inhibition of evoked IPSCs. In the presence of TTX, baclofen reduced frequency of spontaneous IPSC however, showed slight effect on frequency and amplitude of miniature IPSCs. The P/Q calcium channel blocker, agatoxin IV_B prominently reduced both calcium current and evoked IPSCs whereas pertussis toxin (PTX), abolished completely inhibitory effect of baclofen on GABA release. It was shown that the prominent presynaptic inhibition of GABA release at SCN neuron, may be primarily by $GABA_B$ autoreceptor modulation of P/Q calcium channel at GABArgic axonal terminal.[66]

VIII-(b)

Presynaptic GABArgic heteroreceptors

VIII –$(b)_{(1)}$

Presynaptic GABArgic $GABA_B$ (Glu-R) inhibitory heteroreceptors

VIII-$(b)_{(1)}$.1

Cortical slice preparation in KO mice

The presynaptic GABArgic $GABA_B$ (Glu-R) heteroreceptors controlled the release of glutamate from glutaminergic nerve terminals in cortical slice preparation. The [^{3}H] GABA release per pulse by $GABA_B$ agonist, baclofen and selective GABA antagonist, GP55845, from KO $GABA_{B\,(1a)}$ and KO $GABA_{B\,(1b)}$ cortical slice preparation, remain unaffected indicating the absence of $GABA_B$ autoreceptor function. The $GABA_B$ agonist, baclofen was ineffective in modulating the release of glutamate in mouse cortical slices from KO $GABA_{B\,(2)}$ and KO $GABA_{B\,(1a)}$ indicating loss of presynaptic GABArgic heteroreceptor function. It was shown that $GABA_{B\,(1a)}$ and $GABA_{B\,(2)}$ heteroreceptors primarily involved in the regulation of glutamate release.[65]

VIII-$(b)_{(1)}$ .2

Rat entorhinal cortex preparation

The spontaneous excitatory and inhibitory synaptic currents were recorded in the presence of TTX using whole cell patch clamp recording from layers II and V of wistar rat entorhinal cortex preparation to monitor release of glutamate and GABA. Application of $GABA_B$-R agonist decreased the release of both GABA and glutamate from layers II and V. However, depression of glutamate release was higher in layer II suggesting greater level of presynaptic GABArgic $GABA_B$ (Glu-R) heteroreceptor expression. Application of $GABA_B$ antagonist however did not activate tonically $GABA_B$ autoreceptor or $GABA_B$ heteroreceptor by ambient GABA in the presence of TTX.[67]

SUMMARY AND CONCLUSION

To summarise, presynaptic autoreceptors and presynaptic heteroreceptors types and subtypes of seven neurotransmitters acetylcholine, epinephrine (nor-epinephrine), serotonin (5HT), dopamine, histamine, glutamate and GABA classified into eight

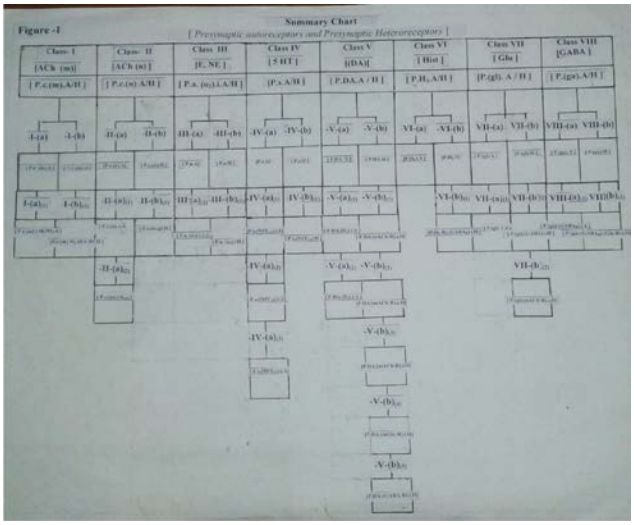

Figure 1: Summary chart (Presynaptic autoreceptors / Presynaptic heteroreceptors.

classes on the basis of stimulatory and inhibitory functions, are exemplified in the form of summary chart (Figure 1) to simplify classification using smart art graphical design of hierarchical relationship from the origin of neurotransmitter type to it's subtypes. In conclusion in the present review prominent neurotransmitters of nervous system involved in the release mechanism via activation of presynaptic autoreceptors or presynaptic heteroreceptors and their subtypes, identified on the basis of *in vivo* or *in vitro* tissue model system are described .The functioning of central and peripheral nervous system is through complex control of inter or intra-neuronal communication via various neurotransmitters released in response to activation of autoreceptors or heteroreceptors and hence are targets for the diseases of nervous system which will provide valuable clues for the investigation of leads in the search of drug molecules targeting the diseases.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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