Central Nervous System Depressant Drugs: Updated Review

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Abstract

Objectives: The mechanism of action of drugs that depress the central nervous system (CNS) was unknown until molecular pharmacology discovered each drug's exact role. The benefit of knowing the mechanism of action is to design a new drug that could have the same efficacy as the prototype drug but with fewer side effects. Some of the available CNS depressant drugs that were abused or illegally used could be modified to make them used medically.

Methods: We reviewed various published articles in PubMed and Google Scholar that focused on CNS depressants' molecular pharmacology.

Results: It was clear that at specific plasma concentrations of ethyl alcohol showed almost same mode of action of propofol by targeting the extrasynaptic GABA-A receptors, which causes tonic GABAergic inhibition. Besides, the High affinity of some benzodiazepines (e.g., midazolam) to α1 subunit of GABA-A receptor causes sedative, hypnotic, amnesic, and some antiepileptic effects; however, some other benzodiazepines (e.g., diazepam) have high affinity to α3 subunits, which causes anxiolytic, muscle relaxant, and strong antiepileptic effects. The CB1 receptor partial agonism effect of tetrahydrocannabinol has a sedative advantage over full agonism due to desensitization of CB1 receptors.

Conclusion: From the molecular pharmacology prospect, it is possible to design new drugs with more specific CNS depressants effect and fewer side effects by targeting particular receptors with a precise reaction.

Keywords: CNS; Drug receptors; GABA; Cannabinoid; Opioid; Serotonin; Dopamine

Introduction

The mechanism of action of drugs that depress the central nervous system (CNS) was unknown until molecular pharmacology discovered each drug's exact role.[1] The central nervous system (CNS) depressant drugs mainly acting on gamma-Aminobutyric acid (GABA), serotonin, dopamine, opioid, cannabinoid, and adrenergic receptors.[2] The benefit of knowing the mechanism of action is to design a new drug that could have the same efficacy as the prototype drug but with fewer side effects. Some of the available CNS depressant drugs that were abused or illegally used could be modified to make them used medically.

We reviewed several published articles in PubMed and Google Scholar that focused on CNS depressants' molecular pharmacology. This review showed the classification of CNS depressants drugs depends on receptor type.

Drugs Acting on GABA Receptors

Ethanol

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Ethanol acts on the extra-synaptic GABA-A receptor by binding to the δ subunit, which causes tonic GABAergic inhibition by enhancing the Chloride (Cl) channel.[3] Ethanol has different CNS depressant effects depend on ethanol concentration: euphoria and anxiolytic effect (at plasma concentration 30-100 mg/dl), disorganization and impairment of memory and drowsiness (at plasma concentration 100-150mg/dl).

Other medical indications can be used: as antidote for methanol toxicity and ethylene glycol toxicity since ethanol causes saturation of alcohol dehydrogenase enzyme.[4] Ethanol could cause a common side-effect called "hangover" characterized by nausea, vomiting, and headache.[5]

Barbiturates

This class of sedatives and hypnotics drugs were common in the past but not nowadays; because of low safety profile and low therapeutic index, which could cause severe respiratory depression and interact with many drugs since barbiturates described as enzyme inducers that induce Cytochrome P450 3A4(CYP3A4), Cytochrome P450 2C9 (CYP2C9) and Cytochrome P450 2C19 (CYP2C19). Barbiturates include phenobarbital, pentobarbital, secobarbital, amobarbital, thiopental, and methohexital. Low doses of barbiturates can bind to the picrotoxin site (α/β subunits) of the synaptic GABA-A receptor, leading to increased Cl channel opening lifetime. However, high doses can also mimic GABA action and reduce Na and K voltages.[6]

Barbiturates drugs have different indications depend on each drug's characteristics. For example, thiopental indicated general anesthesia and induced barbiturate coma to treat refractory cases having a secondary traumatic injury. On the other hand, phenobarbital can be used for all types of epilepsy and used as an adjuvant drug with other drugs used for psychiatric disorders.[6]

Benzodiazepines

After the 1960s, benzodiazepines were commonly used over barbiturates because of high therapeutic window and rarely interact with other drugs: Chlordiazepoxide, diazepam, lorazepam, clonazepam, temazepam, alprazolam, triazolam, bromazepam, and midazolam. Benzodiazepines bind to the benzodiazepine site, which located between α/γ subunits of synaptic GABA-A receptor, thus will increase the frequency of Cl channel opening and enhance GABA binding to its receptor. High affinity of some benzodiazepines (temazepam, midazolam, and triazolam) to α1 subunit causes sedative, hypnotic, amnesic and little antiepileptic effects. However, some other benzodiazepines (diazepam, lorazepam, clonazepam, and bromazepam) have high affinity to α3 subunits; it causes anxiolytic, muscle relaxant, and strong antiepileptic effects.[7]

Benzodiazepines indicated for status epilepticus (Diazepam), intensive care unit (ICU) sedation (Midazolam), adjuvant with antipsychotics (Lorazepam), muscle relaxant (Temazepam), and anxiolytic (Bromazepam and Alprazolam).[7]

Non-Benzodiazepines

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Drugs have the same mode of action as benzodiazepines, but different chemical structure is called non-benzodiazepines. The unique characteristic of these drugs acting only on the α1 subunit of GABA-A synaptic receptor, resulting in sedative, hypnotic and amnesic effect and acting only for a short time (maximum 6 hours) which avoid sedation on next day. These drugs include zopiclone (t½ six h), zolpidem (t½ two h), and zaleplon (t½ one h), which are mainly indicated for insomnia.[7]

Propofol

This drug is commonly used nowadays in general anesthesia and ICU sedation. One of the propofol's advantages is the fast onset of action (effect seen within 15-45 seconds).[8] Propofol acts mainly on the α4 subunit of extrasynaptic GABA-A receptors, which causes tonic GABAergic inhibition.[9]

Some disadvantages of propofol include anaphylaxis shock (for those who have egg or soy allergies), cardiovascular shock by reducing blood pressure, and propofol infusion syndrome may occur if high or prolonged dose infusion is used. Note that propofol infusion syndrome is characterized by metabolic acidosis, hyperkalemia, cardiac failure, renal failure, hepatomegaly, elevated triglyceride blood level, and rhabdomyolysis.[9]

Etomidate

In high-risk cardiac surgery, etomidate is the drug of choice for general anesthetic agents because of its hemodynamic stability. Etomidate acts mainly on β2 subunit of synaptic GABA-A receptor, that cause sedative and anesthetic effect. Besides that, etomidate also inhibits cortisol secretion after a single-dose, and cortisol blood level could remain low for at least 24 hours.[10]

Baclofen

Activation of the GABA-B receptor can be achieved by using a drug called baclofen. Baclofen acts mainly in the spinal cord by acting as a GABA-B agonist, reducing substance P release. The net results are muscle relaxant, sedative, analgesic, and anxiolytic effects. Baclofen is mainly indicated for spasticity but also could be used for trigeminal neuralgia. The common side effect is the drowsiness effect.[11]

Drugs Acting on Cannabinoid Receptors

Natural cannabinoids are very old, as ancient Indians used the leaves, flowers, and resinous extract from the flower of Cannabis Indica or Cannabis Sativa. The active ingredients of cannabis are tetrahydrocannabinol, cannabidiol, and cannabinol, which act on inhibitory cannabinoid receptors, mainly Cannabinoid receptor type 1 (CB1). Cannabinoids receptors are located as presynaptic receptors and inhibit the release of neurotransmitters.[12]

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Tetrahydrocannabinol act as a partial agonist on CB1, thus will results in anxiolytic, sedative, euphoric, analgesic, appetite stimulant, antiemetic, and cognitive impairment effects. Prolonged or higher intake of cannabis could cause desensitization of CB1 receptors, which cause withdrawal symptoms like anxiety, restlessness, dysphoria, and nausea.[12]

Dronabinol is synthetic tetrahydrocannabinol but mainly approved as an antiemetic and appetite stimulant (not indicated for any CNS effect). However, cannabidiol mainly approved as an anticonvulsant that indicated for seizures associated with Dravet or Lennox-Gastaut syndromes.[13]

Drugs Acting on Adrenergic Receptors

Dexmedetomidine

This drug act as an agonist on presynaptic α2 adrenergic receptor thus inhibits noradrenaline release. Dexmedetomidine has good sedative, mild analgesic, anxiolytic, and muscle relaxant effects that could be used in the intensive care unit. Unlike clonidine and tizanidine, dexmedetomidine has a higher binding affinity to α2 receptor, which means that clonidine and tizanidine have the same effect as dexmedetomidine but with lower potency, and that could be an advantage for outpatients.[13]

Drugs Acting on Serotonin Receptors

Central nervous system depressants drugs acting on serotonin receptors are mainly antagonize the 5-hydroxytryptamine receptor 2A (5-HT2A) receptor, which reduces the neuronal excitation.[14]

Aripiprazole, Clozapine, Olanzapine, Quetiapine and Risperidone

These drugs act as 5-HT2A antagonists and are commonly used to treat bipolar mania and schizophrenia.[14]

Drugs Acting on Opioids Receptors

Morphine

Morphine is the prototype of the opioids class of drugs derived from the opium plant. Morphine is acting as an agonist strongly on mu opioid receptor (MOR) and weakly on kappa and delta opioids receptors. The CNS depressant actions are: analgesia, sedation, respiratory depression, and depression of the vasomotor center in high doses.[15]

Fentanyl

It is a synthetic opioid and more potent than morphine, but lack effect on delta receptor. Fentanyl has the same effect as morphine when given as an equivalent dose but has a short period of action. Other opioids include codeine, oxycodone, tramadol, hydromorphone, pethidine, and methadone.[15]

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Drugs Acting on Dopamine Receptors

There are two main dopamine receptors:

D1 like receptors: these include D1 and D5 receptors, which contain Gs protein, and some have Gq protein. When dopamine binds to D1 or D5 receptors, it will have an excitatory effect on neurons.[16]

D2 like receptors: these include D2, D3, and D4 receptors, which can be found as Gi protein (inhibitory) or Gq protein (excitatory) depend on the receptor site in the body and also depend on some disease which cause mutation of receptors.[16]

Haloperidol, sulpiride, chlorpromazine, fluphenazine, and perphenazine: these drugs are called typical antipsychotics and mainly antagonize D2 receptors, which reduce excitation of neurons in the brain and cause CNS depressant effect like sedation, antiemetic, dizziness and reduce seizure threshold.[17]

Conclusion

It was clear that at specific plasma concentrations of ethyl alcohol showed almost same mode of action of propofol by targeting the extrasynaptic GABA-A receptors, which causes tonic GABAergic inhibition. Besides, the High affinity of some benzodiazepines (e.g., midazolam) to α1 subunit of GABA-A receptor causes sedative, hypnotic, amnesic, and some antiepileptic effects; however, some other benzodiazepines (e.g., diazepam) have high affinity to α3 subunits, which causes anxiolytic, muscle relaxant, and strong antiepileptic effects. The CB1 receptor partial agonism effect of tetrahydrocannabinol has a sedative advantage over full agonism due to desensitization of CB1 receptors. From the molecular pharmacology prospect, it is possible to design new drugs with more specific CNS depressants effect and fewer side effects by targeting particular receptors with a precise reaction. The summary of CNS depressant drugs and targeted receptors seen in table.1 and figure.1.

References

1. Crestani F, Löw K, Keist R, Mandelli M, Möhler H, Rudolph U. Molecular targets for the myorelaxant action of diazepam. Mol Pharmacol. 2001; 59(3): 442-445.
2. Taylor C, Fricker AD, Devi LA, Gomes I. Mechanisms of action of antidepressants: from neurotransmitter systems to signaling pathways. Cell Signal. 2005; 17(5): 549-557.
3. Santhakumar V, Wallner M, Otis TS. Ethanol acts directly on extrasynaptic subtypes of GABAA receptors to increase tonic inhibition. Alcohol. 2007; 41(3): 211-221.
4. Pierce DR, West JR. Blood alcohol concentration: a critical factor for producing fetal alcohol effects. Alcohol. 1986; 3(4): 269-272.
5. Barker CT The alcohol hangover and its potential impact on the UK armed forces: a review of the literature on post-alcohol impairment. J R Army Med Corps. 2004; 150(3): 168-174.
6. Ito T, Suzuki T, Wellman SE, Ho IK. Pharmacology of barbiturate tolerance/dependence: GABAA receptors and molecular aspects. Life Sci. 1996; 59(3): 169-195.
7. Puustinen J. Benzodiazepines and Z-drugs may cause prolonged cognitive issues in young adults - are hypnotics not only a geriatric dilemma? Sleep Med. 2018; 52: 219-220.
8. Jin YH, Zhang Z, Mendelowitz D, Andresen MC. Presynaptic actions of propofol enhance inhibitory synaptic transmission in isolated solitary tract nucleus neurons. Brain Res. 2009; 1286: 75-83.
9. Houston CM, McGee TP, Mackenzie G, Troyano-Cuturi K, Rodriguez PM, Kutsarova E, Diamanti E, Hosie AM, Franks NP, Brickley SG. Are extrasynaptic GABAA receptors important targets for sedative/hypnotic drugs? J Neurosci. 2012; 32(11): 3887-3897.
10. Forman SA. Clinical and molecular pharmacology of etomidate. Anesthesiology. 2011; 114(3): 695-707.
11. Finnimore AJ, Roebuck M, Sajkov D, McEvoy RD. The effects of the GABA agonist, baclofen, on sleep and breathing. Eur Respir J. 1995; 8(2): 230-234.
12. Mukhopadhyay P, Mohanraj R, Bátkai S, Pacher P. CB1 cannabinoid receptor inhibition: promising approach for heart failure? Congest Heart Fail. 2008; 14(6): 330-334.
13. Budney AJ, Moore BA, Rocha HL, Higgins ST. Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. J Consult Clin Psychol. 2006; 74(2): 307-316.
14. Zhang G, Stackman RW Jr. The role of serotonin 5-HT2A receptors in memory and cognition. Front Pharmacol. 2015; 6: 225.
15. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008; 11(2 Suppl): S133-153.
16. Brennan KA, Carati C, Lea RA, Fitzmaurice PS, Schenk S. Effect of D1-like and D2-like receptor antagonists on methamphetamine and 3,4-methylenedioxymethamphetamine self-administration in rats. Behav Pharmacol. 2009; 20(8): 688-694.
17. Choi WY, Morvan C, Balsam PD, Horvitz JC. Dopamine D1 and D2 antagonist effects on response likelihood and duration. Behav Neurosci. 2009; 123(6): 1279-1287.

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Table.1 Classification and targeted receptors of drugs that depress CNS.

Classification	CNS Depressant Drugs	Targeted Receptors
Drugs Acting on GABA Receptors	Ethanol	Extra-synaptic GABA-A receptor
	Phenobarbital Pentobarbital Secobarbital Thiopental	α/β subunits of the synaptic GABA-A receptor
	Diazepam Lorazepam Clonazepam Temazepam Alprazolam Midazolam	α/γ subunits of synaptic GABA-A receptor
	Zopiclone Zolpidem Zaleplon	α1 subunit of GABA-A synaptic receptor
	Propofol	α4 subunit of extrasynaptic GABA-A receptors
	Etomidate	β2 subunit of synaptic GABA-A receptor
	Baclofen	GABA-B receptor
Drugs Acting on Adrenergic Receptors	Dexmedetomidine Tizanidine	Presynaptic α2 adrenergic receptor
Drugs Acting on Cannabinoid Receptors	Tetrahydrocannabinol Cannabidiol Dronabinol	CB1 receptor
Drugs Acting on Serotonin Receptors	Aripiprazole Clozapine Olanzapine Risperidone	5-HT2A receptor
Drugs Acting on Opioids Receptors	Morphine Fentanyl	Mainly Mu opioid receptor (MOR)
Drugs Acting on Dopamine Receptors	Haloperidol Sulpiride Chlorpromazine	D2 receptors

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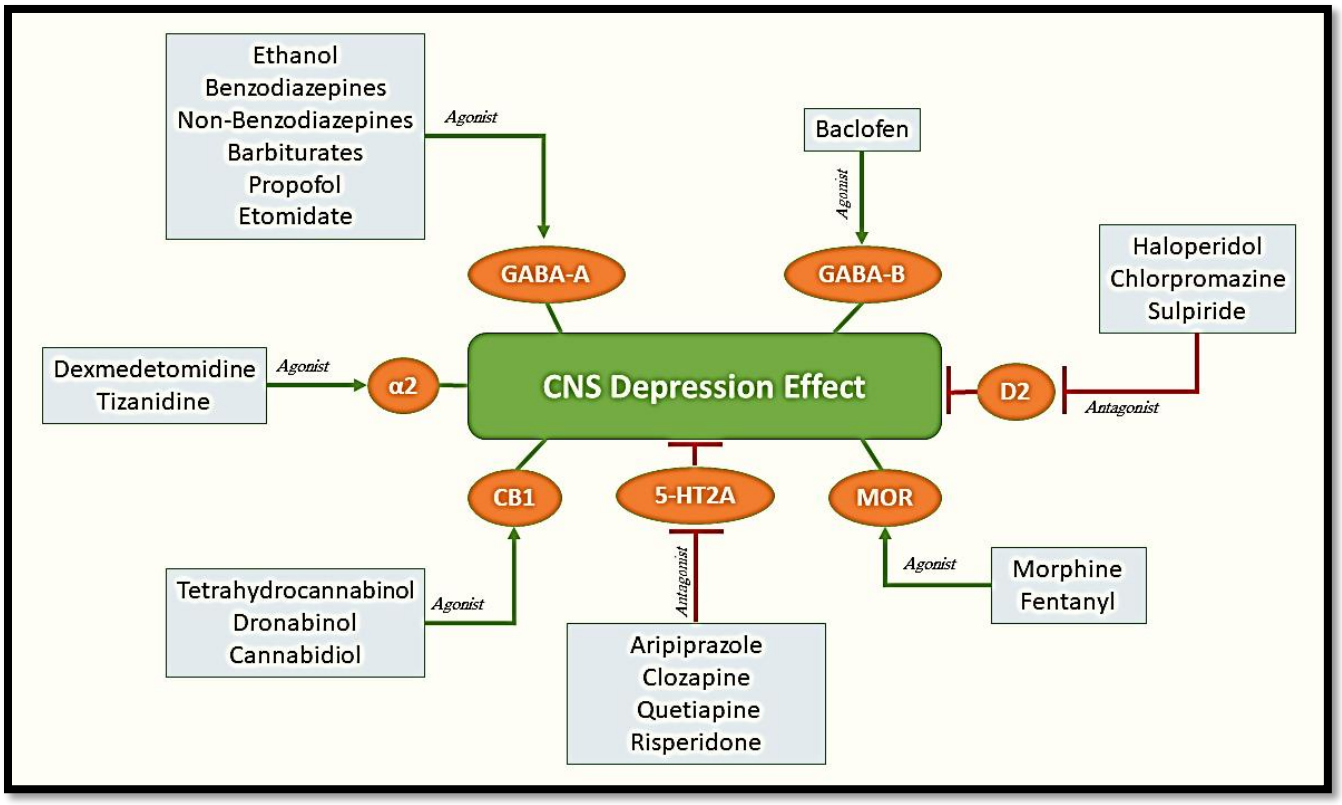

Figure.1 The mode of action of various drugs to depress CNS.