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Review Article

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Beta-blocker and its neuropsychiatric effects

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ABSTRACT

Norepinephrine from locus coeruleus plays roles in memory processes and behavioral controls. Locus coeruleus change is found in the primary neurodegenerative disease. The disruption of this central adrenergic pathway could contribute to neuropsychiatric symptoms. β-blockers which are indicated in many conditions both cardiovascular and non-cardiovascular diseases directly interrupt the adrenergic pathway. Their peripheral effects are well understood, but the neuropsychiatric effects are still questionable. The previous evidence postulated that the medication may cause behavioral impairment. This review focused on neuropsychiatric effects which were related to β-blockers and their underlying mechanisms. These neuropharmacologic properties should be necessary for health-care personnel to be aware of the side effects and closely take care of the patients who taking β-blockers.

Keywords: Beta-blocker, central adrenergic pathway, neurodegenerative disease, neuropsychiatric effects

INTRODUCTION

β-blockers are commonly prescribed in general practice due to their wide range of indications, including ischemic heart disease, heart failure, arrhythmias, hypertension, migraines, and essential tremor. Studies have found that almost 30% of elderly patients have taken β-blockers; however, some prescriptions might inappropriately be indicated.[1-3]

Cognitive and neuropsychiatric effects attributable to β-blockers are questionable. The previous studies have reached contradictory conclusions, used varying formulations, dosages, and measured different cognitive domains.[4-11] Data pertaining to the neuropsychiatric side effects of β-blockers are limited and heterogeneous because the neuropsychiatric effects are difficult to measure in clinical trials and often require prolonged follow-up. Both neuropsychiatric side effects and primary neurodegenerative diseases are also common among patients with cardiovascular diseases, so it may be difficult to compare neuropsychiatric symptoms among different β-blocker users.[12-17] Therefore, this article objectively reviews the pharmacokinetics, pharmacodynamics, and pathophysiology of β-blockers and their effects on cognition and neuropsychiatric symptoms.

PHARMACOLOGICAL PROPERTIES OF β-BLOCKERS

All β-blockers interact with, and have a high affinity for, β-adrenoceptors and form drug-receptor complexes which deprive endogenous norepinephrine and epinephrine of β-adrenoreceptor interaction.[18] β-blockers are classified by their pharmacodynamic and pharmacokinetic properties as the first generation (nonselective blockage of β-adrenergic receptors), second generation (selective blockade of β-adrenergic receptors), and third generation (β-blocker with vasodilatation action). Furthermore, the selective blockade of β-adrenergic receptors has a greater affinity for the β_1-receptor,[19] so this action affects the cardiovascular system.[20] Cardioselective β-blockers are less likely to cause constriction of the airways or peripheral vasculature.[20] Vasodilating β-blockers have an affinity for binding with alpha-adrenoceptors. This leads to vasodilation without affecting cardiac output.[21]

β-blockers are also categorized as lipophilic or hydrophilic, which determine their diffusion property through biological barriers (e.g., blood-brain and placenta), duration of action, metabolism, the volume of distribution, and renal clearance. Propranolol and metoprolol are examples of highly lipid-soluble β-blockers, and atenolol and esmolol are examples of hydrophilic β-blockers.[19,22]

Lipophilic β-blockers such as propranolol and metoprolol diffuse through the blood–brain barrier and cause neuropsychological symptoms, as shown in Table 1.[15,23] In a previous study, side effects of β-blockers, especially propranolol, were observed in 9.9% of users, and central nervous system adverse effects were reported in 1.1%.

The pharmacokinetic properties of β-blockers depend on their absorption through the gastrointestinal tract, hepatic first-pass metabolism, lipid solubility, plasma protein binding, and renal or biliary elimination, which are altered by much pathology. Lipophilic β-blockers are nearly absorbed by the gastrointestinal lumina, whereas hydrophilic β-blockers are not.[19,24] Metoprolol and propranolol have a high first-pass effect and are mainly eliminated by hepatic enzymes, as shown in Table 1. Cimetidine and proton-pump inhibitors also directly inhibit their enzymatic oxidation, so these medications increase the levels of lipophilic β-blockers.[19] On the other hand, hydrophilic β-blockers such as atenolol are mainly eliminated through the kidneys. Thus, renal impairment tends to decrease clearance and increase their plasma half-life. The binding of β-blockers with plasma proteins also correlates to drug levels and their half-lives, and determines their duration of action, as shown in Table 1.[22,25] The pharmacodynamics and pharmacokinetic properties of β-blockers are summarized in Table 1.

CENTRAL ADRENERGIC PATHWAY AND THE EFFECTS OF β-BLOCKERS

In the central nervous system, norepinephrine is mainly produced by the locus coeruleus, which is in the brainstem. Norepinephrine also exerts widespread effects throughout the prefrontal cortex, hippocampus, thalamus, striatum, and olfactory bulb.[26-28] Patterns of norepinephrine secretion are changed by external stimuli. During alertness or attention, norepinephrine is secreted as a burst rhythm signal on top of a low, stable background, called the tonic state. When experiencing stressful stimuli or anxiety, norepinephrine levels increase and remain high throughout the duration of the stressful period, called a phasic state.[29,30] Secreted norepinephrine interacts with the adrenergic receptors, including α1, α2, and β receptors. In particular, α2 receptors are found to be concentrated within the superficial layer of the prefrontal cortex.[31-33]

Norepinephrine has a direct role in selective attention and working memory and works cooperatively with dopamine within the prefrontal cortex. In addition, norepinephrine stimulates synaptic plasticity through G-proteins, adenylyl cyclase, and cAMP. Norepinephrine is essential for the learning, consolidation, and retrieval aspects of memory.[32-34] Furthermore, the density of Tau protein progressively accumulates in locus coeruleus along with Braak's Alzheimer's staging and is related to prodromal symptoms in dementia.[32,35-38]

The effects of β-blockers within the central nervous system depend on several mechanisms. First, β-blockers must penetrate the blood–brain barrier and bind directly with β-adrenergic receptors, after which they suppress information flow from the β receptor mediator. Second,

Table 1: Pharmacodynamic and pharmacokinetic properties of ß-blockers[76-83]

ß-blockers	Pharmacodynamic properties				Pharmacokinetic properties							
	$ß_1$-selectivity	Intrinsic sympathomimetic activity	Membrane stabilizing activity	Vasodilator effect	Lipophilicity	Bioavailability (%)	First-pass effect	Plasma protein binding (%)	Volume of distribution (L/kg)	Plasma half-life (h)	Elimination	Total clearance (mL/min)	Renal clearance (mL/min)
First generation (nonselective)													
Propranolol	0	0	++	0	High	30	+	93	3.6	3-4	Hepatic	1000	0
Second generation (selective ß-blockers)													
Atenolol	++	0	0	0	Low	50	-	3	0.7	6-9	Renal	100-180	100-170
Bisoprolol	++	0	0	0	Mod	88	-	30	3.2	10-12	Renal/hepatic	257	140
Esmolol	++	0	0	0	Low	100 (IV)	-	56	3.4	9	Renal	19,950	0
Metoprolol	++	0	+	0	High	50	+	12	5.6	3-4	Hepatic	1100	109
Third generation (ß-blockers with vasodilating action)													
Carvedilol	0	0	++	++ ($α_1$-blockade)	Mod	25	+	98	2	7	Hepatic	600	0
Labetalol	0	+	+	++ ($α_1$-blockade)	Low	100 (IV)	+	50	5.4	5	Hepatic	33*	55
Nebivolol	++	0	0	++ (NO availability increases)	Mod	12	+	98	10	22	Hepatic	860	7.4

NO: Nitric oxide, * mL/min/kg

β-blockers may also interact with the non-adrenergic receptors, interrupt their signals, or disturb the membrane stabilization, thereby interfering with the neurotransmitter network. For example, serotonin network interference may result in neuropsychiatric behaviors. Moreover, β-blockers also interact with peripheral nerves and can change autonomic nervous system activity.[39]

β-BLOCKERS AND THEIR NEUROPSYCHIATRIC EFFECTS

Although the therapeutic benefits of β-blockers are clearly identified, their neuropsychiatric effects are still undetermined.

Delirium

Delirium is the well-defined encephalopathy syndrome which is common in hospitalized patients. The mechanisms of delirium are uncertain; however, multiple etiologies and risk factors (including medications) precipitate the common pathological pathway and produce symptoms. Medications are common predisposing and precipitating factors. β-blockers can cause delirium, especially in elderlies or those with preexisting cognitive dysfunction. Moreover, relationship of the dosage increment and delirium was reported.[39-41] The proposed mechanisms are β-blockers that may have the competitive interaction with serotonin-sensitive adenylate cyclase system that may related to the underlying pathogenesis.[40] A case report of the elderly was prone to side effects from β-blockers due to increased total body fat, decreased lean body mass and water, low albumin levels, and decreased glomerular filtration rates. After medication was discontinued, the delirium improved, as shown in Table 2.[40] Propranolol or bisoprolol, the lipophilic β-blockers, tends to exhibit increased distribution and half-life in patients with increased body fat. Low albumin levels increase the free drug form and allow a larger free fraction to cross the blood–brain barrier. Moreover, pre-operative administration of β-blockers increases the odds of post-operative delirium by 2.06 times.[39-41]

Disruptive Behavior

Disruptive behavior is the cluster of hyperactivity, impulsivity, irritability, disinhibition, aggression, and agitation. The specific underlying mechanism is still unknown. The dysfunction of orbitofrontal cortex, cingulate, and brainstem monoaminergic nuclei which contributes to the dysregulation of serotonin and norepinephrine may underline the symptoms.[25,42,43] Propranolol (mean 106 mg/day) was studied to be beneficial for controlling agitation and emotion-related impulsivity in a clinical trial, as shown in Table 2.[44] Pindolol also showed a benefit for aggression and was related to norepinephrine changes, as shown in Table 2.[45] Comparing with antipsychotic, β-blockers were less studied and showed modest effect.[43] The use of β-blockers for the treatment of disruptive behavior is still off-label.[44,46-48]

Anxiety

Anxiety can result from maladaptive memories due to dysregulation and imbalance of neurotransmitters between the amygdala, hypothalamus, and prefrontal cortex.[49] According to the previous studies, β-blockers, especially propranolol, have a modest benefit in patients with anxiety disorders. Some prescribe β-blockers for fear prevention before dental surgery. The past studies found that β-blockers impair the consolidation phase of memory, so the medication might be useful for treating or preventing fear or anxiety, as shown in Table 2.[50-54] β-blockers also are beneficial for anxiety patients who present with cardiac symptoms.[55] Systematic review found that no significant difference between propranolol and benzodiazepine for panic disorder is shown in Table 2.[56]

Hallucination

Hallucination is a neuropsychiatric symptom that is related to high caregiver stress and patient self-injury.[57,58] Data of β-blockers and hallucination are still limited and contradictory. β-blockers are used to treat patients with schizophrenia by unknown underlying mechanism. β-blockers may interact with neuroleptic metabolism, resulting in increased neuroleptic drug levels, leading to control the hallucination.[15,59,60] On the other hand, several reports have showed that the lipophilic β-blockers such as propranolol and metoprolol may be the causative agent of hallucination and after discontinuation the medication, hallucination was resolved, as shown in Table 2.[61,62]

Sleep Disturbances and Nightmare

Melatonin helps synchronize circadian rhythms and the sleep-wake cycles.[63] The synthesis and secretion of melatonin are influenced by norepinephrine through the β1 receptor.[64] β-blockers could reduce melatonin levels and are related to poor sleep quality, nightmares, or vivid dreams. Lipophilic β-blockers such as metoprolol may cause more sleep disturbances than hydrophilic agents such as nebivolol.[64-67]

Fatigue

Fatigue is a subjective lack of mental or physical energy. Its underlying mechanism is complex and poorly understood. Due to the multifactorial causes of fatigue, both the central and peripheral nervous systems are symptom contributors.[68-71] Fatigue depends on intrinsic factors and extrinsic factors such as the weather or mood, which can exacerbate fatigue.[72] Na^+-K^+-ATPase pumps, which control ion movement between muscle and plasma, may be related to fatigue reported in patients who use β-blockers users. β-blockers might interfere with Na^+-K^+-ATPase pumps and result in an imbalance of the K^+ shift between muscle and plasma.[73] Cardioselective β-blockers are less likely to induce muscle fatigue than nonselective β-blockers. A report of β-blockers found significantly higher associations with fatigue for early generation or first-generation drugs, compared to newer β-blockers.[74] Moreover, β-blockers cause a muscle fatigue during acute treatment and are significantly associated with an increased risk of medication withdrawal due to fatigue.[74] In contrast, the long-term treatment with β-blockers such as in hypertensive patients, the fatigue seems to disappear.[75]

Table 2: Summarized ß-blockers induced neuropsychiatric side effects

Neuropsychiatric effects	Population (ref)	Number of population	Type of research	Intervention	Comparison	Outcome	Results	Remark
Delirium	Female, 94 years old[40]	1	Case report	Bisoprolol (2.5–5 mg/day)		Delirium (nighttime confusion CAM positive)	Delirium was occurred and improved after the medication was discontinued 14 days	
	Male, 51 years old[84]	1	Case report	Carvedilol (6.25 mg bid)		Delirium (agitation, disorientation, aggression, confusion)	Delirium was occurred and improved after the medication was discontinued 12 h	
Disruptive behavior	Patients with Alzheimer's disease[44]	31	Randomized, double-blind study	Propranolol (106±38 mg/d)	Placebo	Neuropsychiatric inventory, clinical global impression of change	Improvement in agitation/ aggression, anxiety, and Clinical Global Impression Of Change score	The benefit diminished after 6 months
	Patients with Alzheimer's disease[45]	15	Cross-over study	Pindolol 7 weeks (max dose 20 mg b.i.d)	Placebo	Retrospective overt aggression scale	Improvement on the retrospective overt aggression scale verbal aggression subscale	No improvement of retrospective overt aggression scale total
Anxiety	Patients with self-reported high to extreme fear of dental extraction[50]	34	Multicenter, randomized, placebo-controlled, two-group, parallel, double-blind trial	Propranolol 80 mg prior a dental extraction and 40 mg postoperatively	Placebo	Dental anxiety score (baseline and 4-week follow-up)	Reducing short-term anxiety, fear memory reconsolidation	
	• Panic disorder with or without agoraphobia 4 studies • Specific phobia 2 studies • Social phobia 1 study • Post-traumatic stress disorder 1 study[56]	8 studies	Systematic review and meta-analysis			The efficacy of oral propranolol against placebo or other medications as a treat anxiety	The efficacy of propranolol is insufficient to support the routine use of treatment anxiety disorders.	
Hallucination	Female, 84 years old[61]	3 case reports	Case series	Metoprolol 50 mg bid 2 years		Visual hallucination and sleep disturbance	Hallucination was occurred and improved after the medication was discontinued	
	Male, 57 years old[62]	2 case reports	Case series	Metoprolol 25 mg bid		Visual hallucination and mild anxiety	Hallucination was occurred and improved after the medication was discontinued	
Sleep disturbances	Patients with mild hypertension[66]	39	Prospective, randomized, open-label, parallel-group study	Metoprolol (25 mg) for 6 weeks	Nebivolol (2.5 mg) for 6 weeks	Pittsburgh sleep quality index	Global Pittsburgh Sleep Quality Index score improved in the nebivolol group, whereas worsened in the metoprolol group	

CONCLUSION

β-blockers are a two-sided coin. These medications are beneficial for the treatment of many indications and are especially effective at decreasing mortality in patients with cardiovascular diseases. We examined β-blockers from a neuropsychological viewpoint with attention to their mechanisms of action for specific neuropsychiatric symptoms. Lipophilic β-blockers can diffuse through the blood–brain barrier and are likely to contribute to neuropsychological outcomes. β-blockers are beneficial and can be used for the treatment of some neuropsychiatric effect of e.g., anxiety, disruptive behavior; however, well designed clinical trial are needed to prove the benefits clinically. Consequently, physicians and pharmacists need to aware of these side effects. Hydrophilic β-blockers should be the option or principle to select the best of β-blockers for patient to avoid the neuropsychiatric effects. Future research is needed if we are to accurately identify patients who are at increased risk for β-blocker side effects. Further, it is important that we use β-blockers for the correct indications, at the correct doses, while closely monitoring side effects.

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