CNS Drug Reviews
Vol. 7, No. 4, pp. 471–481

HISTORY OF DRUG DEVELOPMENT

Phenibut (β-Phenyl-GABA): A Tranquilizer and Nootropic Drug

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Key Words: Amphetamine—Anxiety—Anxiolytic—Baclofen—Cognition enhancement—GABA—Nootropic—PEA—Phenethylamine—Phenibut.

ABSTRACT

Phenibut (β-phenyl-γ-aminobutyric acid HCl) is a neuropsychotropic drug that was discovered and introduced into clinical practice in Russia in the 1960s. It has anxiolytic and nootropic (cognition enhancing) effects. It acts as a GABA-mimetic, primarily at $GABA_B$ and, to some extent, at $GABA_A$ receptors. It also stimulates dopamine receptors and antagonizes β-phenethylamine (PEA), a putative endogenous anxiogenic. The psychopharmacological activity of phenibut is similar to that of baclofen, a *p*-Cl-derivative of phenibut. This article reviews the structure-activity relationship of phenibut and its derivatives. Emphasis is placed on the importance of the position of the phenyl ring, the role of the carboxyl group, and the activity of optical isomers. Comparison of phenibut with piracetam and diazepam reveals similarities and differences in their pharmacological and clinical effects. Phenibut is widely used in Russia to relieve tension, anxiety, and fear, to improve sleep in psychosomatic or neurotic patients; as well as a pre- or post-operative medication. It is also used in the therapy of disorders characterized by asthenia and depression, as well as in post-traumatic stress, stuttering and vestibular disorders.

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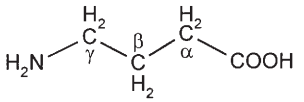
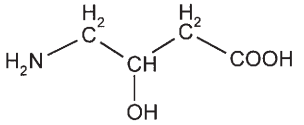
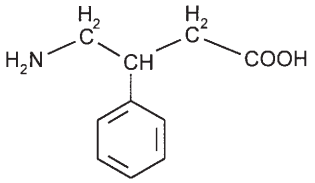


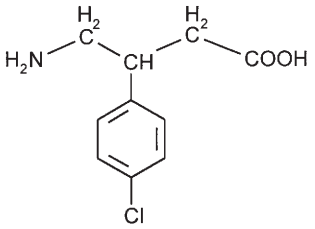
GABA – γ-amino-butyric acid



GABA-OH – β-hydroxy-γ-amino-butyric acid



Phenibut (PB) – β-phenyl-γ-amino-butyric acid



Baclofen (BAC) – β-p-Cl-phenyl-γ-amino-butyric acid, Cl-PB

Fig. 1

INTRODUCTION

Phenibut (β-phenyl-γ-aminobutyric acid, β-phenyl-GABA, PB; Fig. 1) was synthesized by Perekalin and his associates at the Department of Organic Chemistry of the Herzen Pedagogic Institute in St. Petersburg, Russia. In initial publications (16–18,36,37) phenibut was known as phenigamma.

The pharmacological properties of PB were evaluated by Khaunina and her associates (16–18,20,45). The *in vitro* neuronal effects of PB and related GABA derivatives were studied on isolated cat cerebral neurons (10,11). The first review on the pharmacology of PB and related compounds was published in 1964 (32). Pharmacological properties of PB, including its effects on $GABA_A$, $GABA_B$, dopaminergic, and benzodiazepine (BDZ) receptors, were compared with those of diazepam (DZP) and piracetam (PIR) (38). Kovalev et al. studied the effects of PB on the central regulation of circulation (22). More recently Khaunina and Lapin reviewed the clinical use of phenibut (19). The bibliography of PB currently exceeds 300 references, although most of them are in Russian.

STRUCTURE–ACTIVITY RELATIONSHIPS

Importance of the phenyl ring. Incorporation of a phenyl ring into the GABA molecule was expected to improve the entry of the molecule into the brain. Following incorporation, Maslova and Khaunina (36,37) demonstrated that in mice and rats PB penetrates the blood-brain barrier significantly better than GABA. Subsequently, Davies and Watkins (11) studied the effects of β-phenyl derivatives of GABA on chemically induced firing of isolated cat cerebral neurons. All derivatives reversibly reduced the firing rate of the neurons. Among the β-phenyl derivatives baclofen (BAC) was the most potent compound. It was, however, only 0.7 times as potent as GABA. The duration of action of all derivatives tested was substantially shorter than that of GABA.

Better penetration of the blood-brain barrier by PB as compared to GABA did not lead to stronger pharmacological effects. Marked qualitative differences between PB and GABA have been observed. Unlike GABA, PB completely lacks anticonvulsant activity by either systemic or intracerebroventricular (i.c.v.) administration (16,20,25,32,37,38). The lack of anticonvulsant activity of PB may be related to the reduction in norepinephrine-independent [^{3}H]GABA binding to brain synaptic membranes by β-substituted GABA derivatives. In addition, certain neuropharmacological effects of GABA were lost with β-substitution (14).

Position of the phenyl ring. Comparison of the pharmacological effects of α-, β-, and γ-phenyl derivatives of GABA demonstrated that among the three derivatives PB has the strongest sedative and hypothermic effects in mice. PB was also stronger than the other three derivatives of GABA in the ability to potentiate the activity of anticonvulsants (17,32). Only α-phenyl GABA at a high dose has a stimulant component of action. The hypothermic effect of PB was found to be independent of the route of administration (i.p. or i.c.v.), suggesting that its effect on the central nervous system is direct.

Role of the carboxyl group. Khaunina et al. studied pharmacological effects of methyl- and ethyl esters of PB in mice (17,32). Both esters have been shown to have pharmacological effects similar to those of PB. Ethyl ester was even more potent than PB in reducing motor activity, lowering body temperature, and potentiating anesthetics. Like PB, both esters lack anticonvulsant activity. Like the methyl ester of GABA and GABA-amide, both esters and PB amide are more toxic than PB.

Importance of the length of carbon chain between amino and carboxyl groups. Amino acids with a longer carbon chain than GABA have strong excitatory activity, whereas amino acids with a shorter chain have depressant activity that is stronger than that of GABA (32). The cationic charge determines the inhibitory effects and the anionic charge the excitatory activity.

Pharmacological activity of optical isomers of PB. Pharmacological effects of optical isomers of PB and PB racemate have been compared in mice (18). In all tests used (motor activity, coordination, muscle relaxation, body temperature, potentiation of barbiturates) only the d-isomer was active. The d-isomer was also twice as potent as the racemate. The acute (48 h) LD_{50} of the d-isomer was 1025 while that of the racemate was 1085 mg/kg i.p. Therefore, the therapeutic index of the d-isomer was higher than that of the racemate. Binding of BAC isomers to $GABA_B$ receptors was studied by Bowery et al. (8). According to them, only the (–)isomer of BAC binds to $GABA_B$ receptors, so that [^{3}H](–)BAC provides a more reliable tool to study $GABA_B$ receptors.

PHARMACOLOGY

General Neuropsychopharmacological Effects

General effects on the central nervous system. Systemically administered PB produces a great variety of central effects. At doses that do not affect motor activity (e.g., 20 mg/kg i.p.) PB inhibits food conditioned reflexes in mice. At doses higher than 70 mg/kg i.p. PB reduces motor and exploratory activities, rearings, muscle tone, coordination and body temperature. It potentiates central effects of the anesthetics: ether, chloral hydrate, and barbiturates.

Anticonvulsant effects. By either systemic or intracerebroventricular (i.c.v.) administration PB does not antagonize convulsions induced by electroshock, pentylenetetrazol, strychnine, bemegride or nicotine. It reduces, however, hyperkinesis, induced by barbiturates, and arecoline-induced tremor. In adult animals PB is ineffective against penicillin-induced seizures, but in immature animals it suppresses penicillin-induced hyperactivity (25). In rats genetically prone to audiogenic seizures, PB potentiates the anticonvulsant effects of barbiturates, phenytoin, trimethadione, and ethosuximide (20). This observation suggested that the audiogenic seizure model may not be useful in screening for anticonvulsant activity. In addition to PB, many different drugs (e.g., chlorpromazine, phenelzine, and nialamide) prevent convulsive fits in the audiogenic seizure model, but have no anticonvulsant activity in the clinic (19). The survival time of mice or rats treated with convulsants is significantly prolonged and the lethality reduced by PB. Since hypoxia is the usual cause of death of animals treated with convulsants, the antihypoxic effects of PB were studied. PB was shown to have antihypoxic activity in various models of hypoxia (38). The demonstration of the antihypoxic effects of PB prompted its evaluation as a potential nootropic drug.

Nootropic (cognition enhancing) activity. In the passive avoidance test in mice PB at small doses (5 to 10 mg/kg i.p.) facilitated formation of the conditioned reflex (38). The latency for the entry into the dark section of a chamber was 91 ± 154 sec in control animals and 284 ± 45 sec in animals treated with 5 mg/kg i.p. of PB ($p < 0.05$). The total time spent in the dark part of the chamber was 108 ± 28 sec in control animals and 38 ± 12 sec in PB-treated animals ($p < 0.02$). In addition, PB antagonized the amnestic effects of chloramphenicol, 100 mg/kg i.p. At doses of 10 to 20 mg/kg i.p. PB enhanced the performance of mice in the swimming and rotating rod tests (38). Chronic administration of PB (50 mg/kg i.p., twice daily for 5 days) promoted a tolerance to its sedative action on the last day of treatment while its nootropic effect was enhanced.

Tranquilizing effect. In mice, PB, at 50 to 100 mg/kg i.p., suppressed emotional reaction to pain induced by electrical stimulation. It also had an anxiolytic effect in the conflict situation test. Diazepam (DZP) produced similar effects at 0.5 to 1.0 mg/kg i.p. In the elevated-plus maze a DZP-like tranquilizing effect was observed with PB, at 10 to 25 mg/kg i.p. (38). In the social interaction test PB at 10 to 50 mg/kg i.p. (unlike DZP, 1 mg/kg i.p.) did not increase the rate or duration of contacts in pairs of mice (34).

Anxiolytic effect. The anxiolytic effect of PB appears to be dependent on the emotional reactivity of the animals. In anxious and passive cats, PB abolished or suppressed fear and brought about an aggressive reaction to provocation. In aggressive cats PB had no effect on aggression. In non-aggressive cats without obvious fear, PB expanded the scope

of positive emotional symptoms. In experimental models of fear induced by electrical stimulation of the hypothalamus or by peripheral aversive stimulation, PB had a selective antiphobic action and facilitated escape from stressful situations. This action was not associated with sedative or muscle relaxant effects. It was suggested that the antiphobic effect of PB is mediated by a GABA-mimetic action. In mice, aggressiveness induced by electrical stimulation was antagonized by PB but only at very high doses (300 mg/kg i.p. and higher). At these high doses PB inhibited motor coordination.

Effects on electroencephalogram (EEG) and electromyogram (EMG) of rabbits. PB, at 50 to 100 mg/kg i.v. or i.p., produced slow amplitude spikes in the EEG. The spikes appeared 15 to 30 min after administration of the drug and lasted for 2 h. On the next day the EEG was normal (36). The primary effects of PB, unlike those of GABA, were subcortical. Cortical inhibition was secondary (45). In the EMG PB did not alter the rate of spikes of miotic reflex. It only reduced their amplitude by 20 to 25% (38).

Putative Mechanisms of the Central Action of PB

GABA-mimetic action. Release of GABA from presynaptic nerve endings was reported to be increased by PB (21). PB and GABA had similar electrophysiological effects on ion channels of isolated neurons from *Planorbarius corneus* (50). Numerous studies reported activation of $GABA_B$ receptors by PB (1,7,8,10,11,35,43,44). *In vitro* PB binds to bicuculline-insensitive $GABA_B$ receptors. In a result typical of GABA-mimetic compounds, direct application of PB to the substantia nigra of rats produced contralateral rotation (38). This effect was not antagonized by bicuculline and suggested that it is mediated by $GABA_B$, rather than $GABA_A$ receptors (2,43). However, a secondary activation of $GABA_A$ receptors by PB was not excluded. Direct administration of muscimol (an agonist at $GABA_A$ receptors) to substantia nigra of rats induces contralateral rotation. PB is also known to cause this effect. Discontinuation of chronic injections of PB to rats increases the density of $GABA_A$ and BDZ receptors in striatum while that of $GABA_B$ is decreased (38). Chronically administered BDZs have opposite effects.

In various animal models of anxiety PB, GABA derivatives and BDZs produced similar neurochemical effects in nuclei accumbens and caudatus (47,48). An antagonist of BDZ receptors, Ro 15-1788, antagonized sedative and potentiated antiaggressive effects of PB. In an "open-field" test DZP, an agonist at BDZ receptors, potentiated all behavioral effects of PB. As shown by *ex vivo* studies, PB, like muscimol, increased binding of 3-flunitrazepam to BDZ receptors. Pretreatment with PB (100 mg/kg i.p.) diminished the density and increased the affinity of BDZ receptors in stressed rats. In animals adapted to stress, PB (administered for 10 days) was ineffective. Testing in the elevated plus-maze, PB (at 12.5 mg/kg i.p.) prevented the anxiogenic effect of the BDZ receptor ligand, methyl-6,7-dimethoxy-4-ethyl-carboline-3-carboxylate. In this model of anxiety neither DZP, nor PB alone, altered behavior of mice (38). Chronic i.p. administration of PB in mice antagonized the development of morphine dependence (5,6). BAC and sodium valproate had similar effects. PB also reduced naloxone-induced withdrawal effects in mice addicted to morphine (6).

Activation of dopamine metabolism. In striatum of rats, PB, at 50 to 100 mg/kg i.p., increased the levels of dopamine and its metabolites: homovanilic and 3,4-dihydroxyphenylacetic acids (1,38). It was suggested that PB may activate dopaminergic processes and that this effect may be important for the sedative and tranquilizing effects of the drug

(3,15). Pretreatment with haloperidol (a dopamine receptor antagonist) or α-methyl-*p*-tyrosine (an inhibitor of tyrosine hydroxylase) antagonized the effects of PB on the levels of dopamine or its metabolites in mouse brain (15). PB-induced activation of dopamine metabolism in the striatum of rats was found to be bicuculline-insensitive (38).

Antagonism of β-phenethylamine (PEA). PB has been traditionally viewed as a GABA derivative (Fig. 1). Therefore, most of the pharmacological studies with PB were devoted to its GABA-like properties, its effects on GABA receptors and to comparison with other GABAergic compounds (1–3,5,6,9,11,16–23,32,43,47–50). PB can be viewed, however, also as a derivative of PEA (Fig. 2). The questions are whether the chemical similarity of PEA and PB is of any relevance to the pharmacology of PB and since PEA was thought to function as an endogenous anxiogenic substance, could not the anxiolytic action of PB be due to the antagonism of PEA by PB?

These questions led to two series of experiments:

1) PEA was compared to standard anxiolytics (e.g., pentylenetetrazol, caffeine, and yohimbine) in animal models of anxiety. In these models the behavioral effects of PEA were typical of standard anxiogens (27,29,30,34). In the social interaction test PEA, at 5 to 10 mg/kg i.p., decreased the number and the duration of contacts of previously isolated mice. PB and DZP prevented this effect of PEA (34). In a conflict situation of a dark-light chamber PEA reduced the movements of mice from one chamber to the other. It also prolonged the time period spent in the dark compartment. PB and DZP antagonized these effects of PEA. In an elevated plus-maze, PEA, like d-amphetamine, reduced the ratio of entries into open arms/total number of entries. It also shortened the time spent in open arms (31). PB prevented the effects of either PEA or of d-amphetamine. Ethanol was the strongest antagonist of PEA in the elevated plus-maze (31). It is conceivable that the PEA moiety of PB is responsible for the dopaminergic effects of PB and BAC. PEA is known to reduce the release of dopamine from presynaptic terminals. It is also metabolized to dopamine.

2) Studies on the interaction of PB and PEA revealed that PB or BAC antagonize the sedative, as well as, the excitatory effects of PEA. The sedative effects are observed in mice with PEA at 5 to 10 mg/kg i.p. The excitatory effects of PEA were observed at 40 to 50 mg/kg i.p. Seizures produced by PEA (100 mg i.c.v.) can be prevented by anxiolytics: PB, BAC, buspirone, ethanol, or benzodiazepines. Many other drugs, including anticonvulsants, neuroleptics, tricyclic antidepressants, and anticholinergics, did not prevent PEA-induced seizures (30).

The results of these two series of experiments suggest that: 1) PEA can be viewed as an endogenous anxiogen, and 2) the antagonism of PEA by PB may conceivably represent the mechanism of the anxiolytic action of PB.

Anxiolytic activity of BAC. Since BAC is a *p*-chloro derivative of PB, we considered the possibility that its psychotropic activity profile may be similar to that of PB. Therefore, we evaluated BAC under experimental conditions similar to those with PB. As an antianxiety drug in mice and as an antagonist of the sedative and tranquilizer effects of PEA, BAC had PB-like effects. However, its effective doses were 10 to 12 times lower than those of PB (27,28,30,42). The anticonflict effect of BAC appears to be mediated by $GABA_B$ receptors (44). As an analgesic, BAC is much stronger than PB. It has antinociceptive activity when administered by either parenteral or intrathecal routes. Intrathecal administration of BAC in the rat hind paw formalin test produced addictive analgesia (12). BAC has been reported to increase aggressivity in mice at a low dose (3 mg/kg i.p.) and to

decrease aggressivity at a higher dose (15 mg/kg i.p.). The behavioral effects of BAC appear to be similar to those of benzodiazepines (46).

PHARMACOKINETICS AND TOXICOLOGY

Very little information is available on the pharmacokinetics or toxicology of PB in animals. Following intravenous administration to either rabbits or rats PB is not metabolized. PB is largely excreted in the urine. At 15, 30, 60, or 90 min following i.v. administration PB was found in liver, kidneys, and urine. Traces of PB (~4 mg%) were found in blood and brain. 180 min after i.v. injection only traces of the drug were found in all tissues studied. *In vitro* tissue binding studies indicated that PB binds to liver, kidney, and brain tissue. In cats and dogs PB, after a single dose of 50 mg/kg i.v., is excreted in the urine unchanged.

The acute toxicity of PB is low. Its LD_{50} is 900 mg/kg i.p. in mice and 700 mg/kg i.p. in rats.

CLINICAL STUDIES WITH PB AND BAC

PB was administered orally to healthy volunteers at a single dose of 250 mg. 65% of the dose was recovered unchanged in the urine. The plasma half-life of PB was 5.3 h. Its renal clearance approximated creatinine clearance.

Placebo controlled double-blind studies were conducted in neurotic or psychotic patients with PB administered orally at 0.25 to 0.5 g, three times a day over one or two weeks periods. PB was found to activate intellectual functions, improve physical strength, motivate activity, and to reduce asthenia and tiredness (38).

BAC (2.5 to 3 mg/day) was also evaluated in placebo controlled studies and found to reduce the rate and severity of panic attacks. The effects were similar to those of benzodiazepines, but inferior to those of imipramine (42). The combination of BAC and imipramine was very effective. In alcoholics with secondary affective disorders, BAC was superior to placebo and equally effective to benzodiazepines or amitriptyline. The effectiveness of drugs in these studies was evaluated using clinical psychological tests (Spielberger, Zung, MMPI) and electrophysiological tests (superslow ω-potentials). No side effects or complications were reported (26,32). BAC was also found to be effective in the treatment of affective manifestations of opiate and alcohol withdrawal syndromes (5).

CLINICAL USE OF PB

PB is widely used in Russia in different neurological and psychiatric disorders. In some Russian reference books PB is listed as a tranquilizer, in others as a nootropic agent. In reality the drug appears to have both types of activity. It has been reported to diminish

tension, alleviate anxiety and fear, and to potentiate neuroleptics and antiparkinsonian drugs (15,19). It has also been reported to enhance memory and intellectual function. The largest amount of information (19,38) is available on the clinical use of PB in neuroses (i.e., mental disorders characterized by anxiety). In geriatric patients, PB appears to be superior to tranquilizers or neuroleptics. Like BAC, PB reduces spasticity. It has been successfully used in the treatment of post-traumatic stress disorder, "asthenic-depressive" syndrome, stuttering, and even vestibular disorders.

In children, PB has been claimed to be effective in neurotic disorders, "organic brain syndrome," insomnia and various forms of hyperactivity. In preschool age children PB has been successfully used for speech disorders, particularly stuttering. Due mainly to its tranquilizing activity, it is useful in epileptic patients. As a tranquilizer, PB appears to be weaker than BDZs. However, unlike BDZs, PB does not reduce performance and controls irritability and fatigue. No toxic effects of PB have been reported. Somnolence in geriatric patients was occasionally mentioned as a side effect. A drawback of PB therapy is the de-

TABLE 1. Comparison of phenibut, diazepam, and piracetam based on experimental and clinical findings (19,38,40)

Activity	Phenibut	Diazepam	Piracetam
Anticonflict (tranquilizing)	±	+	±
Anticonvulsant (against putative anxiogens)			
pentyleneterazol	–	+	–
caffeine	+	+	?
bicuculline	–	+	?
yohimbine	+	+	?
phenylethylamine	+	+	?
kynurenine	+	±	?
Sedation	+	+	–
Activation of cognitive and emotional processes	+	–	+
Central muscle relaxation	±	+	–
Learning facilitation	+	–	+
Memory improvement	±	–	+
Inhibition of nystagmus	+	–	+
Affinity to benzodiazepine receptors			
at a single dose	–	+	–
by chronic administration	+	+	+
Activation of GABA receptors			
$GABA_A$	–	+	?
$GABA_B$	+	–	?
Anti-withdrawal (alcohol, morphine)	+	+	+
Antihypoxic	+	–	+
Neuroprotective in trauma, edema, stress	+	±	±
Augmentation of cell energy potential (effect on the metabolism of adenylnucleotides)	+	–	+
Synthesis of RNA	–	–	+

Abbreviations: +, activity demonstrated; –, found ineffective; ±, slight or inconsistent activity; ?, not evaluated or unknown to author.

velopment of tolerance. In some patients, after two weeks of therapy the dose has to be increased by one fourth to one third.

CONCLUSION

The experimental and clinical observations with PB are summarized in Table 1 and compared with those for diazepam and piracetam. On the basis of the above reviewed findings PB was classified as an atypical tranquilizer, or "day-tranquilizer." It has antistress, thymoleptic (activating), and nootropic (cognition enhancing) components of action.

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