

# ALTERATION IN THE CONVULSIVE EFFECT OF KYNURENINE, CORAZOL AND CAFFEINE UNDER THE ACTION OF BICUCULLINE

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**Abstract:** In male mice of two strains SHR and C57BL/6, pretreatment with bicuculline (1 mg/kg, s.c.), an antagonist of GABA-A receptors, potentially the convulsant effect of pentylenetetrazole (40mg/kg, ip.) and caffeine (200mg/kg, ip.) and had no effect on that of L-kynurenine (11 meg, i.c.v.). Data suggest that the convulsant effect of L-kynurenine, an endogenous convulsant from neuroactive tryptophan metabolites, is not related to GABA-A receptors. Other data reported elsewhere (e.g. the antagonism of phenibut and baclofen, agonists of GABA-B receptors, to L- kynurenine) suggest that kynurenine-induced seizures are related to GABA-B receptors.

**Keywords:** convulsive effect, bicuculline, corazol, kinurenin, GABA-A-B receptors, caffeine.

# ИЗМЕНЕНИЕ СУДОРОЖНОГО ЭФФЕКТА КИНУРЕНИНА, КОРАЗОЛА И КОФЕИНА ПОД ДЕЙСТВИЕМ БИКУКУЛЛИНА

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**Аннотация:** У самцов мышей двух штаммов SHR и C57BL / 6, предварительной обработки бикуккуллином (1 мг / кг, подкожно), антагонистом рецепторов ГАМК-А, потенциально судорожный эффект пентилентетразола (40 мг / кг, внутрибрюшинно) и кофеина ( 200 мг / кг, внутрибрюшинно) и не оказывал влияния на L-кинуренин (11 мг, icv). Данные свидетельствуют о том, что судорожный эффект L-кинуренина, эндогенного судороги из нейроактивных метаболитов триптофана, не связан с рецепторами ГАМК-А. Другие данные, представленные в других источниках (например, антагонизм фенибута и баклофена, агонистов рецепторов ГАМК-В к L-кинуренину), свидетельствуют о том, что вызванные кинуренином судороги связаны с рецепторами ГАМК-В.

**Ключевые слова:** судорожный эффект, бикукуллин, коразол, кинуренин, рецепторы ГАМК-А-В, кофеин

## BIKUULLIN TA'SIRIDA KINURENIN, KORAZOL VA KOFEINING KONVULSIV TA'SIRINING O'ZGARISHI

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**Annotatsiya:** SHR va C57BL / 6 ikkita shtamining erkak sichqonlarida, bikuullin (1 mg / kg, teri ostiga) yuborish, GABA-A retseptorlari antagonisti, pentilenetrazolning potensial konvulsiv ta'siri (40 mg / kg, ichkariga) va kofein (200 mg / kg), qorin bo'shlig'ida) va L-kinureninga (11 mg, iv) ta'sir ko'rsatmadi. Dalillar shuni ko'rsatadiki, L-kinurening konvulsiv ta'siri, neyroaktiv triptofan metabolitlaridan endogen ushlanishi GABA-A retseptorlari bilan bog'liq emas. Boshqa manbalarda keltirilgan boshqa ma'lumotlar (masalan, fenibut va baklofenning antigonizmi, GABA-A retseptorlarining L-kinureninga bo'lgan agonistlari) kinurenin bilan tutilish GABA-B retseptorlari bilan bog'liqligini ko'rsatadi.

**Kalit so'zlar:** konvulsiv ta'sir, bikukullin, korazol, kinurenin, GABA-AB retseptorlari, kofein.

### Introduction

Gamma-aminobutyric acid (GABA) is a major neurotransmitter widely distributed throughout the central nervous system (CNS). Because too much excitation can lead to irritability, restlessness, insomnia, seizures, and movement disorders, it must be balanced with inhibition. GABA – the most important inhibitory neurotransmitter in the brain – provides this inhibition, acting like a “brake” during times of runaway stress. Medications for anxiety, such as benzodiazepines, stimulate GABA receptors and induce relaxation. Either low GABA levels or decreased GABA function in the brain is associated with several psychiatric and neurological disorders, including anxiety, depression, insomnia, and epilepsy. Studies indicate GABA can improve relaxation and enhance sleep [1].

Numerous experimental studies have found that the  $\gamma$ -aminobutyric acid (GABA) system of the brain is important in protecting against arousal and seizures caused by excitatory neurokynurenine - the endogenous metabolites of the essential amino acid tryptophan [2]. Of the excitatory neurokynurenins, the most active are L-kynurenine (kynurenine) and quinolinic acid. Among the receptors involved in the excitatory effects of neurokynurenins, the most studied GABA receptors and excitatory amino acid receptors [2, 3]. When comparing kynurenine convulsions with convulsions caused by standard convicts (corazol, caffeine, etc.), it was found that the GABA-B receptors and dopamine (DA) receptor blockade play a leading role in the mechanism of kynurenine convulsions [2]. GABA-A receptors seem to be much less important, since even such a universal and powerful anticonvulsant, as diazepam, a typical

agonist of GABA-A receptors, is much less effective in protecting against kynurenine convulsions than GABA-B receptor agonists. Experimental therapy of kynurenine convulsions [4] found that protection from them requires first of all the activation of GABA-ergic processes, for example, with the help of GABA-mimetics, and also the strengthening of DA-ergic processes by isolating DA or its predecessors.

The purpose of the study was to obtain additional information about the role of GABA-A receptors in protection against kynurenine seizures. For the analysis, the selective antagonist of the GABA-A receptor bicuculline was used, which has been widely used in recent years for this purpose [3].

**Materials and research methods.** The experiments were performed on male mice of two lines: outbred albinos (originating from the SHR line) and black C57BL/6 weighing 20-21 g, obtained from the Rappolovo farm near St. Petersburg. Bicuculline in the form of a solution freshly prepared on distilled water was injected subcutaneously 15 minutes before the convulsant. Solutions of corazol and caffeine were injected intraperitoneally, kynurenine into the cerebral ventricles using a semi-automatic device [2].

All preparations were obtained from “Sigma” (USA). The number of animals with typical clonic-tonic convulsions (within 2 hours after the introduction of convulsants) and the number of dead animals were recorded after 2 and 24 hours. Work performed in the **Laboratory of Psychopharmacology, Bekhterev Psychoneurological Research Institute, St. Petersburg.**

**Results and discussion.** The results of the experiments showed (table) that the preliminary administration of bicuculline significantly enhances the convulsive effect of corazol and caffeine, but not kynurenine. It should also be emphasized that convulsants are used in equally effective - minimal convulsive doses.

Table

**The effect of bicuculline on the convulsive effect of kynurenine, corazol and caffeine**

Preparations	dose			Amount of mice					
	s/c	i/p	i/bv	outbred (SHR)			C57BL/6		
				all with dead by convulsion			all with dead by convulsion		
mg/kg									
S+ kynurenine	-		12	20	2	0	26	6	2
BCC- kynurenine	1		12	20	3	0	26	12	6
S-corazol	*	40		28	6	0	28	4	0
BCC+ corazol	1	40		28	20*	6*	28	24*	0
S+ caffeine	-	200		30	9	1	24	6	2
BCC+caffeine	1	200		30	19*	1	24	16*	6

Abbreviations: S –saline (control), BCC - bicuculline \*  $p < 0,05$  (with control). s/c – subcutaneously, i/p – intraperitoneally, – inside the ventricle of the brain

**Conclusions.** The obtained data give reason to support the proposal [2] that GABA-A receptors, which are crucial in the mechanism of corazol and caffeine convulsions, are not involved in the mechanism of kynurenine convulsions, and mainly associated with GABA-B receptors.



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