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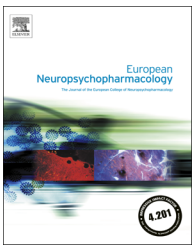

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Low single dose gabapentin does not affect prefrontal and occipital gamma-aminobutyric acid concentrations

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Abstract
The γ-aminobutyric acid (GABA) system has been proposed as a target for novel antidepressant and anxiolytic treatments. Emerging evidence suggests that gabapentin (GBP), an anticonvulsant drug that significantly increases brain GABA levels, is effective in the treatment of anxiety disorders. The current study was designed to measure prefrontal and occipital GABA levels in medication-free healthy subjects after taking 0 mg, 150 mg and 300 mg GBP. Subjects were scanned on a 3T scanner using a transmit-receive head coil that provided a relatively homogenous radiofrequency field to obtain spectroscopy measurement in the medial prefrontal (MPFC) and occipital cortex (OCC). There was no dose-dependent effect of GBP on GABA levels in the OCC or MPFC. There was also no effect on Glx, choline or N-acetyl-aspartate concentrations. The previously reported finding of increased GABA levels after GBP treatment is not evident for healthy subjects at the dose of 150 and 300 mg. As a result, if subjects are scanned on a 3T scanner, low dose GPB is not useful as an experimental challenge agent on the GABA system.

1. Introduction

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the brain, which is formed from the alpha-decarboxylation of glutamate by glutamic acid

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decarboxylase (GAD) and metabolized by GABA-transaminase. Decreases in GABA have been associated with mood and anxiety disorders specifically in the occipital lobe (Goddard et al., 2001; Sanacora et al., 1999) but also in the prefrontal cortex (Hasler et al., 2007, 2010b; Simpson et al., 2012). Therefore, the GABA system has been proposed as a target for novel antidepressant and mood-stabilizing treatments (Krystal et al., 2002). There are a number of anti-epileptic, anxiolytic, and anesthetic drugs that enhance GABAergic activity in the brain (Petroff, 2002). Among these, gabapentin (GBP) is a relatively novel drug that has been approved for the treatment of epilepsy (Andrews and Fischer, 1994; Chadwick, 1994). GBP significantly increased occipital GABA levels in epilepsy patients after one hour of the first oral dose of 1200 mg GBP (Petroff et al., 2000). Although GBP was designed to mimic GABA, the underlying mechanism of action remains unclear (Bryans and Wustrow, 1999; Taylor et al., 1998). Clinical studies suggest that GBP plays a role in the treatment of anxiety disorders (Pande et al., 1999, 2000). Interestingly, already low doses of adjunctive GBP (100 mg/day) seem to have a beneficial effect on anxiety (Pollack et al., 1998). Magnetic resonance spectroscopy studies could show that high-dose GBP administration is also associated with increased GABA concentrations in the occipital lobe in healthy subjects (Cai et al., 2012; Kuzniecky et al., 2002). Cai et al. (2012) reported an average increase in GABA concentration of 55.7% (6.9–91.0%) after 900 mg GBP administration. Furthermore, Kuzniecky et al. (2002) could show that 17 mg/kg single dose GBP moderately increases GABA concentration within 6 h.

In the present study, we used a magnetic resonance spectroscopy (MRS) method developed by GE and implemented by NIH in order to measure prefrontal and occipital GABA levels. 11 healthy medication-free human subjects were examined by GABA MRS in a controlled trial using placebo, 150 mg and 300 mg GBP. The goal of the present study was to examine, whether low dose GBP is useful as a safe experimental challenge agent in MRS studies on the GABA system. We expected that the effect of GBP on prefrontal GABA in healthy volunteers is similar to the effect of GBP on occipital GABA in healthy subjects and in patients with epilepsy (Cai et al., 2012; Kuzniecky et al., 2002; Petroff et al., 2000). Given that GBP increased GABA levels in the occipital cortex (Cai et al., 2012; Kuzniecky et al., 2002; Petroff et al., 2000), we assume that GBP will produce a measurable increase in prefrontal GABA in all study subjects.

2. Experimental procedures

2.1. Subjects

11 healthy volunteers (3 men, mean age=36.14±11.97; range 22–60) were recruited from community centers through posted advertisements by the Mood and Anxiety Disorders Program. Advertisements were placed in local newspapers and local radio stations. Study procedure was approved by the NIMH Human Studies Committee. All subjects gave written informed consent. Subjects were screened for present or past psychiatric axis I diagnoses using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, non-patient version (First et al., 1996). Family history of mental illness (mood and anxiety disorders, schizophrenia and other psychotic disorders, substance abuse disorders) was obtained in all 1st degree relatives using the Family Interview of Genetic Studies (Maxwell, 1992). Subjects were not under centrally active medication for at least 3 weeks prior to the study. Exclusion criteria were, medical or neurological illnesses likely to affect physiology or anatomy, i.e. hypertension, cardiovascular disorders, a history of drug (including benzodiazepines [BZD]) or alcohol abuse, smokers, serious suicidal ideation or behavior, lactose intolerance, caffeine dependency, history of allergic reaction to GBP, and general MRI exclusion criteria. Subjects above the age 60 were excluded because of slower elimination of GBP in older adults, and the age-related increase in brain structural abnormalities. In women, there were additional exclusion criteria: current pregnancy (as documented by pregnancy testing at screening or at days of the challenge studies), current breast-feeding, and lack of reliable contraception method. Physical examinations, including electrocardiogram, blood (CBC+diff, coagulation panel, Chem 20, cortisol, thyroid screening, HIV, Hep screen, serum pregnancy test in women) and urine tests established that all participants were medically healthy.

2.2. Procedure

Subjects received 0 mg, 150 mg and 300 mg GBP during three test days in a randomized and balanced order. GBP was orally administered. To avoid carry-over effect between the different test sessions, an interval of at least 7 days was established. Subjects underwent medical examination by a physician before they returned home at the end of each study day. Thereafter, they were able to contact a clinician of the research team if needed.

2.3. Magnetic resonance spectroscopy

Subjects underwent scanning two hours post GBP administration. They were scanned on a 3T GE scanner with a whole head coil for homogeneous radiofrequency (RF) field and spectroscopic measurements from the prefrontal and occipital part of the brain. The levels of GABA, choline, N-acetyl aspartate (NAA), and co-edited glutamate/glutamine (Glx) were measured using an interleaved PRESS-based J-editing method (Hasler et al., 2007, 2009, 2010b). Two voxels were scanned, the MPFC voxel extended $3 \times 3 \times 2\ cm^3$, was placed with the posterior border abutting the rostrum of the corpus callosum, and was centered on the midline in horizontal planes and on the bicommissural line in sagittal planes. The OCC voxel sized $3 \times 3 \times 3\ cm^3$ was placed just superior of the cerebellum in the occipital lobe centered on the midline of the brain. Every scan consisted of 1024 acquisitions with a repetition time of 1.5 s for a total scan time of 26 min. The spectroscopic peak for NAA, choline and creatine were automatically fitted (Hasler et al., 2007, 2009, 2010b) in the unedited spectrum and the peaks for GABA and the partially edited Glx were fitted in the subtraction spectrum (Fig. 1). In a last step all metabolites were normalized by the creatine amplitude.

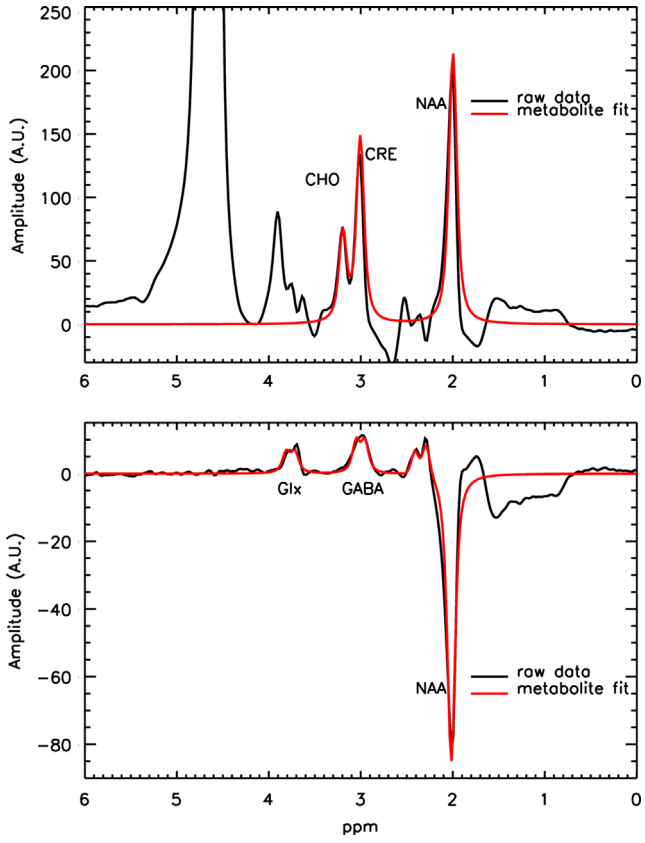

Fig. 1 Plot of a representative data set: The top panel shows the unedited spectrum and the bottom panel shows the difference spectrum with the GABA signal. Fits to the spectra are shown in red, NAA, choline and creatine signals are fitted in the unedited spectrum and GABA and Glx (glutamate+glutamine) are fitted in the difference spectrum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.4. Statistics

GABA levels in the prefrontal and occipital cortex were examined using repeated measure ANOVA with the factors 'brain region' (MPFC, OCC) and 'treatment' (Placebo, 150 mg GBP, 300 mg GBP). Simple effects tests were used to examine the effect of GBP on GABA, GLX, NAA & Choline concentrations in both PFC and OCC (table 1).

3. Results

Repeated measure ANOVA revealed that there was no main effect for the factor 'treatment', $F(2, 6)=1.18$, $p=0.3$. Hence, there was no difference in GABA concentrations after 0 mg, 150 mg and 300 mg GBP administration. Furthermore, there was no main effect for the factor 'brain region', $F(1, 3)=4.73$, $p=0.12$. That means there was no difference between GABA concentrations in the MPFC and OCC. There was no interaction between GBP dose and cortical GABA concentration measured in the PFC and OCC, $F(2, 6)=0.13$, $p=0.88$. Hence, GBP, depending on dose, did not differentially affect prefrontal and occipital GABA concentrations. Further analysis revealed no effect of GBP dose on GLX, NAA and choline in both PFC and OCC ($p>0.23$, Table 1).

4. Discussion

The present study represents a first time investigation of the effect of GBP on GABA concentrations in the PFC. Previous magnetic resonance spectroscopy (MRS) studies that have examined the effects of action of GABA enhancing compounds, primarily measured GABA in the occipital cortex due to technical limitations. In the present study, GBP had no effect on prefrontal or occipital GABA concentrations. Furthermore, there was no effect on GLX, NAA and choline concentrations. All subjects were healthy and medication free. The results suggest that low dose GBP does not lead to detectable changes in GABA synthesis in healthy subjects.

Previous studies could show, that higher doses of GBP increase occipital GABA concentration in epilepsy patients (Petroff et al., 1996, 2000). However, GBP did not seem to directly affect GABA-specific enzymes, GABA receptors, and GABA uptake (Petroff et al., 2000; Rock et al., 1993; Su et al., 1995; Taylor, 1995). To date, the effect of GBP on brain amino-acid transmitters is not completely understood. GBP does not seem to interact directly with GABA receptors, however it may selectively counteract GAD inhibitors (Taylor et al., 1998). In vitro, GBP stimulates GAD at a concentration of 1.0–2.5 mM and inhibits GABA-transaminase, the enzyme that catabolizes GABA, at higher concentrations (23–25 mM) (Löscher et al., 1991; Taylor, 1995; Taylor et al., 1992). Therefore, GBP might increase the activity of partially-purified GAD in vitro, implying that GBP might increase the synthesis of GABA from glutamate in brain tissues (Taylor et al., 1992, 1998). In vivo, intravenous GBP (25 mg/kg) in rats raised GBP brain levels up to 0.07 mM (Vollmer et al., 1986) whereas standard doses (plasma concentration, 6.75 μg/ml) in humans resulted in a GBP concentration of 0.03 mM (Ojemann et al., 1988). Although the results of the rodent model have not been consistent with result in humans regarding GBP pharmacodynamics (Errante et al., 2002), the inhibition of GABA-transaminase and the stimulation of GAD may partly account for the rise in human brain GABA following GBP (Löscher et al., 1991; Taylor, 1995; Taylor et al., 1992).

Several additional hypotheses have been proposed to explain the pharmacology of GBP (for overview see Taylor et al., 1998): GBP may cross several membrane barriers in the body via a specific system l-amino acid transporter and binds with high affinity to a subunit of voltage-sensitive Ca^{2+} channels (Gee et al., 1996; Stewart et al., 1993; Su et al., 1995; Thurlow et al., 1993). Furthermore, GBP inhibits voltage-activated Na^{+} channels and increases serotonin concentration in humans (Rao et al., 1988; Wamil and McLean, 1994).

An emerging body of evidence suggests the utility of GBP in the treatment of anxiety (Frye et al., 2000; Ménigaux et al., 2005; Mula et al., 2007; Pande et al., 1999, 2000; Pollack et al., 1998). Animal models suggest that GBP produces anxiolytic effects with a minimum dose of 3–30 mg/kg (Singh et al., 1996). Furthermore, GBP demonstrated dose-dependent "anxiolytic-like" effects in preclinical

Table 1 Metabolite concentration ratio (mmol/liter), standard deviations and *p*-values after 0 mg, 150 mg and 300 mg GBP respectively[a].

Gabapentin (mg)	MPFC			OCC		
	GABA/CRE	SD	*p* Value	GABA/CRE	SD	*p* Value
0	0.107	0.016		0.115	0.008	
			0.98			0.82
150	0.108	0.008		0.116	0.009	
			0.50			0.76
300	0.104	0.009		0.117	0.007	
	GLX/CRE			GLX/CRE		
0	0.102	0.015		0.080	0.005	
			0.50			0.29
150	0.107	0.012		0.083	0.007	
			0.32			0.35
300	0.101	0.010		0.080	0.005	
	NAA/CRE			NAA/CRE		
0	1.524	0.126		1.612	0.109	
			0.85			0.91
150	1.539	0.180		1.606	0.097	
			0.99			0.62
300	1.540	0.115		1.627	0.080	
	CHO/CRE			CHO/CRE		
0	0.860	0.086		0.520	0.068	
			0.35			0.92
150	0.899	0.066		0.516	0.069	
			0.23			0.76
300	0.856	0.063		0.527	0.071	

Abbreviations: GABA, γ-aminobutyric acid; GLX, Glutamate/Glutamine; NAA, N-acetyl-aspartate; CHO, choline; CRE, creatine; MPFC, medial prefrontal cortex; OCC, occipital cortex; SD, standard deviation.

[a]The creatine concentration was set at 93 mg/dL (7100 μmol/L). Metabolite concentrations are indicated as mean.

studies (Singh et al., 1996). Studies in epilepsy patients reported both an increase of cortical GABA as well as improvements in mood and general well being (Dimond et al., 1996; Petroff et al., 1996, 2000). Petroff et al. (2000) could show that patients with low starting GABA levels increased at faster rate than epilepsy patients with higher starting concentrations. The speed of GBP effects suggest that already low concentrations of GBP may rapidly increase the rate of GABA synthesis or decrease the rate of catabolism. Beauclair et al. (1996) reported a reduction in anxiety symptoms in 18 psychotic patients treated adjunctively with GBP. Pande and colleagues showed an anxiolytic effect of GBP in patients with social phobia and more severely ill patients with panic disorder (Pande et al., 1999, 2000). Furthermore, Pollack et al. (1998) found clinical improvement in 4 patients with anxiety disorders after low dose (100–400 mg/day) adjunctive GBP treatment. Interestingly, GBP has also shown to affect monoamine neurotransmitter (dopamine, noradrenaline, serotonin) release in vitro (Dooley et al., 2002; Reimann, 1983; Schlicker et al., 1985). Taylor et al. (1998) concluded that these changes in monoamine function might relate to anxiolytic effects of GBP. Furthermore, research suggests that GBP might interact with glutamatergic synapses and that GBP might change glutamate metabolism or release (Bartoszyk et al., 1986; Taylor, 1995; Taylor et al., 1998). Interestingly, in addition to reduced GABA concentrations altered glutamate concentrations were also found in mood disorders (Hasler et al., 2007, 2010a). However, we did not find an effect of GBP on Glx concentration.

In contrast to previous findings of increased occipital GABA concentration after GBP intake, we did not find a dose-dependent effect of GBP on GABA concentrations in the MPFC or OCC. Previous GBP treatment studies showed an effect of high-dose GBP challenge on GABA levels in healthy subjects (Cai et al., 2012; Kuzniecky et al., 2002). In both studies, the average increase in occipital GABA was around 50%. Hence, one possible limitation might be the relatively low dose of GBP used in the present study. However, it is important to note that subjects in the present study were healthy and medication free. Therefore, using low-dose GBP might have provided a safe experimental challenge agent to examine the GABA system. Furthermore, using higher doses reduces the feasibility of experimental studies given that higher doses of GBP frequently induce somnolence, which requires monitoring of research subjects over several hours. Positive effects of low dose adjunctive GBP treatment were already shown in psychiatric patients (Beauclair et al., 1996; Pande et al., 1999, 2000; Pollack et al., 1998). Since GABA levels appear reduced in patients

with an anxiety disorder compared to healthy controls (Baldessarini, 1985; Goddard et al., 2001; Simpson et al., 2012) it is conceivable that low doses of GBP exert a stronger effect on GABA synthesis in patients with lower starting GABA levels. This is supported by Cai et al. (2012), who could show that drug-induced changes in GABA levels were inversely correlated with individuals' baseline GABA level. In contrast to the present study, Cai et al. (2012) used a 7T scanner. Since baseline GABA levels are higher in healthy subjects, it is possible that low dose GBP induces smaller changes in GABA levels, which are out of the detected sensitivity of 3T scanners. As MRS sensitivity increases with magnetic field, an effect of low single dose GBP might be found at 7T or ultra-high field human scanner.

Although the probability of a possible drug-drug interaction appears low, since GBP is not metabolized in the body, GBP as well as anxiolytic and antidepressant drugs both alter central GABA and Glutamate neurotransmission (Bhagwagar et al., 2004; Krystal et al., 2002). Furthermore, both have an effect on monoamine neurotransmitter release (Bartoszyk et al., 1986; Taylor, 1995; Taylor et al., 1998) and specifically change serotonin metabolism (Rao et al., 1988). Therefore, the possibility of a confounding effect of adjunctive GBP treatment in patients cannot be fully excluded.

Although we did not find an effect of GBP on cortical GABA concentrations, behavioral studies have shown a positive effect of adjunctive low dose GBP treatment in anxiety disorders (Pande et al., 1999, 2000; Pollack et al., 1998). GBP is a safe and well-tolerated drug, with dizziness and sedation being the most common adverse effects. Demonstrating a dose-dependent relationship for GBP and brain GABA would be an important step to validate GBP as a potential challenge agent for neuropsychiatric disorders. Future studies should investigate the effect of GBP on cortical GABA concentrations in patients with psychiatric conditions that are associated with reduced cortical GABA concentration (Goddard et al., 2001; Hasler, 2010; Hasler, 2007, 2010b,; Sanacora et al., 1999; Simpson et al., 2012) and examine GBP as an experimental challenge agent at doses higher than 300 mg.

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Contributors

Gregor Hasler designed the study and wrote the protocol. Nora Preuss managed literature research, statistical analysis and wrote the first draft of the manuscript. Jun Shen and Jan Willem van der Veen were responsible for the imaging methods and undertook the imaging data analysis. Paul Carlson managed data collection and MRS scanning. All authors contributed to and have approved the final manuscript.

Conflict of interest

Nora Preuss, Jan Willem van der Veen, Paul Carlson, Jun Shen and Gregor Hasler have no conflict of interest.

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References

Andrews, C.O., Fischer, J.H., 1994. Gabapentin: a new agent for the management of epilepsy. Ann. Pharmacother. 28, 1188–1196.
Baldessarini, R.J., 1985. Drugs and the treatment of psychiatric disorders. The Pharmacological Basis of Therapeutics, vol. 8 MacMillan Publishing Co., NY, USA, 383–435.
Bartoszyk, G., Meyerson, N., Reimann, W., Satzinger, G., von Hodenberg, A., Meldrum, B., Porter, R., 1986. New Anticonvulsant Drugs. John Libbey, London147–163.
Beauclair, L., Sultan, S., Balanger, M., 1996. Antianxiety and hypnotic effects of gabapentin in psychotoca patients with comorbid anxiety related disorders. In: Proceedings of the 35th Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico.
Bhagwagar, Z., Wylezinska, M., Taylor, M., Jezzard, P., Matthews, P.M., Cowen, P.J., 2004. Increased brain GABA concentrations following acute administration of a selective serotonin reuptake inhibitor. Am. J. Psychiatry 161, 368–370.
Bryans, J.S., Wustrow, D.J., 1999. 3-Substituted GABA analogs with central nervous system activity: a review. Med. Res. Rev. 19, 149–177.
Cai, K., Nanga, R.P., Lamprou, L., Schinstine, C., Elliott, M., Hariharan, H., Reddy, R., Epperson, C.N., 2012. The impact of gabapentin administration on brain GABA and glutamate concentrations: a 7T 1H-MRS study. Neuropsychopharmacology 37, 2764–2771.
Chadwick, D., 1994. Gabapentin. The Lancet 343, 89–91.
Dimond, K.R., Pande, A.C., Lamoreaux, L., Pierce, M.W., 1996. Effect of gabapentin (neurotonin®) on mood and well-being in patients with epilepsy. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 20, 407–417.
Dooley, D.J., Donovan, C.M., Meder, W.P., Whetzel, S.Z., 2002. Preferential action of gabapentin and pregabalin at P/Q-type voltage-sensitive calcium channels: Inhibition of K^+-evoked [3H]-norepinephrine release from rat neocortical slices. Synapse 45, 171–190.
Errante, L.D., Williamson, A., Spencer, D.D., Petroff, O.A., 2002. Gabapentin and vigabatrin increase GABA in the human neocortical slice. Epilepsy Res. 49, 203–210.
First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W., 1996. Structured Clinical Interview for DSM-IV Axis I Disorders: Non-patient Edition (SCID-I/NP). New York State Psychiatric Institute, New York.
Frye, M.A., Ketter, T.A., Kimbrell, T.A., Dunn, R.T., Speer, A.M., Osuch, E.A., Luckenbaugh, D.A., Corá-Locatelli, G., Leverich, G.S., Post, R.M., 2000. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. J. Clin. Psychopharmacol. 20, 607–614.
Gee, N.S., Brown, J.P., Dissanayake, V.U.K., Offord, J., Thurlow, R., Woodruff, G.N., 1996. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the subunit of a calcium channel. J. Biol. Chem. 271, 5768–5776.
Goddard, A.W., Mason, G.F., Almai, A., Rothman, D.L., Behar, K.L., Petroff, O.A., Charney, D.S., Krystal, J.H., 2001. Reductions in occipital cortex GABA levels in panic disorder detected with 1 h-magnetic resonance spectroscopy. Arch. Gen. Psychiatry 58, 556–561.
Hasler, G., 2010. Reduced cortical GABA concentration as putative endophenotype in major depression. Biol. Psychiatry 67, 198S.
Hasler, G., van der Veen, J.W., Tumonis, T., Meyers, N., Shen, J., Drevets, W.C., 2007. Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression

determined using proton magnetic resonance spectroscopy. Arch. Gen. Psychiatry 64, 193–200.
Hasler, G., van der Veen, J.W., Geraci, M., Shen, J., Pine, D., Drevets, W.C., 2009. Prefrontal cortical gamma-aminobutyric acid levels in panic disorder determined by proton magnetic resonance spectroscopy. Biol. Psychiatry 65, 273–275.
Hasler, G., Deschwanden, A., Karolewicz, B., Buck, F., Ametainey, S.M., Drevets, W.C., Van der Veen, J.W., Shen, J., Treyer, V., 2010a. Abnormalities of glutamate and GABA systems in depression: novel findings from studies using MRS and PET. Eur. Neuropsychopharmacol. 20, S207–S208.
Hasler, G., van der Veen, J.W., Grillon, C., Drevets, W.C., Shen, J., 2010b. Effect of acute psychological stress on prefrontal GABA concentration determined by proton magnetic resonance spectroscopy. Am. J. Psychiatry 167, 1226–1231.
Krystal, J.H., Sanacora, G., Blumberg, H., Anand, A., Charney, D.S., Marek, G., Epperson, C.N., Goddard, A., Mason, G.F., 2002. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. Mol. Psychiatry 7, S71–S80.
Kuzniecky, R., Ho, S., Pan, J., Martin, R., Gilliam, F., Faught, E., Hetherington, H., 2002. Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults. Neurology 58, 368–372.
Löscher, W., Hönack, D., Taylor, C.P., 1991. Gabapentin increases aminooxyacetic acid-induced GABA accumulation in several regions of rat brain. Neurosci. Lett. 128, 150–154.
Maxwell, M.E., 1992. Manual for the Family Interview of Genetic Studies (FIGS). National Institute of Mental Health, Bethesda, MD.
Ménigaux, C., Adam, F., Guignard, B., Sessler, D.I., Chauvin, M., 2005. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth. Analg. 100, 1394–1399.
Mula, M., Pini, S., Cassano, G.B., 2007. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. J. Clin. Psychopharmacol. 27, 263.
Ojemann, L., Friel, P., Ojemann, G., 1988. Gabapentin concentrations in human brain. Epilepsia 29, 109–114.
Pande, A.C., Davidson, J.R.T., Jefferson, J.W., Janney, C.A., Katzelnick, D.J., Weisler, R.H., Greist, J.H., Sutherland, S.M., 1999. Treatment of social phobia with gabapentin: a placebo-controlled study. J. Clin. Psychopharmacol. 19, 341–348.
Pande, A.C., Pollack, M.H., Crockatt, J., Greiner, M., Chouinard, G., Lydiard, R.B., Taylor, C.B., Dager, S.R., Shiovitz, T., 2000. Placebo-controlled study of gabapentin treatment of panic disorder. J. Clin. Psychopharmacol. 20, 467–471.
Petroff, O.A., 2002. GABA and glutamate in the human brain. Neuroscientist 8, 562–573.
Petroff, O.A., Hyder, F., Rothman, D.L., Mattson, R.H., 2000. Effects of gabapentin on brain GABA, homocarnosine, and pyrrolidinone in epilepsy patients. Epilepsia 41, 675–680.
Petroff, O.A.C., Rothman, D.L., Behar, K.L., Lamoureux, D., Mattson, R.H., 1996. The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy. Ann. Neurol. 39, 95–99.
Pollack, M.H., Matthews, J., Scott, E.L., 1998. Gabapentin as a potential treatment for anxiety disorders. Am. J. Psychiatry 155, 992–993.
Rao, M.L., Clarenbach, P., Vahlensieck, M., Krätzschmar, S., 1988. Gabapentin augments whole blood serotonin in healthy young men. J. Neural Transm. 73, 129–134.
Reimann, W., 1983. Inhibition by GABA, baclofen and gabapentin of dopamine release from rabbit caudate nucleus: are there common or different sites of action? Eur. J. Pharmacol. 94, 341–344.
Rock, D.M., Kelly, K.M., Macdonald, R.L., 1993. Gabapentin actions on ligand-and voltage-gated responses in cultured rodent neurons. Epilepsy Res. 16, 89–98.
Sanacora, G., Mason, G.F., Rothman, D.L., Behar, K.L., Hyder, F., Petroff, O.A., Berman, R.M., Charney, D.S., Krystal, J.H., 1999. Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. Arch. Gen. Psychiatry 56, 1043–1047.
Schlicker, E., Reimann, W., Gothert, M., 1985. Gabapentin decreased monoamine release without affecting acetylcholine release in the brain. Drug Res. 35, 1347–1349.
Simpson, H.B., Shungu, D.C., Bender, J., Mao, X., Xu, X., Slifstein, M., Kegeles, L.S., 2012. Investigation of cortical glutamate-glutamine and γ-aminobutyric acid in obsessive-compulsive disorder by proton magnetic resonance spectroscopy. Neuropsychopharmacology 37, 2684–2692.
Singh, L., Field, M., Ferris, P., Hunter, J., Oles, R., Williams, R., Woodruff, G., 1996. The antiepileptic agent gabapentin (Neurontin) possesses anxiolytic-like and antinociceptive actions that are reversed by D-serine. Psychopharmacology 127, 1–9.
Stewart, B.H., Kugler, A.R., Thompson, P.R., Bockbrader, H.N., 1993. A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. Pharm. Res. 10, 276–281.
Su, T.Z., Lunney, E., Campbell, G., Oxender, D.L., 1995. Transport of gabapentin, a γ-amino acid drug, by system L α-amino acid transporters: a comparative study in astrocytes, synaptosomes, and CHO cells. J. Neurochem. 64, 2125–2131.
Taylor, C., 1995. Gabapentin: mechanisms of action. Antiepileptic Drugs 4, 829–841.
Taylor, C.P., Vartanian, M.G., Andruszkiewicz, R., Silverman, R.B., 1992. 3-alkyl GABA and 3-alkylglutamic acid analogues: two new classes of anticonvulsant agents. Epilepsy Res. 11, 103–110.
Taylor, C.P., Gee, N.S., Su, T.Z., Kocsis, J.D., Welty, D.F., Brown, J.P., Dooley, D.J., Boden, P., Singh, L., 1998. A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Res. 29, 233–249.
Thurlow, R.J., Brown, J.P., Gee, N.S., Hill, D.R., Woodruff, G.N., 1993. [^{3}H] Gabapentin may label a system-L-like neutral amino acid carrier in brain. Eur. J. Pharmacol.: Mol. Pharmacol. 247, 341–345.
Vollmer, K.O., von Hodenberg, A., Kölle, E.U., 1986. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. Arzneim. Forsch. 36, 830–839.
Wamil, A.W., McLean, M.J., 1994. Limitation by gabapentin of high frequency action potential firing by mouse central neurons in cell culture. Epilepsy Res. 17, 1–11.