Acta Physiologica Sinica, August 25, 2004, 56 (4): 427-435
http://www.actaps.com.cn

Brief Review

GABAergic neurotransmission in globus pallidus and its involvement in neurologic disorders

CHEN Lei, YUNG Wing-Ho*
Department of Physiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

Abstract: The globus pallidus occupies a critical position in the 'indirect' pathway of the basal ganglia and, as such, plays an important role in the modulation of movement. In recent years, the importance of the globus pallidus in the normal and malfunctioned basal ganglia is emerging. However, the function and operation of various transmitter systems in this nucleus are largely unknown. GABA is the major neurotransmitter involved in the globus pallidus. By means of electrophysiological recording, immunohistochemistry and behavioral studies, new information on the distribution and functions of the GABAergic neurotransmission in the rat globus pallidus has been generated. Morphological studies revealed the existence of $GABA_A$ receptor, including its benzodiazepine binding site, and $GABA_B$ receptor in globus pallidus. At subcellular level, $GABA_A$ receptors are located at the postsynaptic sites of symmetric synapses (putative GABAergic synapses). However, $GABA_B$ receptors are located at both pre- and postsynaptic sites of symmetric, as well as asymmetric synapses (putative excitatory synapses). Consistent with the morphological results, functional studies showed that activation of $GABA_B$ receptors in globus pallidus reduces the release of GABA and glutamate by activating presynaptic auto- and heteroreceptors, and hyperpolarizes pallidal neurons by activating postsynaptic receptors. In addition to $GABA_B$ receptor, activation of $GABA_A$ receptor benzodiazepine binding site and blockade of GABA uptake change the activity of globus pallidus by prolonging the duration of GABA current. In agreement with the *in vitro* effect, activation of $GABA_B$ receptor, $GABA_A$ receptor benzodiazepine binding site and blockade of GABA uptake cause rotation in behaving animal. Furthermore, the GABA system in the globus pallidus is involved in the etiology of Parkinson's disease and regulation of seizures threshold. It has been demonstrated that the abnormal hypoactivity and synchronized rhythmic discharge of globus pallidus neurons associate with akinesia and resting tremor in parkinsonism. Recent electrophysiological and behavioral studies indicated that the new anti-epileptic drug, tiagabine, is functional in globus pallidus, which may present more information to understand the involvement of globus pallidus in epilepsy.

Key words: globus pallidus; GABA; Parkinson's disease; seizure

苍白球γ-氨基丁酸能神经传递及其与神经系统疾病的关系

陈 蕾, 容永豪*
香港中文大学医学院生理系, 香港

摘 要: 苍白球是基底神经节间接环路的重要核团, 在机体运动功能调节中发挥重要作用。近年来, 苍白球在基底神经节正常及异常功能调节中的重要性已日渐受到重视。然而, 目前对苍白球内各种神经递质系统的功能活动了解较少。GABA 是苍白球主要的神经递质。采用电生理记录、免疫组织化学及行为测试等实验方法, 人们对大鼠苍白球 GABA 能神经传递系统的受体分布及功能活动有了新的认识。形态学研究揭示, 苍白球存在 $GABA_A$ 受体及其苯二氮卓结合位点和 $GABA_B$ 受体。在亚细胞水平, $GABA_A$ 受体主要位于对称性突触(GABA 能突触)的突触后膜, 而 $GABA_B$ 受体则位于对称性突触和非对称性突触(兴奋性突触)的突触前膜及突触后膜。功能学研究进一步揭示, 激活苍白球突触前膜 $GABA_B$ 自身和异源性受体可分别减少 GABA 和谷氨酸释放; 激活突触后膜 $GABA_B$ 受体, 可引起苍白球神经元超极化。除 $GABA_B$ 受体外, 激活苍白球 $GABA_A$ 受体苯二氮卓结合位点及阻断 GABA 重摄取可延长 GABA 电流持续时间, 从而改变苍白球神经元兴奋性。与离体实验结果相一致, 激活苍白球 $GABA_B$ 受体和苯二氮卓结合位点及阻断 GABA 重摄取可引起整体动物旋转行为。苍白球 GABA 神经递质系统与帕金森病病因学及癫痫发病有关。已证实, 苍白球神经元放电频率的降低及簇状放电的产生与帕金森病运动减少

Received 2004-03-29 Accepted 2004-06-02
*Corresponding author. Tel: 852-26096880; Fax: 852-26035022; E-mail: whyung@cuhk.edu.hk

及静止性震颤等症状直接相关。此外，电生理及行为学实验发现，新型抗癫痫药物替加平可调节苍白球神经元功能活动，这为进一步了解苍白球与癫痫发病的关系提供了新的理论及实验依据。

关键词: 苍白球; γ-氨基丁酸; 帕金森病; 癫痫
中图分类号: Q426; Q741.02

Motor control is one of the best-known functions of the basal ganglia. This fact is revealed by the spectrum of motor disorders originating from the basal ganglia, including Parkinson's disease, Huntington's disease and tardive dyskinesia. Within the basal ganglia, the globus pallidus has long been regarded merely as a relay station between the striatum and subthalamic nucleus in the so-called 'indirect pathway'[1]. However, as the widespread connections between the globus pallidus and other nuclei within and outside the basal ganglia have been revealed, this nucleus is now believed to be a critical and strategically placed component that can integrate the actions of the inhibitory inputs from the striatum and the excitatory inputs from the subthalamic nucleus, neocortex and thalamus[2-4]. In turn, the globus pallidus controls the activity of the whole basal ganglia[5].

By influencing the output of the basal ganglia, the globus pallidus plays a significant role in mediating movement in health and in diseased state. It is well known that the abnormal activity of the globus pallidus is involved in the manifestation of Parkinson's disease, which includes decreased activity and increased rhythmic burst firing[6]. In addition, the globus pallidus has also been implicated in the control of epileptic seizure[7,8] and drug-induced tardive dyskinesia [9,10]. GABA is the major neurotransmitter used in the globus pallidus. In order to fully understand the functions of the globus pallidus in the basal ganglia, one must have a detailed knowledge of the GABAergic neurotransmission in the globus pallidus. This brief review will first describe the nature of this GABA system, highlighting some of our efforts that combine morphological, electrophysiological and behavioral approaches. Then, the contemporary view of the role of the globus pallidus in some specific neurological disorders and the involvement of the GABA system will be described. In the course of discussion, some interesting but still unanswered questions will be mentioned.

GABAergic innervation of globus pallidus neurons

The globus pallidus receives GABAergic innervation mainly from the striatum and local axon collaterals. In the squirrel monkey, the local axon collaterals have been estimated to represent 10% of the terminals in contact with the perikarya of external globus pallidus neurons[11, 12]. Previous ultrastructural studies indicated that striatal terminals are located more distally on the dendritic trees, whereas pallidal terminals form a typical perineuronal nets covering the soma and proximal dendrites of adjacent neurons. Consistent with this anatomical observations, electrophysiological studies showed that pallidal stimulation induced inhibitory postsynaptic currents (IPSCs) not only with a shorter latency, but also a faster rise time and a different reversal potential compared with those obtained by striatal stimulation, suggesting that the pallidal inputs were evoked in more proximal regions of the neurons[13]. The effects of GABA are mediated by two receptor subtypes: $GABA_A$ and $GABA_B$ receptors. While the functions of the $GABA_A$ receptors in globus pallidus and other areas have been recognized for a long time, detailed characterization of the $GABA_B$ systems was enabled only relatively recently, following the cloning of the $GABA_B$ receptor[14]. As a result, much less had been known about the distributions and functions of the $GABA_B$ receptors in the globus pallidus.

$GABA_A$ neurotransmission

$GABA_A$ receptors are assembled from various subunits including α1~6, β1~4, γ1~3, δ, ε and ρ1~3, which are differentially expressed throughout the brain[15]. By using subunit-specific antibodies, an extremely diverse expression of $GABA_A$ receptor subunits in the globus pallidus has been demonstrated[16-19]. For example, previous studies indicated that there is distinct γ subunit labelling in the globus pallidus, subunits γ1 and γ3 staining were observed on the soma while subunits γ1 and γ2 were found on the dendrites[20,21]. Similarly, in human external globus pallidus, α3 subunit has been shown to be restricted to soma and proximal dendrites in high level, but not distal dendrites[22]. Most GABAergic symmetric synapses in globus pallidus are labeled for α1β2/3γ2[23]. Manipulation or change of the $GABA_A$ receptor system has been shown to affect motor functions. It has been revealed that intrapallidal injection of bicuculline into the

external globus pallidus in monkeys induced dyskinesia which is induced by hyperactivity of pallidal neurons[24,25]. Microinjection of $GABA_A$ receptor antagonist, bicuculline, into the globus pallidus had marked antiparkinsonian effects[26]. In MPTP or 6-OHDA-induced parkinsonism, the level of $GABA_A$ receptor in the globus pallidus was significantly decreased[27-29]. By using the specific α1 subunit antibody, Caruncho[30] reported that the expression of α1 subunits was reduced significantly in globus pallidus early after 6-OHDA lesion.

Benzodiazepine modulation site on $GABA_A$ receptor

In addition to GABA binding site, $GABA_A$ receptors contain many other binding sites that interact with a diverse range of compounds such as benzodiazepines, barbiturates, anesthetics and zinc. The benzodiazepine binding site within the $GABA_A$ receptor is a modulation site of significant clinical interest[31]. Upon binding to this site, benzodiazepine potentiates the GABA currents, leading to anxiolytic, anticonvulsant and sedative effects[32,33]. Since autoradiographic studies revealed a relatively high binding density for zolpidem in globus pallidus[34], the electrophysiological effects of zolpidem on globus pallidus neurons has been studied recently, in order to better understand the significance of this modulation site. Patch-clamp recordings from the *in vitro* brain slices showed that zolpidem enhances the action of GABA on postsynaptic $GABA_A$ receptors by prolonging the half decay time of IPSCs[35]. The effect of zolpidem is sensitive to the benzodiazepine antagonist flumazenil, which had no effect on its own. The *in vitro* effect of zolpidem implies that modulation of the benzodiazepine site *in vivo* would enhance the inhibition on pallidal neurons. In this regard, it has also

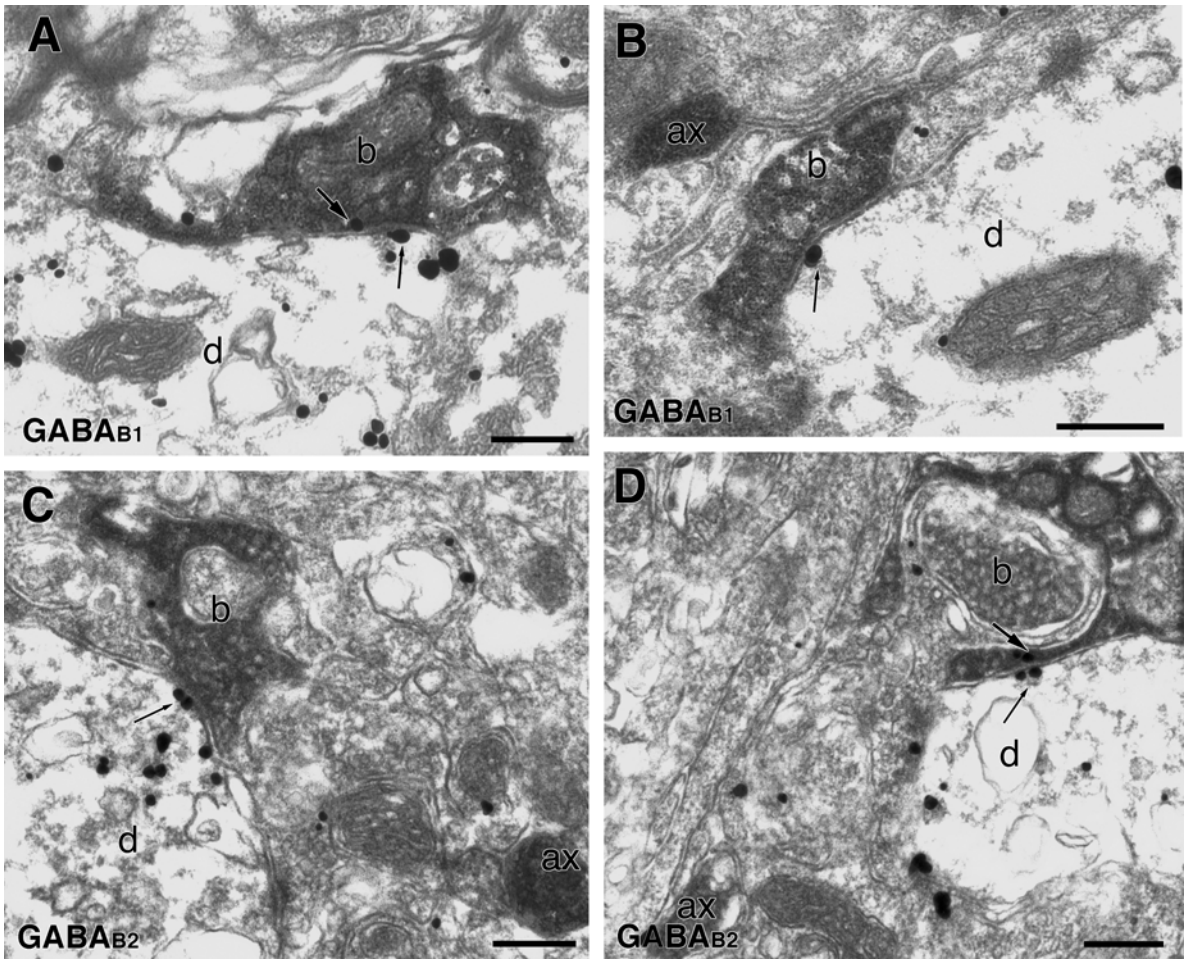

Fig. 1. Double immunolabelling for $GABA_{B1}$ or $GABA_{B2}$ (immunogold) and PHA-L (immunoperoxidase) in the globus pallidus. *A, B*: Presynaptic (large arrow) and postsynaptic (small arrows) $GABA_{B1}$ immunogold particles at symmetric synapses formed by striatal boutons (b) anterogradely labelled with PHA-L. *C, D*: Presynaptic (large arrow) and postsynaptic (small arrows) $GABA_{B2}$ immunogold particles at symmetric synapses formed by PHA-L labelled striatal boutons (b). PHA-L labelled axons (ax) were visible in *B, C* and *D*. b, bouton; d, dendrite. Scale bars, 0.25 μm.

been shown that microinjection of zolpidem into the globus pallidus resulted in ipsilateral rotation in the behaving animals[35], consistent with inhibitory action on pallidal neurons.

Subcellular localization of pre- and postsynaptic $GABA_B$ receptors

$GABA_B$ receptors belong to G-protein coupled receptors and are divided functionally into pre- and postsynaptic receptors. There is abundant evidence from autoradiographic studies that $GABA_B$ receptors are expressed in the globus pallidus[36,37]. More recent studies by *in situ* hybridization and immunocytochemistry revealed the regional and cellular distribution of $GABA_B$ receptor subunits and their splice variants in the globus pallidus[38-41]. Recently, by means of pre-embedding immunogold labeling, a detailed description of the subcellular localization of both $GABA_{B1}$ and $GABA_{B2}$ receptor subunits in rat globus pallidus[42] has been achieved. At symmetric synapses, including those formed by anterogradely-labelled striatopallidal terminals, most $GABA_{B1}$ and $GABA_{B2}$ immunogold labelling was found in the main body of pre- and postsynaptic sites (Fig.1). However, at asymmetric synapses, mainly formed by vesicular glutamate transporter 2 (VGLUT2)-positive terminals, most $GABA_{B1}$ and $GABA_{B2}$ subunits were found at the edges of both pre- and postsynaptic sites (Fig.2). These results demonstrate the existence of presynaptic

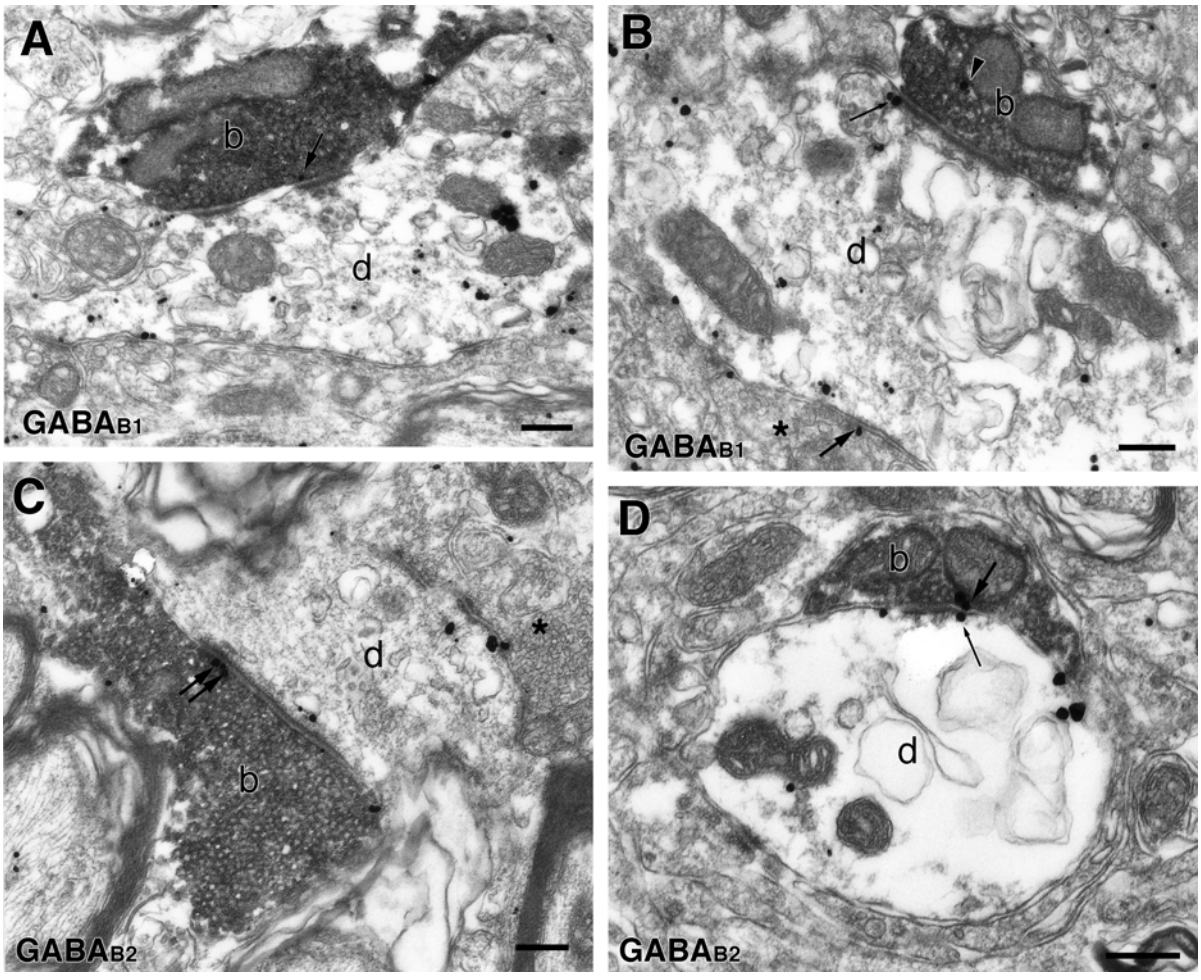

Fig. 2. Double immunolabelling for $GABA_{B1}$ or $GABA_{B2}$ (immunogold) and VGLUT2 (immunoperoxidase) in the globus pallidus. *A*, *B*: Presynaptic (large arrow) and postsynaptic (small arrow) $GABA_{B1}$ immunogold particles at asymmetric synapses formed by VGLUT2-labelled boutons (b). In *B*, a gold particle was located within the bouton (arrowhead). Note a presynaptic gold particle (large arrow) in the main body of a symmetric synapse formed by an unlabelled bouton (*). *C*, *D*: Presynaptic (large arrows) and postsynaptic (small arrow) $GABA_{B2}$ immunolabelling at asymmetric synapses formed by VGLUT2-labelled boutons (b). In *C*, the postsynaptic density was not prominent in the plane of this section, but subjunctional dense bodies were visible. Note an unlabelled bouton (*) formed symmetric synapse with the same dendrite (d). b, bouton; d, dendrite. Scale bars, 0.25 μm.

$GABA_B$ auto- and hetero- and postsynaptic $GABA_B$ receptors. This distribution pattern for $GABA_B$ receptors is markedly different from that observed for $GABA_A$ receptors in the globus pallidus, in which most $GABA_A$ receptors are located at symmetric synapses and rarely, if ever, occur in the presynaptic sites[22,23].

Functions of pre- and postsynaptic $GABA_B$ receptors

Consistent with the morphological observations, patch-clamp recordings revealed that the presynaptic $GABA_B$ auto-, hetero- and postsynaptic $GABA_B$ receptors are functional in globus pallidus. Thus, activation of presynaptic $GABA_B$ receptors inhibits the release of GABA as well as glutamate, while activation of postsynaptic $GABA_B$ receptors hyperpolarizes the pallidal neurons[43,44]. All these effects are sensitive to the potent and specific $GABA_B$ receptor antagonist CGP55845. Furthermore, activation of pallidal $GABA_B$ receptors by unilateral microinjection of the agonist baclofen induced ipsilateral turning in awake animals[44]. These results suggest that $GABA_B$ receptor in the globus pallidus plays an important role in the regulation of movement.

The morphological observation that some postsynaptic $GABA_B$ receptors were found at perisynaptic site of the glutamatergic synapses is intriguing. This observation raises the possibility that, in addition to activating pre- and postsynaptic $GABA_B$ receptors at GABAergic synapses, GABA released from GABA terminals may spill out to activate $GABA_B$ receptors at the glutamatergic synapses. Whether GABA does modulate glutamate transmission on the postsynaptic site, the mechanism involved and the significance of this process, are questions worth further pursuing.

Globus pallidus and neurological disorders

Parkinson's disease

Parkinson's disease is an age-related neurodegenerative disorder, characterized by resting tremor, rigidity and bradykinesia. Abnormal activity of the globus pallidus has been demonstrated to be involved in the manifestation of parkinsonian motor symptoms. In Parkinson's disease and its animal models, it is widely believed that depletion of dopamine in basal ganglia leads to overactivity of the striatopallidal pathway. This results in the abnormal hypoactivity of the globus pallidal neurons, and then the decreased GABAergic output of the globus pallidus contributes to excessive inhibition of basal ganglia targets, leading to akinesia and hypokinetic symptoms of Parkinson's disease[1,45]. Furthermore, in the absence of normal dopaminergic innervation, there is increased synchronized rhythmic discharge and burst firing in the globus pallidus, which may underlie resting tremor in parkinsonism[46,47]. Similar firing pattern in the globus pallidus neurons has also been reported in human suffering form Parkinson's disease[48]. Recent studies on the firing properties of neurons from organotypic culture of the globus pallidus-subthalamic nucleus network showed that the excitatory subthalamic nucleus and the inhibitory globus pallidus spontaneously produce synchronized oscillating bursts, and pallidal lesion abolishes this bursting[49]. However, from the *in vivo* brain, Magill *et al*.[50,51] reported that the rhythmic oscillatory activity in the subthalamic nucleus and the globus pallidus network in Parkinson's disease states might be driven by the cortex. More recently, Stanford[52] demonstrated that the bursting firing appears to arise due to the presence of intrinsic voltage- and sodium-dependent subthreshold membrane oscillations. Taken together, the intrinsic properties of the globus pallidus neurons and/or the extrinsic cortical inputs are important in the generation of these rhythmic firings. In addition, the firing variability of the globus pallidus neurons has been found to be associated with the severity of Parkinson's disease[53], together with a significant relationship between the neuronal activity and tremor as well as dyskinesia[47,48]. All these findings suggest that the modification of the firing patterns of the globus pallidus neurons constitutes the central origin of parkinsonian symptoms.

Recently, a therapeutic effect of the zolpidem on some groups of Parkinson's patients has been reported[54,55]. Quantitative autoradiography revealed that the binding for zolpidem is reduced significantly following lesions of the nigrastriatal tract[56]. Taken together these observations and the electrophysiological data described above, it is likely that the reduction of zolpidem binding in globus pallidus may reflect a compensatory mechanism for Parkinson's disease. The beneficial effect of zolpidem administration in some groups of Parkinson's patient may therefore derives from the interaction of its effects on various basal ganglia nuclei including the internal globus pallidus/entopeduncular nucleus and substantia nigra. Thus, more information derived from experiments is needed before one can fully understand the *in vivo* effects of zolpidem. Anyhow, this study suggests that the benzodiazepine binding site in globus pallidus is a possible drug target for the management of basal ganglia motor symptoms.

If GABA neurotransmission is important for the function of the basal ganglia, selective modulation of the GABA pathways by neuromodulator is expected to alter motor

function under normal or pathological conditions. 5-HT is a good example. It has been shown by Chadha et al[57] that administration of $5HT_{1B}$ agonist inhibits [^{3}H]-GABA release from rat globus pallidus and reverses akinesia following intrapallidal injection in reserpine-treated rat. This finding is consistent with the concept that disinhibition or excitation of the pallidal neurons would lead to decreased inhibitory output from the basal ganglia to target areas, and in line with our own observation that activation of presynaptic $5HT_{1B}$ receptors on striato-pallidal nerve terminals leads to decreased frequency of miniature IPSCs (unpublished observation).

Epileptic seizures

The basal ganglia are considered to be involved in the genesis and/or spread of epileptic activity. It has been demonstrated that the neocortical epileptiform activity is modulated by the basal ganglia[58-60]. Among the nuclei in basal ganglia, the substantia nigra pars reticulata has been shown to be involved in epilepsy control in different animal models of epilepsy through its GABAergic projections[61,62]. In the case of globus pallidus, early studies reported that the globus pallidus lesions prevented the generalized convulsions induced by cerebral cortex application of nicotine[63]. Electrical stimulation of the globus pallidus enhanced the neocortex interictal seizure activity, proceeding to generalized seizure activity[60,64]. Recently, Sawamura[65] reported that kainic acid injection into the globus pallidus induced transient epileptogenesis, presumably due to the transient enhancement of the globus pallidus-substantia nigra circuit or epileptic excitation of the cortex.

A link between epileptic seizures and GABA neurotransmission in the globus pallidus is suggested by the following findings. First, the globus pallidus displays a very high density of binding site for tiagabine[66], a selective blocker of the GAT-1 GABA transporter[67] and a drug used clinically to treat epilepsy. Second, systemic administration of tiagabine significantly increased the extracellular GABA levels in the globus pallidus[68]. Experiments had been performed to gauge the importance of this GABA uptake system on GABA neurotransmission in the globus pallidus, and to examine its involvement in experimental seizure. First, it was found that superfusion of tiagabine in globus pallidus slices significantly prolonged the decay kinetics and simultaneously decreased the frequency of $GABA_A$ receptor-mediated IPSCs. The latter effect was reversed by the $GABA_B$ receptor antagonist CGP55845, indicating the involvement of presynaptic $GABA_B$ receptors[69]. These data suggest that overspill of GABA, for instance, under intense presynaptic activity, could activate the presynaptic $GABA_B$ receptors on the terminals to maintain the excitability of the pallidal neurons. At the same time, there is prolonged inhibition on postsynaptic $GABA_A$ receptors. Behavioral studies showed that intrapallidal microinjection of tiagabine caused ipsilateral rotation, arguing that prolonged action of GABA on GABA receptors would dominate over its inhibitory effect on GABA release[69]. Second, intrapallidal administration of tiagabine could inhibit significantly the occurrence of pentylenetetrazol (PTZ)-induced tonic seizure significantly[65]. The additional finding that balcofen microinjection into the globus pallidus completely suppresses PTZ-induced tonic seizure suggests that $GABA_B$ receptors play a significant role in modulating the threshold of seizure activity[70].

Concluding remarks

The importance of the globus pallidus in the basal ganglia circuit is emerging in recent years. By combining morphological, electrophysiological and behavioral studies, our laboratory has contributed some novel information on GABA neurotransmission in globus pallidus and its involvement in neurological disorders. However, the functioning of the globus pallidus also depends on other neurotransmitter/neuromodulator systems including, notably, glutamate, dopamine, enkephalins, neurotensin and 5HT. The functions and interplay between this rich repertoire of neuroactive compounds must be elucidated in detail before one could better understand the role of the globus pallidus.

REFERENCES

1 Albin RL, Young AB, Penny JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989; 12:366-375.

2 Naito A, Kita H. The cortico-pallidal projection in the rat: an anterograde tracing study with biotinylated dextran amine. Brain Res 1994; 653:251-257.

3 Bolam JP, Hanley JJ, Booth PA, Bevan MD. Synaptic organisation of the basal ganglia. J Anat 2000; 196:527-542.

4 Mouroux M, Hassani OK, Feger J. Electrophysiological and Fos immunohistochemical evidence for the excitatory nature of the parafascicular projection to the globus pallidus. Neurosci 1997; 81:387-397.

5 Bolam JP, Smith Y. The striatum and the globus pallidus send convergent synaptic inputs into single cells in the entopeduncular nucleus of the rat: a double anterograde labelling study combined with post-embedding immunocytochemistry for GABA. J Comp Neurol 1992; 321:456-476.

6 Filion M, Tremblay L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced

parkinsonism. Brain Res 1991; 547:142-151.

7 André V, Pineau N, Motte J, Marescauz C, Nehlig A. Mapping of neuronal networks underlying generalized seizures induced by increasing doses of pentylenetetrazol in the immature and adult rat: a c-Fos mmunohistochemical study. Eur J Neurosci 1998; 10:2094-2106.

8 Deransart C, Riban V, LLBT, Hechler V, Marescauz C, Depaulis A. Evidence for the involvement of the pallidum in the modulation of seizures in a genetic model of absence epilepsy in the rat. Neurosci Lett 1999; 265:131-134.

9 McCormick SE, Stoessl AJ. Blockade of nigra and pallidal opioid receptors suppresses vacuous chewing movements in a rodent model of tardive dyskinesia. Neuroscience 2002; 112:851-859.

10 McCormick SE, Stoessl AJ. Central administration of the neurotensin receptor antagonist SR48692 attenuates vacuous chewing movements in a rodent model of tardive dyskinesia. Neuroscience 2003; 119:547-555.

11 Shink E, Smith Y. Differential synaptic innervation of neurons in the internal and external segments of the globus pallidus by the GABA- and glutamate-containing terminals in the squirrel monkey. J Comp Neurol 1995; 358:119-141.

12 Sato F, Lavallee P, Levesque M, Parent A. Single-axon tracing study of neurons of the external segment of the globus pallidus in primate. J Comp Neurol 2000; 417:17-31.

13 Kita H. Neostriatal and globus pallidus stimulation induced inhibitory postsynaptic potentials in entopeduncular neurons in rat brain slice preparations. Neuroscience 2001; 105:871-879.

14 Bettler B, Kaupmann K, Bowery N. $GABA_B$ receptors: drugs meet clones. Curr Opin Neurobiol 1998; 8:345-350.

15 Rudolph U, Crestani F, Mohler H. GABA(A) receptor subtypes: dissecting their pharmacological functions. Trends Pharmacol Sci 2001; 22:188-194.

16 Zhang JH, Sato M, Tohyama M. Different postnatal development profiles of neurons containing distinct $GABA_A$ receptor beta subunit mRNAs in the rat forebrain. J Comp Neurol 1991; 308:586-613.

17 Wisden W, Laurie DJ, Monyer H, Seeburg PH. The distribution of 13 $GABA_A$ receptor subunit mRNAs in the rat brain, I. Telencephalon , diencephalons, mesencephalon. J Neurosci 1992; 12:1040-1062.

18 Henderson Z. Expression of $GABA_A$ receptor subunit messenger RNA in non-cholinergic neurons of the rat basal forebrain. Neuroscience 1995; 65:1077-1086.

19 Peng Z, Hauer B, Mihalek RM, Homanics GE, Sieghart W, Olsen RW, Houser CR. GABA(A) receptor changes in delta subunit-deficient mice: altered expression of alpha4 and gamma2 subunits in the forebrain. J Comp Neurol 2002;446:179-197.

20 Pirker S, Schwarzer C, Wieselthaler A, Sieghart W, Sperk G. $GABA_A$ receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. Neuroscience 2000;101:815-850.

21 Schwarzer C, Berresheim U, Pirker S, Wieselthaler A, Fuchs K, Sieghart W, Sperk G. Distribution of the major γ-aminobutyric $acid_A$ receptor subunits in the basal ganglia and associated limbic brain areas of the adult rat. J Comp Neurol 2001;433:526-549.

22 Waldvogel HJ, Kubota Y, Fritschy J, Mohler H, Faull RL. Regional and cellular localization of $GABA_A$ receptor subunits in the human basal ganglia: An autoradiographic and immunohistochemical study. J Comp Neurol 1999; 415:313-340.

23 Somogyi P, Fritschy JM, Benke D, Roberts JD, Sieghart W. The gamma 2 subunit of the $GABA_A$ receptor is concentrated in synaptic junctions containing the alpha 1 and beta 2/3 subunits in hippocampus, cerebellum and globus pallidus. Neuropharmacology 1996;35:1425-1444.

24 Crossman AR, Mitchell IJ, Sambrook MA, Jackson A. Chorea and myoclonus in the monkey induced by gamma-aminobutyric acid antagonist in the lentiform complex. Brain 1988;111:1211-1233.

25 Matsumura M, Tremblay L, Richard H, Filion M. Activity of pallidal neurons in the monkey during dyskinesia induced by injection of bicuculline in the external pallidum. Neuroscience 1995; 65:59-70.

26 Maneuf YP, Mitchell IJ, Crossman AR, Brotchie JM. On the role of enkephalin cotransmission in the GABAergic striatal efferents to the globus pallidus. Exp Neurol 1994; 125:65-71.

27 Pan HS, Penney JB, Young AB. Gamma-aminobutyric acid and benzodiazepine receptor changes induced by unilateral 6-hydroxydopamine lesions of the medial forebrain bundle. J Neurochem 1985; 45:1396-1404.

28 Yu TS, Wang SD, Liu JC, Yin HS. Changes in the gene expression of GABA-A receptor alpha1 and alpha2 subunits and metabotropic glutamate receptor 5 in the basal ganglia of the rats with unilateral 6-hydroxydopamine lesion and embryonic mesencephalic grafts. Exp Neurol 2001; 168:231-241.

29 Schroeder JA, Schneider JS. GABA-A and mu-opioid receptor binding in the globus pallidus and endopeduncular nucleus of animals symptomatic for and recovered from experimental Parkinsonism. Brain Res 2002; 947:284-289.

30 Caruncho HJ, Liste I, Rozas G, Lopez-Martin E, Guerra MJ, Labandeira-Garcia JL. Time course of striatal, pallidal and thalamic alpha 1, alpha 2 and beta 2/3 $GABA_A$ receptor subunit changes induced by unilateral 6-OHDA lesion of the nigrostriatal pathway. Brain Res Mol Brain Res 1997; 48:243-250.

31 Barnard EA, Skolinick P, Olsen RW, Mohler H, Sieghart W, Biggio G, Braestrup C, Bateson AN, Langer SZ. International union pharmacology. XV. Subtypes of γ-aminobutyric $acid_A$ receptors: Classification on the basis of subunit structure and receptor function. Pharmacol Rev 1998; 50:291-313.

32 Lavoie AM, Twyman RE. Direct evidence for diazepam modulation of $GABA_A$ receptor microscopic affinity. Neuropharmacology 1996; 35:1383-1392.

33 Mellor JR, Randall AD. Frequency-dependent actions of benzodiazepines on $GABA_A$ receptors in cultured murine cerebellar granule cells. J Physiol 1997; 503:353-369.

34 Duncan GE, Breese GR, Criswell H.E, Mccown TJ, Herbert JS, Devaud L, Morrow AL. Distribution of [^{3}H] zolpidem binding sites in relation to messenger RNA encoding the α1, β2 and γ2 subunits of $GABA_A$ receptors in rat brain. Neuroscience 1995;64: 1113-1128.

35 Chen L, Chan SCY, Yung WH. Electrophysiological and behavioral effects of zolpidem in rat globus pallidus. Exp Neurol 2004; 186;212-220.

36 Bowery N, Hudson AL, Price GW. $GABA_A$ and $GABA_B$ receptor site distribution in the rat central nervous system. Neuroscience 1987;20:365-383.

37 Chu DMC, Albin RL. Young AB, Penney JB. Distribution and kinetics of $GABA_B$ binding sites in rat central nervous system: a quantitative autoradiographic study. Neuroscience 1990; 34: 341-357.

38 Benke D, Honer M, Michel C, Bettler B, Mohler H. γ-aminobutyric acid type B receptor splice variant proteins GBR 1a and GBR 1b are both associated with GBR 2 in situ and display differential regional and subcellular distribution. J Biol Chem 1999;274: 27323-27330.

39 Charara A, Heilman C, Levey AI, Smith Y. Pre- and postsynaptic localization of $GABA_B$ receptors in the basal ganglia in monkeys. Neuroscience 2000; 95:127-140.

40 Smith Y, Charara A, Hanson JE, Paquet M, Levey AI. $GABA_B$ and group I metabotropic glutamate receptors in the striatopallidal complex in primates. J Anat 2000; 196: 555-576.

41 Waldvogel HJ, Billinton A, White JH, Emson PC, Faull RL. Comparative cellular distribution of $GABA_A$ and $GABA_B$ receptors in the human basal ganglia: immunohistochemical colocalization of the alpha 1 subunit of the $GABA_A$ receptor, and the GABABR1 and GABABR2 receptor subunits. J Comp Neurol 2004; 470:339-356.

42 Chen L, Boyes J, Yung WH, Bolam JP. Subcellular localization of $GABA_B$ receptor subunits in rat globus pallidus. J Comp Neurol 2004; 474:340-352.

43 Chan SCY, Yung KKL, Yung WH. Pre- and postsynaptic distribution of $GABA_B$ receptors in rat globus pallidus revealed by immunocytochemistry and electrophysiology. Soc Neurosci Abstr 2000; 25:622.17.

44 Chen L, Chan SCY, Yung WH. Rotational behavior and electrophysiological effects induced by $GABA_B$ receptor activation in rat globus pallidus. Neuroscience 2002; 114:417-425.

45 Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 1996;6:751-758.

46 Nini A, Feingold A, Slovin H, Bergman H. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. J Neurophysiol 1995;74:1800-1805.

47 Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. J Neurosci 2000; 20:8559-8571.

48 Magnin M, Morel A, Jeanmonod D. Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. Neuroscience 2000;96:549-564.

49 Plenz D, Kitai ST. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. Nature 1999; 400:677-682.

50 Magill PJ, Bolam JP, Bevan MD. Relationship of activity in the subthalamic nucleus-globus pallidus network to cortical electroencephalogram. J Neurosci 2000;20:820-833.

51 Magill PJ, Bolam JP, Bevan MD. Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. Neuroscience 2001;106:313-330.

52 Stanford IM. Independent neuronal oscillators of the rat globus pallidus. J Neurophysiol 2003; 89:1713-1717.

53 El-Deredy W, Branston NM, Samuel M, Schrag A, Rothwell JC, Thomas DG, Quinn NP. Firing patterns of pallidal cells in parkinsonian patients correlate with their pre-pallidotomy clinical scores. Neuroreport 2000;11:3413-3418.

54 Ruzicka E, Roth J, Jech R, Busek P. Subhypnotic doses of zolpidem oppose dopaminergic-induced dyskinesia in Parkinson'S disease. Mov Disord 2000;15:734-735.

55 Farver DK, Khan MH. Zolpidem for antipsychotic-induced Parkinsonism. Ann Pharmacother 2001;35:435-437.

56 Chadha A, Howell O, Atack JR, Sur C, Duty S. Changes in [^{3}H] zolpidem and [^{3}H]Ro 15-1788 binding in rat globus pallidus and substantia nigra pars reticulata following a nigrostriatal tract lesion. Brain Res 2000; 862:280-283.

57 Chadha A, Sur C, Atack J, Duty S. The $5\text{-}HT_{1B}$ receptor agonist, CP-93129, inhibits [^{3}H]-GABA release from rat globus pallidus slices and reverses akinesia following intrapallidal injection in the reserpine-treated rat. Br J Pharmacol 2000;130:1927-1932.

58 Olpe HR, Schellenberg H, Koella WP. Rotational behaviour induced in rats by intranigral application of GABA-related drugs and GABA antagonists. Eur J Phamacol 1977;45:291-294.

59 Garant DS, Gale K. Lesions of substantia nigra protect against experimentally induced seizures. Brain Res 1983;273:156-161.

60 Makulkin RF, Novytskyi SA, Korniienko TV. Role of globus pallidus in mechanisms of antiepileptic caudate-cortical effects. Fiziolog Zhur 1992;38:3-9.

61 Iadarola MJ, Gale K. Substantia nigra: site of anti-convulsant activity mediated by gamma-aminobutyric acid. Science 1982; 218:1237-1240.

62 Depaulis A, Vergnes M, Marescaux C. Endogenous control of epilepsy: the nigral inhibitory system. Prog Neurobiol 1994; 42:

33-52.

63 Hayashi T. A physiological study of epileptic seizures following cortical stimulation in animals and its application to human clinics. Jpn J Physiol 1952; 3:46-64.

64 Sabatino M, Grava nte G, Ferraro G, Savatteri V, La Grutta V. Inhibitory control by substantia nigra of generalized epilepsy in the cat. Epilepsy Res 1988; 2:380-386.

65 Sawamura A, Hashizume K, Tanaka T. Electrophysiological, behavioral and metabolical features of globus pallidus seizures induced by a microinjection of kainic acid in rats. Brain Res 2002; 935:1-8.

66 Suzdak PD, Foged C, Andersen KE. Quantitative autoradiographic characterization of the binding of [^{3}H]tiagabine (NNC 05-328) to the GABA uptake carrier. Brain Res 1994; 647:231-241.

67 Borden LA. GABA transporter heterogeneity: pharmacology and cellular localization. Neurochem Int 1996; 29:335-356.

68 Fink-Jensen A, Suzdak PD, Swedberg MDB, Judge ME, Hansen L, Nielsen PG. The γ-aminobutyric acid (GABA) uptake inhibitor, tiagabine, increases extracellular brain levels of GABA in awake rats. Eur J Pharmacol 1992; 220:197-201.

69 Chen L, Yung WH. Effects of GABA-uptake inhibitor tiagabine in rat globus pallidus. Exp Brain Res 2003; 152:263-269.

70 Chen L, Chan YS, Yung WH. $GABA_B$ receptor activation in the rat globus pallidus potently suppresses pentylenetetrazol-induced tonic seizure. J Biomed Sci 2004; 11:457-464.