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13. ABSTRACT (Maximum 200 Words) Huntington's disease (HD) is a neurodegenerative condition characterized by a loss of projection neurons in the striatum. Although various hypotheses have been proposed to explain the mechanisms that underlie the striatal neuronal death, excitotoxicity still deserves major interest. Recent findings indicate that changes in the genotype of the kainate receptor subunit, GluR6, are associated with variation in the age of onset of HD, which implicates the kainate receptors in the pathogenesis of HD and other basal ganglia disorders. The localization and functions of kainate receptors in the basal ganglia remain unknown. We, therefore, propose to use state-of-the-art electron microscope techniques and in vitro whole cell patch clamp recording techniques to test a series of hypotheses that will help to elucidate the localization and understand better the role of kainate receptors in the striatum and the globus pallidus. The results of these studies will provide a strong basis for studying the potential mechanisms by which these receptors participate in normal and abnormal basal ganglia functions. Moreover, they will help the development of novel therapeutic strategies aimed at targeting pre-synaptic kainate receptors in HD and other basal ganglia disorders.				
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INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by the death of striatal neurons. Chorea is the most common involuntary movement in patients who suffer of HD. This could be combined with cognitive and memory deficits at a later stage of the disease. The HD mutation was identified in 1993 as an unstable expansion of CAG (trinucleotide) repeats on the gene which encodes the protein "Huntingtin" on chromosome 4. In more than 60% of HD patients, there is a high degree of inverse correlation between the number of CAG repeats and the age of onset of the disease or degree of striatal degeneration (Vonsatell and DiFiglia, 1998). However, about 15% of the HD cases of which the age of onset cannot be explained by the CAG repeats, were found to have mutations in the gene encoding for the GluR6 subunit of the glutamatergic kainate receptor (Rubinztin et al., 1997; MacDonald et al., 1999); which highlight the importance of those receptors in the pathogenesis of the striatum in HD. Although the existence of kainate receptors has long been established, little is known about their functions and distribution in the central nervous system. Previous data obtained in our laboratory showed that the kainate receptor subunits GluR6/7 are strikingly enriched in the monkey striatum but, in contrast to other ionotropic glutamate receptors which are found almost exclusively at postsynaptic sites, the GluR6/7 kainate receptor subunits are strongly expressed pre-synaptically in glutamatergic terminals (Charara et al., 1999).

Based on these data, the rationale of experiments proposed originally in this application was that altered functions of pre-synaptic kainate receptors, due to mutations of the GluR6 subunit gene, may induce excessive glutamate release in the striatum, thereby, excitotoxic cell death of striatal projection neurons in Huntington's disease. Before addressing such an issue, a prerequisite is to characterize in detail the synaptic localization of kainate receptors in the striatum. We, therefore, proposed to use a combination of various anatomical and immunocytochemical approaches at the electron microscopic level to elucidate the pattern of subcellular and subsynaptic localization of GluR6 and KA2 subunits of the kainate receptors in the monkey striatum.

BODY

- **SPECIFIC AIMS**

The original proposal comprised the following specific aims:

Hypothesis I: The GluR6/7 kainate receptor subunits are strongly expressed by cortical glutamatergic terminals in the monkey striatum.

Specific Aim #1: To elucidate the subsynaptic localization of GluR6/7 immunoreactivity in the striatum using immunoperoxidase and immunogold techniques at the electron microscope level.

Specific Aim #2: To demonstrate that GluR6/7-immunoreactive terminals arise from the cerebral cortex using a combination of tract-tracing techniques and pre-embedding immunogold methods.

Hypothesis II: The pre-synaptic kainate receptors are more frequently encountered in those regions of the striatum that are more sensitive to degeneration in HD.

Specific Aim #3: To compare the relative frequency of GluR6/7-immunoreactive terminals between the rostral and caudal portions of the putamen and between the tail, body and head of the caudate nucleus.

Hypothesis III: The terminals that express kainate receptor subunits form synaptic contacts preferentially with the "indirect D2-containing" striatofugal neurons which degenerate first in HD.

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Specific Aim #4: To compare the relative frequency of synaptic contacts established by GluR6/7-immunoreactive terminals with "direct D1-containing" and "indirect D2-containing" striatofugal neurons.

Hypothesis IV: The GluR6/7 and KA2 kainate receptor subunits are expressed at pre-and post-synaptic sites in the striatum.

Specific Aim #5: To compare the subsynaptic localization of KA2 and GluR6/7 immunoreactivity in different regions of the striatum. .

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As mentioned in our 2002-2003 report, the specific aims listed above have been addressed and that data presented in various meetings, book chapters and peer-reviewed manuscripts. Over the past year we have used the remaining funds in the grant to expand our studies of kainate receptor function and localization to the globus pallidus, a key component of the basal ganglia circuitry known to play a critical role in the regulation and synchronization of activity in the basal ganglia under both normal and pathological conditions. In fact, the functional interactions between the globus pallidus and the subthalamic nucleus are considered as the "pacemaker" of the basal ganglia circuitry (Plenz and Kitai, 1999). The lack of knowledge of kainate receptor functions in this brain region combined with the fact that glutamate receptor antagonists have beneficial effects in Parkinson's disease (Starr, 1995), most likely through modulation of the overactive excitatory synaptic transmission at subthalamopallidal synapses, set the stage for a deeper understanding of kainate receptor functions in this brain region. In the following account, we will summarize the main findings obtained through this series of studies over the past year and briefly discuss their relevance to better understand the substrate that underlies synaptic transmission in the basal ganglia circuitry and the development of new therapeutic approaches for basal ganglia diseases. The first part of this report was mentioned in our 2002-2003 progress report, but I feel important to repeat it here so that the reviewers get a full picture of the series of studies that have been performed in this project

I. Localization and Functions of Kainate Receptors in the Globus Pallidus

Based on the findings collected in monkeys showing the abundance of pre- and post-synaptic kainate receptors in GPe and GPi (Kane-Jackson and Smith, 2003), we decided to undertake a series of *in vitro* slice electrophysiological studies to address the role of kainate receptor activation on pallidal neurons using whole cell patch clamp recording techniques in rats.

To make sure that the pattern of subcellular localization of kainate receptors described in monkeys is valid in rats, we carried out an electron microscopic analysis of GluR6/7 immunoreactivity in the rat globus pallidus. Although data have not yet been quantified, it appears that the main features of kainate receptor distribution in GPe and GPi are seen in the rodent GP, ie there is heavy GluR6/7 postsynaptic labeling associated with proximal and distal dendritic shafts as well as pre-synaptic labeling in putative GABAergic and glutamatergic axon terminals (Jin and Smith, 2003, 2004).

We have made significant progress in testing the role of postsynaptic kainate receptor activation on GP neuronal activity. In brief, these studies are performed as follows: Fourteen- to 17 days old Sprague Dawley rats are used in these experiments. After decapitation, brains are removed and quickly submerged in the ice-cold oxygenated sucrose buffer. Coronal slices (300 μ M) are made on a vibratome in ice-cold oxygenated sucrose buffer. Slices are then stored at room

temperature in a chamber containing artificial cerebrospinal fluid (ACSF) at pH 7.35-7.45 with 95% O₂, 5% CO₂ bubbling through it. A slice is then transferred to a recording chamber and perfused with room temperature oxygenated ACSF. GP neurons are visualized with a 40X water immersion lens using a Hoffman modulation contrast microscope. Whole cell electrodes are pulled on a vertical patch pipette puller and filled with an intracellular patch solution. Biocytin at 1% is included in the intracellular solution to view the morphology and location of GP neurons. The drugs used to activate kainate receptors (Kainate, domoate) and block AMPA receptors (SYM 2206, GYKI52466, NBQX) are bath applied. TTX (0.5 μ M) and DAP5 (NMDA receptor antagonist-25 μ M) are perfused at least 5 min before experiments. Data are acquired and analyzed using pCLAMP software. Results are presented as mean \pm S.D., and significance evaluated by Student's *t*-test.

Two main groups of GP neurons have been categorized electrophysiologically (Types I and II-Cooper and Stanford, 2000). The type II neurons account for almost 80-90% of the total population of GP neurons, thereby, represent the major subtype of neurons that will be examined in our study. These neurons possess two main cardinal features, both of which are recorded at the beginning of our experiments: (1) A sag in membrane potential during a hyperpolarizing current injection in current clamp that corresponds to a time- and voltage-dependent inward current *I_h*, (2) Anodal breaks after a hyperpolarizing step, suggesting the presence of a low-threshold-activated calcium current *I_t*. These neurons also show high input resistance and spontaneous activity at rest (Figure 1A). In an attempt to correlate the morphology and relative position of GP neurons with their electrophysiological profiles, recorded neurons are filled with biocytin (Figure 1B).

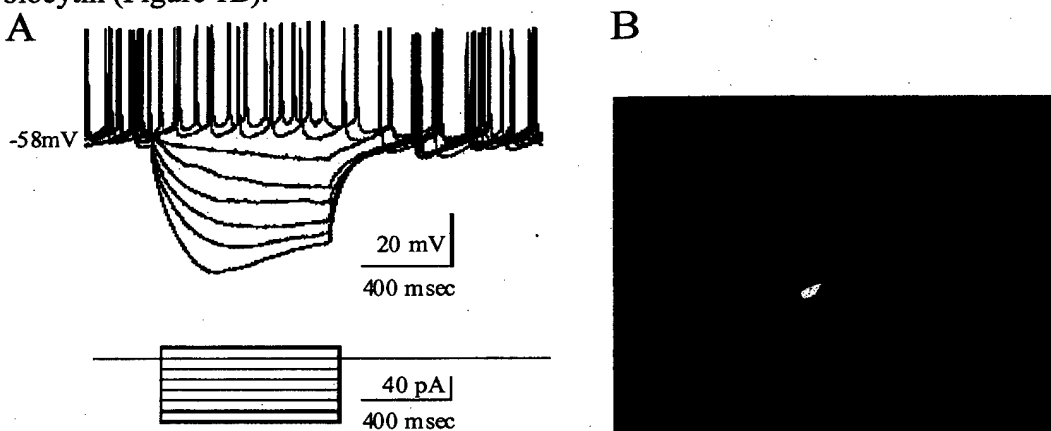


Figure 1: Electrophysiological (A) and morphological (B) characteristics of type II GP neurons

Figure 2 shows evidence for the expression of functional kainate receptors on GP neurons. Panel A illustrates inward currents evoked by 5 μ M kainate in two GP neurons in the presence of AMPAR antagonists SYM 2206 (100 μ M) and NBQX (1 μ M). Antagonists were bath applied for 3 min before exposure to kainate. TTX (0.5 μ M) was bath applied for at least 5 min before the beginning of all experiments. D-AP5 (NMDA antagonist; 25 μ M) was bath applied throughout the experiments. In panel B, we show the mean amplitude of inward current activated by 5 μ M kainate in the presence of SYM 2206 (100 μ M) (mean \pm S.D, n=6 cells) and NBQX (1 μ M) (mean \pm S.D, n=7 cells). These data demonstrate that kainate receptor activation induces inward current in rat GP neurons suggesting the presence of functional postsynaptic kainate receptors in GP.

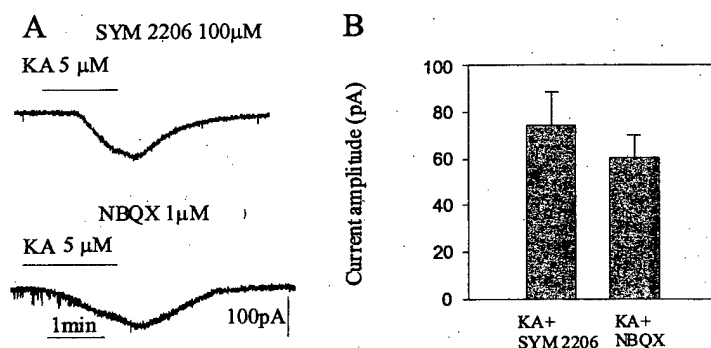


Figure 2: Functional Expression of Postsynaptic Kainate Receptors in rat GP

Further evidence for functional kainate receptors in GP are shown in figure 3. Panels A and B are current-clamp recordings from three GP neurons in the presence of TTX ($0.5 \mu\text{M}$) and DAP5 ($25 \mu\text{M}$). In the presence of AMPAR antagonists GYKI 52466 ($30 \mu\text{M}$) (first trace) and NBQX ($1 \mu\text{M}$) (second trace), bath application of kainate ($5 \mu\text{M}$) depolarizes neuronal membrane of two cells. In panel B, bath application of Domoate ($0.5 \mu\text{M}$), a kainate receptor agonist, depolarizes the cell in the presence of an AMPA receptors antagonist GYKI (52466) ($30 \mu\text{M}$). Finally, panel C shows the mean amplitude of depolarization activated by $5 \mu\text{M}$ kainate in the presence of GYKI 52466 ($30 \mu\text{M}$) (mean \pm S.D, $n=6$ cells), NBQX ($1 \mu\text{M}$) (mean \pm S.D, $n=10$ cells) and by $0.5 \mu\text{M}$ domoate in the presence of GYKI 52466 ($30 \mu\text{M}$) (mean \pm S.D, $n=5$ cells). These findings provide strong evidence that selective kainate receptor activation depolarizes GP

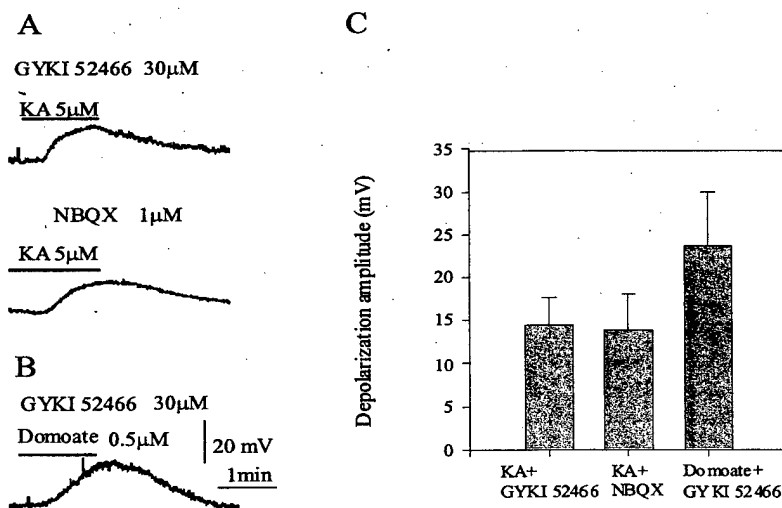


Figure 3: Kainate receptor activation depolarizes GP neurons

The next set of data will demonstrate that post-synaptic KARs can be synaptically activated in GP neurons and that KARs act as pre-synaptic auto-receptors to modulate glutamatergic transmission in the rat GP. To reach this goal, evoked excitatory post-synaptic currents (EPSCs) were recorded from GP neurons by stimulating the internal capsule (IC) with a bipolar tungsten electrode. Based on previous studies from our laboratory and others, stimulation of the internal capsule medial and ventral to the GP is the most efficient approach to impale ascending glutamatergic projections from the subthalamic nucleus (Poisik et al., 2003). Although additional minor glutamatergic inputs from the thalamus, cortex and brainstem may have also been recruited by these stimulations, it is well established that the bulk of glutamatergic innervation to the GP arises from the STN (Smith et al., 1998).

In figure 4 we show that stimulation of internal capsule can elicit a small synaptic component that is resistant to GYKI 52466, but sensitive to CNQX (AMPA/KARs antagonist), suggesting that this component is not mediated by AMPA receptors activation. Panel C illustrates that this small EPSC has slower activation and deactivation kinetics than those mediated by AMPA receptors, a typical feature for KARs in other brain regions (Huettnner, 2003). Finally, the bar graph in B compares the data collected on the amplitude of EPSCs between control conditions and after bath application of 100 μ M GYKI 52466 or 50 μ M CNQX.

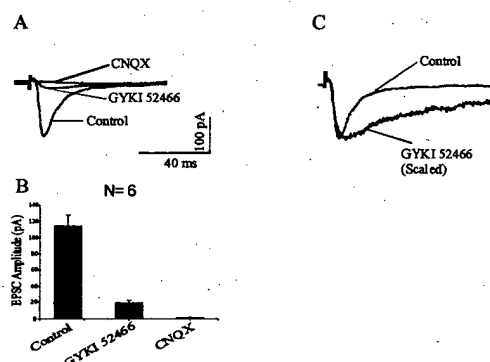


Figure 4: Kainate receptor-mediated excitatory postsynaptic current (EPSCs) in GP neurons

*In figure 5, we demonstrate that KARs application reduces AMPA-mediated EPSCs in the rat GP. Panel A illustrates that averaged, stimulus-evoked AMPA-mediated EPSCs are depressed by 1 μ M KA. The time course of this inhibition is shown in panel B, while panel C provides a summary bar graph showing the effect of bath application of KA (0.1-1 μ M) on AMPA-EPSC amplitude as percent of control \pm SEM. For this series of experiments, all recordings were done in presence of 50 μ M D-AP5, and 50 μ M bicuculline (BIC). Numbers in parentheses indicate the number of cells tested under each different concentration; significant difference from control: * $P < 0.001$ and ** $P < 0.001$.*

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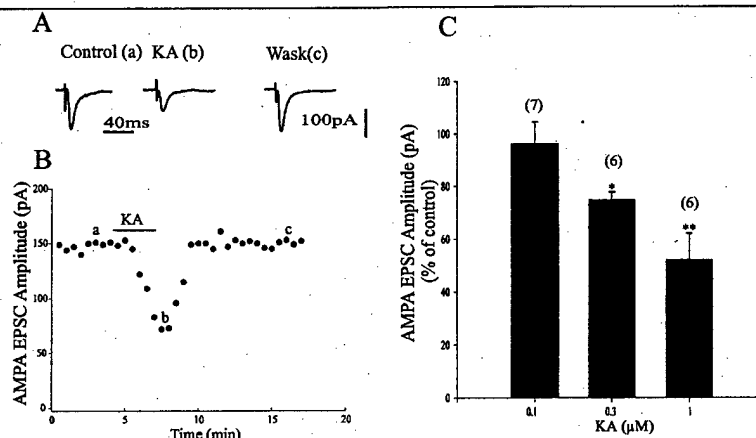


Figure 5: Kainate receptors activation reduces evoked AMPA mediated-EPSCs in GP neurons

In figure 6, we provide some evidence that KARs application also reduces NMDA-mediated EPSCs. To isolate NMDA-mediated EPSCs, all recordings were done in presence of 100 μM GYKI 52466 (AMPA antagonist) and 50 μM bicuculline (BIC-GABA_A receptor antagonist). Panel A shows averaged, stimulus evoked NMDA-EPSCs reduced by bath application of 1 μM KA while panel B demonstrates that this KAR-mediated inhibition is blocked by CNQX. The time course of the KAR-mediated inhibition of NMDA EPSCs is shown in C. In D, a bar graph summarizes the effect of bath application of 1 μM KA on NMDA-EPSC in the absence and presence of CNQX and the effect of 50 μM D-AP5 on NMDA EPSC as percent of control ± SEM. Numbers in parentheses indicate the number of cells tested under each condition; significant difference from control: * $P < 0.001$ and ** $P < 0.001$.

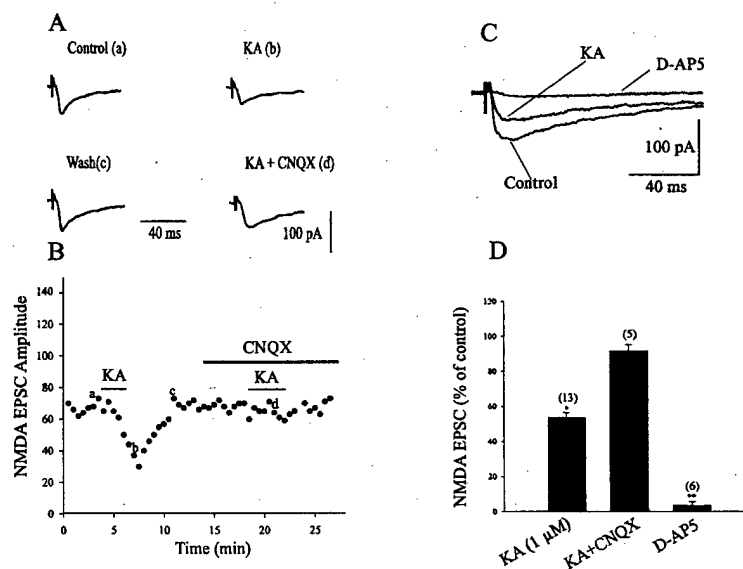


Figure 6: Kainate receptors activation reduces evoked NMDA mediated-EPSCs in GP neurons

Figure 7 demonstrates that KAR-mediated reduction of EPSCs is mediated by pre-synaptic mechanisms. To address this issue, we tested the effects of KA on paired-pulse facilitation (PPF)

of evoked EPSCs, an experimental approach widely used to assess neurotransmitter pre-synaptic effects in the CNS (Zucker and Regehr, 2002). In brief, two stimuli of the internal capsule were paired with an interstimulus interval of 40-50 ms. The ratio of *peak 2/peak1* in the presence and absence of KA was calculated. Evidence for pre-synaptic functions relies on the fact that paired pulse facilitation (PPF) ratio of EPSCs is increased following kainate application. For instance, the top part of panel A shows that kainate has a stronger effect on the first of two EPSCs, while the bottom traces show the paired-pulse response after scaling to the first EPSC. Panel B illustrates the time course of the increase in PPF of AMPA EPSCs in response to 1 μ M KA. Finally, the bar graph in C summarizes the PPF ratio of AMPA EPSCs, expressed as mean ratio of $P2/P1 \pm$ SEM, in the absence or presence of KA. * $p < 0.001$. The ratio $P2/P1$ is significantly higher after kainate application suggesting pre-synaptic inhibitory effects of KARs activation on glutamatergic transmission in the rat GP.

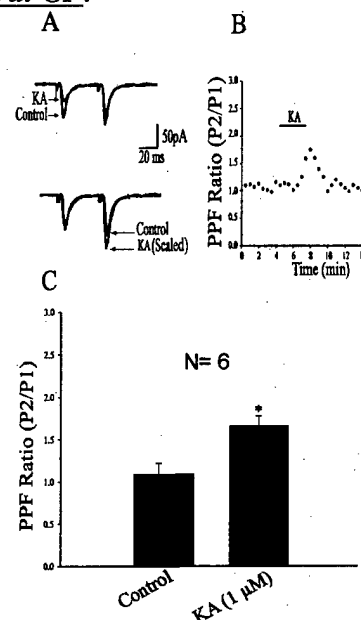


Figure 7: Kainate receptors activation increases EPSC paired-pulse facilitation in the GP

One of the particular features of pre-synaptic KARs-mediated effects that have been shown in the hippocampus is the indirect involvement of G-protein-coupled receptors (Huettner, 2003). To determine whether such receptors were also involved in mediating pre-synaptic KARs effects in the GP, we bath applied various G-protein-coupled receptor antagonists prior to kainate application and measured the impact of these drugs on the kainate-induced inhibition of AMPA EPSCs in GP neurons. In figure 8, we demonstrate that the pre-synaptic functions of KARs on AMPA-mediated EPSCs are not affected by the presence of various G protein-coupled receptor antagonists ruling out the involvement of these receptors in the KAR-mediated pre-synaptic effects in the rat GP. The bar graph below summarizes the effect of 1 μ M KA on AMPA-EPSC, expressed as percent of control \pm SEM, in the presence of mGluR antagonists (1mM MCPG and 100 μ M CPPG), the GABAB antagonist (20 μ M SCH 50911), the adenosine receptor antagonist (10 μ M CGS 15943), or dopamine receptor antagonists (10 μ M SCH 23390 and 10 μ M sulpiride). All the recordings were done in the presence of 50 μ M of D-AP5 and 50 μ M BIC.

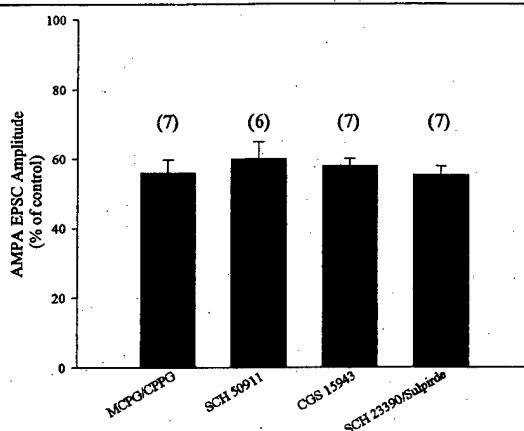
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Figure 8: Kainate receptors activation inhibits evoked AMPA-EPSCs in the presence of mGluRs, GABAB, Adenosine, or Dopamine receptors antagonists

- **Future Experiments**

1. To test the effects of KARs activation on inhibitory synaptic transmission in the rat GP
2. To characterize in more detail the subsynaptic localization of GluR6/7 KARs subunits in the rat GP using pre-and post-embedding immunogold techniques.

KEY RESEARCH ACCOMPLISHMENTS

The main findings obtained in this project over the past year are summarized as follows:

- Pre- and post-synaptic kainate receptors are strongly expressed in the monkey and rat globus pallidus. Pre-synaptic receptors are associated with both GABAergic and glutamatergic terminals suggesting that their activation may lead to auto- or hetero-regulation of neurotransmitters release.
- Kainate receptor activation evokes EPSC's that are insensitive to AMPA or NMDA receptor antagonists in rat GP neurons, which suggest the functional expression of postsynaptic kainate receptors in pallidal neurons.
- Kainate receptors activation depolarizes GP neurons in the presence of TTX and AMPA/NMDA receptor antagonists. The importance of these data regarding basal ganglia pathophysiology of various movement disorders including HD is the potential development of novel drugs that could selectively target GluR6-containing kainate receptors and modulate glutamatergic and GABAergic neurotransmission in the globus pallidus.
- Kainate receptors activation elicits a non-AMPA/non-NMDA small synaptic component that has slower deactivation kinetics than AMPA receptors. These data provide evidence for synaptically activated post-synaptic KARs in GP neurons.
- Kainate receptors activation reduces excitatory synaptic transmission through pre-synaptic mechanisms in the rat GP. These findings provide novel targets whereby kainate receptor agonists may modulate glutamatergic transmission from the overactive STN-GP synapse in Parkinson's disease.

- The pre-synaptic effects of KARs on glutamatergic transmission are not affected by the blockade of various G protein-coupled receptors in the rat GP. This demonstrates a high degree of specificity in KAR-mediated pre-synaptic effects on glutamate release in the GP.

REPORTABLE OUTCOMES

- Kane-Jackson, R. and Y. Smith (2003) Pre-synaptic kainate receptors in GABAergic and glutamatergic axon terminals in the monkey globus pallidus. *Neuroscience* 122: 285-289.
- Smith, Y., D. Raju, J.-F. Pare and M. Sidibe (2004) The thalamostriatal system: A highly specific network of the basal ganglia circuitry. *Trends in Neurosci.* (in press).
- Jin, XT and Y. Smith (2003) Ultrastructural localization and functions of kainate receptors in the rat globus pallidus. *Soc for Neurosci Abstr* 705.7.
- Smith, Y., D. Raju and K.J. Ciombor (2003) Subcellular localization of neuronal and glial glutamate transporters in the monkey striatopallidal complex. *Soc. for Neurosci. Abstr* 917.2.
- Jin, XT and Y. Smith (2004) Kainate Receptors Mediate Excitatory Synaptic Transmission In The Rat Globus Pallidus. *Proc. IBAGS VIII meeting, Crieff, Scotland, p.XX.*

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