

怎样在国际权威杂志上发表科学论文

鲁迅 Lu Xun
(1881-1936)

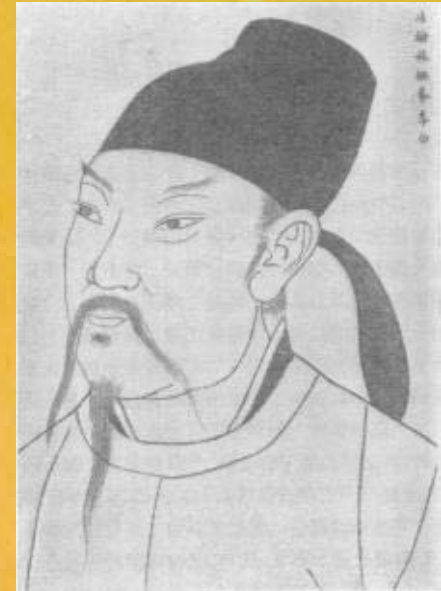


The father of modern
Chinese literatures

Bai Lu
鲁白



李白 Li Bai
(701-762)

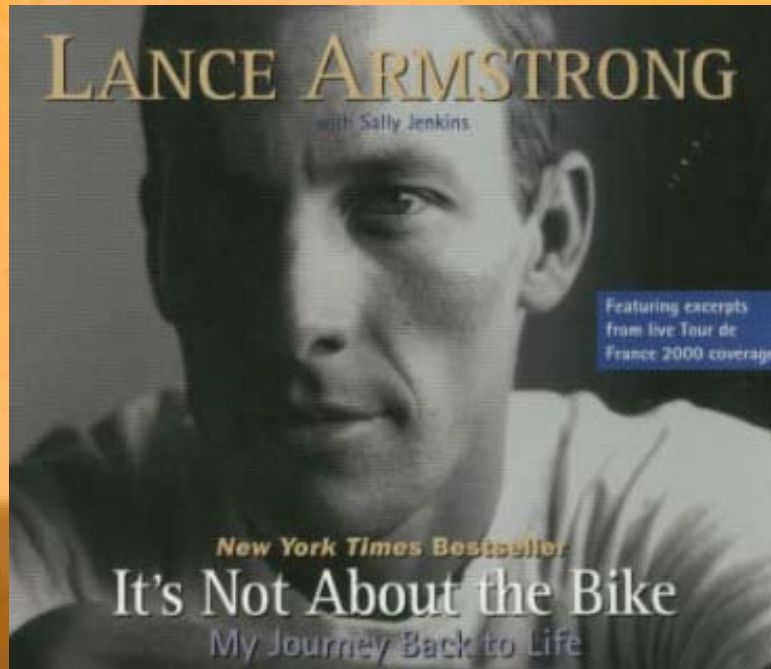


The most influential
poet in Chinese history

2003 research articles

1. M. F. Egan, M. Kojima, J. H. Callicott, T. E. Goldberg, B. S. Kolachana, E. Zaisteve, A. Bertolino, B. Gold, D. Goldman, M. Dean, **B. Lu**, (co-corresponding author) and D. R. Weinberger. (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257-269.
2. L. Ma, Y. -Z. Huang, J. Valtschanoff, L. Feng, **B. Lu**, W. Xiong, R. Weinberg, L. Mei. (2003) Ligand-dependent recruitment of the neuregulin signaling complex into neuronal lipid rafts. J. Neurosci. 23, 3164-3175.
3. J. Wang, C. -Q. Chen, **B. Lu**, and C. -P. Wu. (2003) GDNF acutely potentiates Ca²⁺ channels and excitatory synaptic transmission in midbrain dopaminergic neurons. NeuroSignals 12, 78-88.
4. M. Miura, S. Gronthos, M. Zhao, **B. Lu**, L. W. Fisher, P. G. Robey, and S. Shi (2003) SHED: Stem cells from human exfoliated deciduous teeth. Proc. Natl. Acad. Sci. USA 100, 5807-5812.
5. Y. X. Zhou, M. Zhao, K. Shimazu, K. Sakata, D. Li, C. -X. Deng, **B. Lu**. (2003) Impairments in cerebellum Purkinje cells and motor function in mice lacking Smad4 in the central nervous system. J. Biol. Chem. 278, 42313 - 42320.
6. J. Du, L. Feng, E. Zaitsev, H. S. Je, X. Liu, and **B. Lu**. (2003) Activity- and tyrosine kinase-dependent facilitation of TrkB receptor internalization in hippocampal neurons. J Cell Biol. In press.
7. Z. G. Luo, H. -S. Je, F. Yang, W. C. Xiong, **B. Lu**, and L. Mei (2003) Activation of geranylgeranyltransferase is essential for Agrin-induced AChR clustering. Neuron In press.
8. S. X. Bamji, K. Shimazu, N. Kimes, J. Huelsken, W. Birchmeier, **B. Lu**, L. F. Reichardt. (2003) Regulation of presynaptic assembly and maintenance by β -catenin. Neuron In Press.
9. F. Yang, X. He, J. Russell, and **B. Lu**. (2003) Ca²⁺ influx independent transmitter release mediated by mitochondrial Na⁺-Ca²⁺ exchanger and protein kinase C. J. Cell Biol. In press.

What Is the Purpose of Doing Research?



Publish or perish

1 Nature = 10 JBC

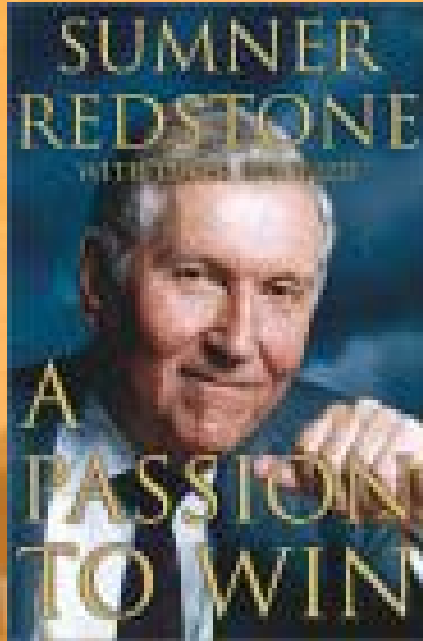
- **It is not about the number of papers**
- **It is not about the impact factor of the papers**
- **It is not about the Nobel Prize**

RESOURCE

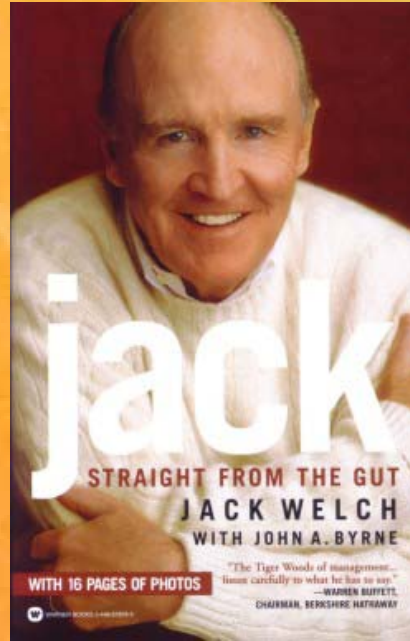
INITIATION

FIRST

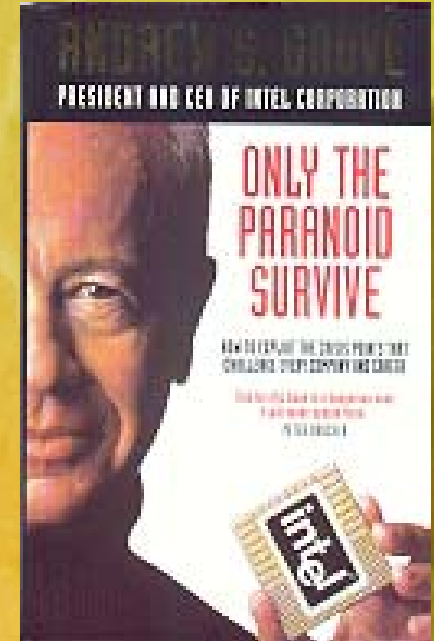
Basic Elements for Basic Research



Passion



6 Sigma



Silver bullet test

Good Research Is the Key

- **My English is not good**
- **They are biased against Chinese (foreigners)**
- 人家没做过 ≠ 你就要做
- 这是新的 ≠ 这是好的

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What Is a First-Class Paper/Research?

- **Major advance in a classic field**

干细胞是如何分化成特定组织细胞的，胆固醇在人体的正常功用

- **New techniques and methods that can be widely used**

人类基因组研究中的自动测序技术, PCR, Patch clamp, Ca²⁺ Imaging, GFP

- **Discoveries with obvious practical implications**

AIDS virus receptor 的发现, 老年痴呆症基因的发现

- **Conceptual breakthrough, novel ideas**

神经营养因子可以促进学习记忆, RNA干扰现象

- **Challenge to traditional views, break dogma**

脑内有可分裂的神经干细胞, 打破了传统观念

- **Opening up new area, cross board**

“细胞凋亡”现象的发现, 开辟了新的科研领域

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What Is a Mediocre Paper/Research?

- **Horizontal growth**

I made the discovery in rats, you find the same in cat.

- **Filling gaps**

EGF activates JNK which is known to induce c-Jun expression. You show that EFG enhances c-Jun expression.

- **Working out details**

I found NO induces the production of cGMP, you work out dose response and time course.

- **Support existing idea, “me too”**

EGF-R endocytosis requires dynamin, PDGF-R too.

- **Follow up**

CREB binds to CRE. Working out CRE sequence.

- **Incomplete study, preliminary**

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How to Read Scientific Papers?

- **The Gilbert way**
- **Keep these in mind when you read**
 - **What is the major question addressed in this paper?**
 - **Is this question important and why?**
 - **What are the approaches used in this paper, and whether they are adequate for the questions?**
 - **What are the novel idea or using innovative approaches?**
 - **What is the concept coming out of this paper?**
 - **Do the results presented support this new concept?**
- **Weekly reading of CNS titles**
- **Critical, appreciative**

What Makes Good Science?

- **Important and significant**
- **Original and innovative**
- **Solid and rigorous**
- **Unique and unusual**

Novelty is essential

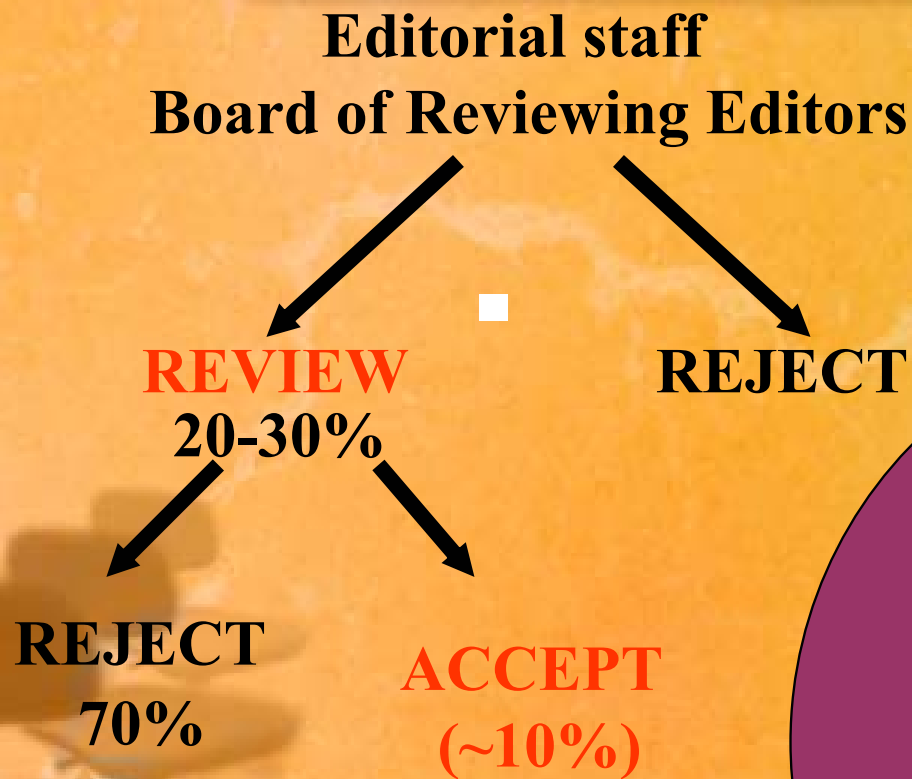
语不惊人誓不休

RESOURCE

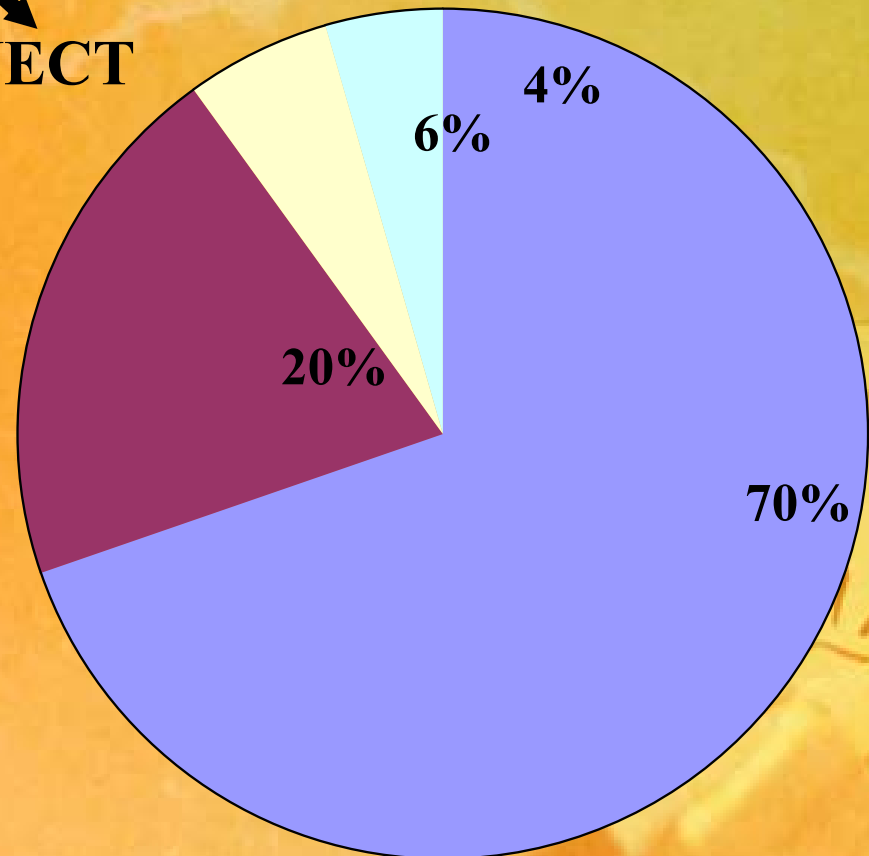
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The evaluation process



- rejected before in-depth review
- rejected after in-depth review
- published (biological)
- published (physical sci)



Should your paper go to *CNS*?

- **Is it your best ever?**
- **Will it have a big impact?**
- **Does it interest scientists in other fields?**
- **Does it overturn conventional wisdom?**
- **Work that represents a large step forward**
 - solution to long-standing problem
 - different way of thinking
 - broad implications

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What helps:

- **Convincing data**
- **Appropriate controls**
- **Careful presentation**
- **Consideration of all viable alternatives**

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What doesn't help

- **The minimal publishable unit.**
- **Excessive or unfounded speculation**
- **Repeat examples of a known phenomenon**
- **Insufficient advance over previously published work**

Editorial Policies of Different Journals

- **Cell/Neuron/Immunity**

Editorial board does a lot of reviews. Editors discuss and decide

- **Nature sister journals**

Editors discuss and decide

- **Science**

Space meeting, board of review editors

- **PNAS**

Communicate, contribute, Track C

- **Others**

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Procedures for High Profile Journals

You

- Pre-submission inquiry
- Submit/cover letter
- Initial screen
- Send out for reviews
- Reject/soft reject/revise
- Rebuttal
- Revise again
- Accept

Editors

Initial screening

- significance/importance
- general interests
- unusual/surprise

Selection of reviewers

- suggest reviewers, may take one
- friends may not always support you
- “not to review” always honored
- “soft” and “harsh” reviewers

Cover Letters

- **main findings**
- **significance**
- **suggested reviewers**
- **“not to review” list**
- **who have read**

RESOURCE

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Dear Editor,

We would like to submit the enclosed manuscript entitled "GDNF Acutely Modulates Neuronal Excitability and A-type Potassium Channels in Midbrain Dopaminergic Neurons", which we wish to be considered for publication in *Nature Neuroscience*.

GDNF has long been thought to be a potent neurotrophic factor for the survival of midbrain dopaminergic neurons, which are degenerated in Parkinson's disease. In this paper, we report an unexpected, acute effect of GDNF on A-type potassium channels, leading to a potentiation of neuronal excitability, in the dopaminergic neurons in culture as well as in adult brain slices. Further, we show that GDNF regulates the K⁺ channels through a mechanism that involves activation of MAP kinase. Thus, this study has revealed, for the first time, an acute modulation of ion channels by GDNF. **Our findings challenge the classic view of GDNF as a long-term survival factor for midbrain dopaminergic neurons, and suggest that the normal function of GDNF is to regulate neuronal excitability, and consequently dopamine release. These results may also have implications in the treatment of Parkinson's disease.**

Due to a direct competition and conflict of interest, we request that Drs. XXX of Harvard Univ., and YY of Yale Univ. not be considered as reviewers. With thanks for your consideration, I am

Sincerely yours,

Dear Editor,

We would like to submit the enclosed manuscript entitled "Ca²⁺-binding protein frequenin mediates GDNF-induced potentiation of Ca²⁺ channels and transmitter release", which we wish to be considered for publication in **Neuron**.

We believe that two aspects of this manuscript will make it interesting to general readers of **Neuron**. First, we report that GDNF has a long-term regulatory effect on neurotransmitter release at the neuromuscular synapses. **This provides the first physiological evidence for a role of this new family of neurotrophic factors in functional synaptic transmission.** Second, we show that the GDNF effect is mediated by enhancing the expression of the Ca²⁺-binding protein frequenin. Further, GDNF and frequenin facilitate synaptic transmission by enhancing Ca²⁺ channel activity, leading to an enhancement of Ca²⁺ influx. **Thus, this study has identified, for the first time, a molecular target that mediates the long-term, synaptic action of a neurotrophic factor. Our findings may also have general implications in the cell biology of neurotransmitter release.**

Dear Editor:

Enclosed are copies of a manuscript entitled "BDNF and NT-4/5 Promote the Development of Long-Term Potentiation in the Hippocampus", which we wish to be considered for publication in **Nature**. As you know, there is a great deal of interest and excitement recently in understanding the role of neurotrophins in synapse development and plasticity. Our manuscript provides, for the first time, the physiological evidence that neurotrophins regulate long-term potentiation (LTP). The main point of the paper is that the neurotrophins BDNF and NT-4 induce an earlier appearance of LTP in developing hippocampus. In contrast to recent Science article by XX's group, we (and several other LTP groups) did not see that BDNF enhance basal synaptic transmission in adult hippocampus. However, we found that in adult hippocampus, inhibition of BDNF/TrkB activity attenuated LTP, and weak tetanus that normally cannot induce LTP produced enduring LTP. These findings may have implications in the basic mechanism for regulation of synapse development and long-term modulation of synaptic efficacy.

Because of the rather competitive nature of the field and the important implication of our findings, we have not yet presented this work in any public forum. However, confidential discussion with several prominent neuroscientists such as 111 and 222 have generated tremendous excitement. Thus, we feel that this work is of general interest and is suitable for publication in **Nature**. We would like to suggest Drs. aaa of Yale Univ., bbb of Harvard Medical School, and ccc of Univ. of California-Berkeley, as reviewers for this manuscript. Due to a direct competition and conflict of interest, we request that Dr. XX and YY. not be considered as reviewers.

Thank you very much for your consideration.

Titles

- **Important/significant**
- **Unexpected/unusual**
- **Function**
- **Mechanisms**
- **Simple**
- **Straight forward**
- **Specific**

SynCAM, a synaptic adhesion molecule that drives synapse assembly

Inhibition of Retroviral RNA production by ZAP, a CCCH-type Zinc finger protein

Protein phosphatase 1 is a molecular constraint on learning and memory

E3 ubiquitin ligase that recognizes sugar chain

Molecular evolution of FOXP2, a gene involved in speech and language

Single cell gene profiling

Structure, mechanism, and regulation of the Neurospora plasma membrane H⁺

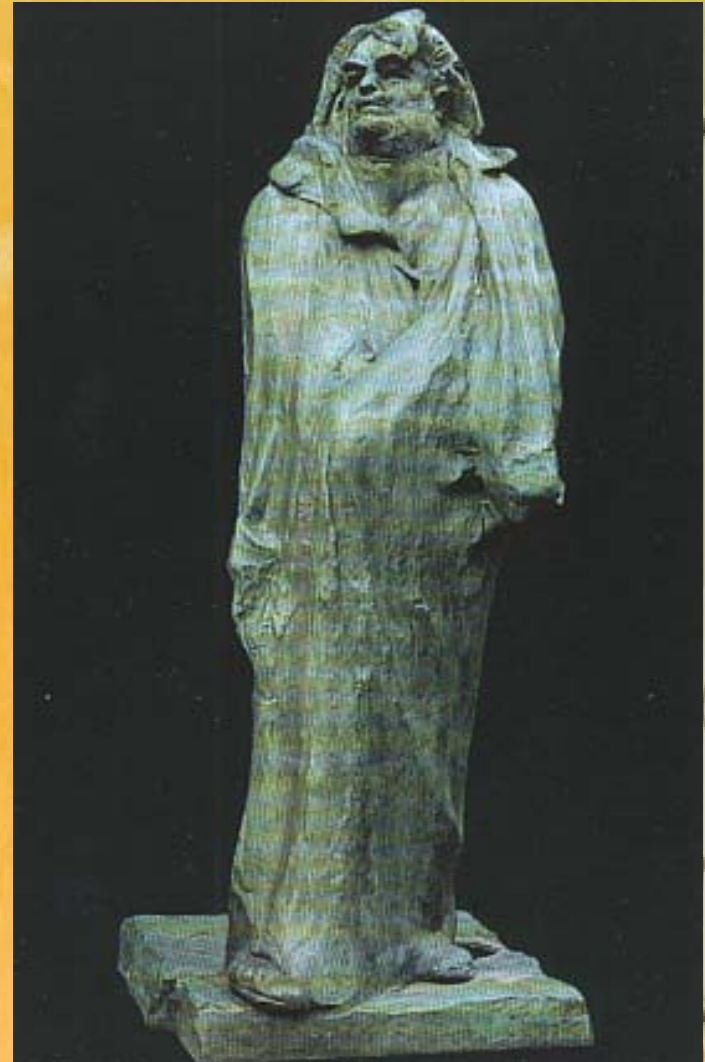
Modulation of postendocytic sorting of G-protein-coupled receptors

Distinct molecular mechanism for initiating TRAF6 signaling

Identification of...; Role of...; Involvement of...

Sequence of writing

- **Abstract**
- **Figure layout**
- **Figure legend**
- **Material and methods**
- **Results**
- **Introduction**
- **Discussion**



Abstract

- **Rationale** “...remain unknown”; “...To determine...”
- **Summary statement** “Here we show...”
- **Body** Don't go into details; don't use many special terms
- **Significance** Must point out, but don't claim too much

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

----- J. D. Watson and F. H. C. Crick

Formation of the normal mammalian cerebral cortex requires the migration of GABAergic inhibitory interneurons from an extracortical origin, the lateral ganglionic eminence (LGE). Mechanisms guiding the migratory direction of these neurons, or other neurons in the neocortex, are not well understood. We have used an explant assay to study GABAergic neuronal migration and found that the ventricular zone (VZ) of the LGE is repulsive to GABAergic neurons. Furthermore, the secreted protein Slit is a chemorepellent guiding the migratory direction of GABAergic neurons, and blockade of endogenous Slit signaling inhibits the repulsive activity in the VZ. These results have revealed a cellular source of guidance for GABAergic neurons, demonstrated a molecular cue important for cortical development, and suggested a guidance mechanism for the migration of extracortical neurons into the neocortex.

Neuronal responses to brain-derived neurotrophic factor (BDNF) are initiated by the activation of the receptor TrkB tyrosine kinase (1). In this study we examined whether cholesterol- and glycolipid-rich microdomains, lipid rafts, provide a functional platform for BDNF-dependent signal transduction (2). Using primary culture of cortical neurons, we demonstrated that TrkB was dramatically translocated into lipid rafts in BDNF-dependent manner (3). This translocation was blocked by the pharmacological effect of general Trk inhibitors, indicating that TrkB activation is required for the translocation mechanism. We also showed that BDNF and TrkB-FL were both concentrated in lipid rafts during development of cerebral cortex, concomitant with that of synaptic vesicle proteins, including soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins and synaptophysin (4). This result, together with the findings that BDNF stimulation caused translocation of synaptophysin into lipid rafts (5) and that BDNF-enhanced glutamate release and exocytosis were both attenuated by depletion of cholesterol from the cell surface with methyl-beta-cyclodextrin (MCD), indicates that lipid rafts are essential for BDNF regulation of neurotransmitter release (6).

Brain-derived neurotrophic factor (BDNF) plays an important role in synaptic plasticity but the underlying signaling mechanisms remain unknown. Here we show that BDNF rapidly recruits full-length TrkB (TrkB-FL) receptor into cholesterol-rich lipid rafts from non-raft regions of neuronal plasma membranes. Truncated TrkB lacking the intracellular kinase domain was not translocated, and the translocation of TrkB-FL was blocked by Trk inhibitors, suggesting a role for TrkB tyrosine kinase in the translocation. Disruption of lipid rafts by depleting cholesterol from the cell surface blocked BDNF-dependent TrkB translocation. Disruption of rafts also prevented the potentiating effect of BDNF on transmitter release in cultured neurons, as well as that on synaptic response to tetanus in hippocampal slices. In contrast, lipid rafts are not required for BDNF regulation of neuronal survival. Thus, ligand-induced TrkB translocation into lipid rafts may represent a selective signaling mechanism for synaptic modulation by BDNF in the CNS.

A calcium-independent but voltage-dependent secretion (CIVDS) coexists with the calcium dependent *exocytosis* in dorsal root ganglion (DRG) neurons (1). Here we have investigated the CIVDS-coupled *endocytosis* (2). Using optical and membrane capacitance measurements, we show that, in calcium-free medium, either step depolarization or a train of action-potential-like stimulation induce a novel form of rapid endocytosis, which occurs immediately after the CIVDS. Surprisingly, this calcium-independent endocytosis is strongly dependent on the stimulation frequency (3). H7 suppress the endocytosis, while PKA agonists enhance it (4). Biochemical experiments show that membrane depolarization directly up-regulate PKA in DRG neurons. Our experiments also showed that the frequency dependency of CIVDS-RE is dynamin-independent (5). Thus, our data indicate that neuronal activity modulates a rapid endocytosis via a Ca^{2+} - and dynamin-independent phosphorylation-dependent manner in DRG neurons (6).

Synaptic vesicle endocytosis is believed to require Ca^{2+} and the GTPase dynamin. Here we report a novel form of rapid endocytosis (RE) that is independent of Ca^{2+} and dynamin in dorsal root ganglion (DRG) neurons. Using FM dye labeling and membrane capacitance measurements, we show that both step depolarization and repetitive stimulation induce RE in Ca^{2+} -free medium. RE also occurs in the presence of a Ca^{2+} chelator (BAPTA). Inhibition of dynamin function by three different approaches does not affect RE. Protein kinase A (PKA) inhibitors suppress the endocytosis, while PKA activators enhance it. Biochemical experiments demonstrate that membrane depolarization directly up-regulated PKA activity. These results reveal a Ca^{2+} - and dynamin-independent form of endocytosis that is controlled by neuronal activity and PKA-dependent phosphorylation in DRG neurons.

Introduction

- **What do we know about the subjects? Only relevant information should be provided; don't write a review**
- **What we don't know**
- **Rationale Why you want to do it? Don't repeat abstract**
- **Approaches How you are going to do it.**
- **Significance Make an appeal to general readers**

In this study we have examined the role of chromogranins CGA and CGB, in dense-core secretory granule biogenesis. We analyzed the effect of specific depletion of either CGA or CGB, using an antisense RNA strategy, on dense-core secretory granule formation in rat pheochromocytoma (PC12) cells, a model neuroendocrine cell line. We also expressed CGA in a pituitary cell line (6T3) lacking the regulated secretory pathway and nonendocrine fibroblast cells to determine its effect on induction of dense-core secretory granule biogenesis and regulated secretion. Finally, we determined whether CGA could regulate the level of other secretory granule proteins in neuroendocrine and endocrine cells, PC12 and 6T3. These studies identified CGA as a key regulator of dense-core secretory granule biogenesis and storage of other granule proteins in endocrine cells.

Results

- **Logic Need to explain the rationales in the beginning**
- **Connections between paragraphs Don't jump**

Previous studies have shown that membrane depolarization-triggered Ca^{2+} influx through L-type VSCCs induces an increase in *BDNF* mRNA expression in cultured neurons (Zafra et al., 1990 ; Ghosh et al., 1994). This increase in *BDNF* mRNA could be the result of increased transcription initiation, or increased *BDNF* mRNA stability, or both. To determine if membrane depolarization stimulates *BDNF* transcription, we....

Given the finding that Ca^{2+} influx through L-type VSCCs induces *BDNF* transcription, experiments were carried out to determine which of the four *BDNF* promoters is capable of mediating a Ca^{2+} response. As described above, the rat *BDNF* gene consists of four distinct 5' exons each driven by a specific promoter and each spliced to a common 3' exon that encodes the BDNF protein. Since each of the four primary *BDNF* transcripts can be polyadenylated at one of two sites, a total of eight *BDNF* transcripts are generated. In principle, the eight transcripts can be distinguished by Northern blotting using 5'exon-specific probes, since each of the four 5' exon probes should detect a short and a long *BDNF* transcript. By identifying the specific *BDNF* mRNAs induced upon Ca^{2+} influx through L-type VSCCs, it should be possible to identify which of the four *BDNF* promoters is Ca^{2+} responsive, since the Ca^{2+} -responsive promoter(s) would be expected to be located just 5' of the initiation site of *BDNF* mRNA synthesis.

Discussion

- **Summary of main findings**
- **Papers that support you, but don't downgrade your novelty**
- **Pitfalls and why**
- **Significance. Don't speculate too much**

There are three main findings in the present study. First, we report a GDNF-induced long-term facilitation of neurotransmitter release at the neuromuscular synapses. Second, we show that the effect of GDNF on synaptic transmission is mediated by an increase in the expression of the Ca²⁺-binding protein frequenin. Finally, we demonstrate that GDNF and frequenin facilitate synaptic transmission by enhancing N-type Ca²⁺ channel activation, leading to an enhancement of Ca²⁺ influx. Thus, this study has identified, for the first time, a molecular target that mediates the long-term, synaptic action of a neurotrophic factor. Our findings may also provide new insights into the regulatory mechanisms of neurotransmitter release.

The results in the present study may have a number of implications in the cell biology of tyrosine kinase receptors. First, we report the ... To our knowledge, this is the first demonstration for ... Thus, our results suggest a cross-talk between Ca²⁺ and tyrosine kinase signaling pathways. Second, the present study reveals an important regulatory effect of ... It will be interesting to determine whether ... Finally, we show that ... Xxx ... Taken together, these results suggest a general role of tyrosine kinase in the endocytosis of growth factor receptors.

Invite thorough critique

- **Run your own review process first**
 - **ask feedback from**
 - **someone in your own specialty**
 - **someone in an unrelated specialty**
 - **a good editor for the English language**
- **Assess both research and presentation**

Common reasons for rejection

- **Belongs in a specialized journal**
- **Too small of an advance over previously published work**
- **Unconvincing data**
- **Observations without interpretations**
- **Interpretations without data**

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Revise your paper

- **Be calm about reviewers criticisms.**
- **Always make editor your friend**
- **Never argue with reviewers**
- **Try to do everything that reviewers ask**
- **Seize the opportunity when reviewers make mistakes**

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When your paper gets rejected — without review

Dear Editor,

I would appreciate if you could reconsider to review our manuscript, “111.” We feel strongly that this is an important subject that touches one of the central dogmas in neuroscience: xxx. It is also very timely, given the publication of the paper by X and Y entitled “222” in the latest issue of Nature Neuroscience. In this paper, the authors xxx. They claimed that xxx. When a paper this provocative has been published by a high profile journal like Nature Neuroscience, we believe that it is worth giving a benefit of doubts. It will be helpful if there are papers that consider other alternative interpretations, or attempt to replicate in the same or different systems.

We have observed similar xxx, but we have a completely different interpretation. We found that 1) xxx 2) xxx; 3) xxx. Thus, our paper raises the possibility that xxx reported by X and Y were due to xxx. Specifically, we would like you to consider the following two issues: First, X and Y used aaa, while we used bbb. ssssssss. Second, ccc used by X and Y may not be so specific.

In addition to the drastically different opinions regarding xxx, we feel that our findings on xxx is also significant in yyy and will be of interests to general readers of Nature Neuroscience. We therefore did not write our paper to directly challenge the paper by X and Y. However, we will be willing to re-write the paper in ways you think that will help debate on this important issue.

When your paper gets rejected — with review

Dear Dr. xx,

We received with some surprise your letter of November 4, rejecting this manuscript on the basis of one reviewer's opinion which you "found persuasive". We wish to indicate our dissatisfaction with this reviewer's comments, which appear to ignore the new experiments submitted as part of the revised manuscript.

This reviewer states: "111." This was precisely the point of the xxx experiment which indicated that there were no such deficits.

This reviewer further states: "222." Again, this is a mystifying statement as the detailed rebuttal accompanying this letter described the xxx. Did the reviewer not understand that xxx?

Finally, concerning the proposal for a xxx experiment, we believe that you and this reviewer already know that xxx. Thus, it is impossible to do such experiments.

While we recognize that the final decision is yours, we feel that reviewer#1 is being unreasonable. We would greatly appreciate it if you would submit this manuscript, reviewer#1's comments, and our rebuttals, to an additional unbiased reviewer. We would be most surprised if the new reviewer would see the comments of the reviewer#1 as reasonable, but if he/she did so, we would accept a negative decision gracefully.

Is it a good paper or not?

- **what makes a great paper?**
 - **Astounding work**
 - **of great value to its own field and/or to the general readership**
- **Common problems resulting in rejection of a manuscript**
 - **too small of an advance**
 - **not of general interest/ belongs in specialized journal**
 - **not scientifically convincing, interpretations poorly supported**
 - **results not well interpreted, poor context**