Science Signaling
AAAS
Sci. Signal., 25 June 2013
Vol. **6**, Issue 281, p. ec144
[DOI: 10.1126/scisignal.2004442]

EDITORS' CHOICE

Neuroscience

Two Endogenous Modulators in One

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GABAergic signaling mediated by ionotropic γ-aminobutyric acid (GABA) type A receptors ($GABA_AR$s) is an important pharmacological target because reduction in inhibitory GABAergic signaling is associated with anxiety and seizures. $GABA_AR$s are composed of five subunits, and at the interface between two of these is an allosteric modulatory site, where benzodiazepines bind to enhance $GABA_AR$ activity in the presence of GABA (see Harward and McNamara). The presence of this allosteric site sparked the hypothesis that there are endogenously produced regulators that bind this site (endozepines) and peptides encoded by *Diazepam binding inhibitor* (*Dbi*) function as negative allosteric modulators. Christian *et al*. focused on the thalamic reticular nucleus (nRT) because abnormal oscillatory activity in this region is associated with absence seizures. Compared to wild-type mice, mice with a $GABA_AR$ with a mutation in the allosteric modulatory site or *nm1054* mice with a genomic deletion encompassing *Dbi* exhibited reduced inhibitory postsynaptic currents (IPSCs) in the nRT and IPSCs were not affected by application of flumazenil, a benzodiazepine antagonist. Viral transduction of DBI into the nRT increased IPSCs and conferred responsiveness to flumazenil in the *nm1054* mice. Because GAB_AARs can be composed of different combinations of subunits, the authors placed "sniffer patches," which are outside-out membrane patches from the ventrobasal nucleus (VB) in the nRT or the VB, and measured their response to uncaging of GABA. When placed in the nRT from wild-type mice, the sniffer patches exhibited enhanced IPSCs compared with those placed in the VB; when placed in the nRT region of slices from *nm1054* mice, there was no potentiation of IPSCs. Thus, Dbi produces positive allosteric modulators in the nRT, not in the VB. Mutant mice that could not respond to the endogenous positive allosteric modulators or could not produce these modulators exhibited higher incidence of spontaneous and pharmacologically induced brain activity associated with seizures, confirming the importance of this endogenous positive allosteric modulation. Thus, *Dbi* appears to encode both positive and negative allosteric modulators that bind the benzodiazepine site of $GABA_AR$s.

C. A. Christian, A. G. Herbert, R. L. Holt, K. Peng, K. D. Sherwood, S. Pangratz-Fuehrer, U. Rudolph, J. R. Huguenard, Endogenous positive allosteric modulation of $GABA_A$ receptors by *Diazepam binding inhibitor*. *Neuron* **78**, 1–12 (2013). [PubMed]

S. C. Harward, J. O. McNamara, In search of the ever-elusive positive endozepine. *Neuron* **78**, 951–952 (2013). [Online Journal] [PubMed]

Citation: N. R. Gough, Two Endogenous Modulators in One. *Sci. Signal.* **6**, ec144 (2013).

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