REFERENCES

1. Bremer PT, Kimishima A, Schlosburg JE, Zhou B, Collins KC, Janda KD. Combatting synthetic designer opioids: a conjugate vaccine ablates lethal doses of fentanyl class drugs. Angew Chem Int Ed Engl. 2016;55:3772–5.
2. Raleigh MD, Laudenbach M, Baruffaldi F, Peterson SJ, Roslawski MJ, Birnbaum AK, et al. Opioid dose- and route-dependent efficacy of oxycodone and heroin vaccines in rats. J Pharmacol Exp Ther. 2018;365:346–53.
3. Sulima A, Jalah R, Antoline JFG, Torres OB, Imler GH, Deschamps JR, et al. A stable heroin analogue that can serve as a vaccine hapten to induce antibodies that block the effects of heroin and its metabolites in rodents and that cross-react immunologically with related drugs of abuse. J Med Chem. 2018;61:329–43.
4. Raleigh MD, Peterson SJ, Laudenbach M, Baruffaldi F, Carroll FI, Comer SD, et al. Safety and efficacy of an oxycodone vaccine: addressing some of the unique considerations posed by opioid abuse. PLoS One. 2017;12:e0184876.
5. Hwang CS, Bremer PT, Wenthur CJ, Ho SO, Chiang S, Ellis B, et al. Enhancing efficacy and stability of an antiheroin vaccine: examination of antinociception, opioid binding profile, and lethality. Mol Pharm. 2018; 15:1062–72.
6. Laudenbach M, Baruffaldi F, Robinson C, Carter P, Seelig D, Baehr C, et al. Blocking interleukin-4 enhances efficacy of vaccines for treatment of opioid abuse and prevention of opioid overdose. Sci Rep. 2018;8:5508.
7. Laudenbach M, Baruffaldi F, Vervacke JS, Distefano MD, Titcombe PJ, Mueller DL, et al. The frequency of naive and early-activated hapten-specific B cell subsets dictates the efficacy of a therapeutic vaccine against prescription opioid abuse. J Immunol. 2015;194:5926–36.

Regulation of raphe serotonin neurons by serotonin 1A and 2B receptors

Arnauld Belmer[1,2,3,4] and Luc Maroteaux[1,2,3]

Neuropsychopharmacology (2019) 44:218–219; https://doi.org/10.1038/s41386-018-0214-6

Several lines of evidence implicate serotonin (5-hydroxytryptamine, 5-HT) in the etiology of mood disorders, including major depressive disorders. Serotonergic neurons have long been recognized as key contributors to the regulation of mood and anxiety as the main target of serotonin selective reuptake inhibitor (SSRI) antidepressants. The therapeutic effects of SSRIs are initially triggered by blockade of the serotonin transporter SERT increasing local extracellular serotonin. Serotonin neurotransmission is tightly regulated by autoreceptors (serotonin receptors expressed by serotonin neurons) known to act through negative feedback inhibition at the cell bodies (5-HT_{1A} receptors) of the raphe nuclei or at the axon terminals (5-HT_{1B} receptors). Beneficial SSRI effects rely on long-term adaptations that are, at least partially, ascribed to a selective desensitization of somatodendritic 5-HT_{1A} autoreceptors [1].

A positive regulation of serotonergic neurons by 5-HT_{2B} receptors has been detected in mice. Local agonist-stimulation of 5-HT_{2B} receptors in dorsal raphe nuclei increased extracellular serotonin suggesting a functional role of this receptor within serotonergic neurons [2]. Expression of 5-HT_{2B} receptors has been detected in subset of serotonergic neurons albeit at low levels [3]. Both acute and long-term behavioral and neurogenic effects of SSRIs are abolished in mice knockout for 5-HT_{2B} receptor gene, (*Htr2b*$^{-/-}$) or after exposure to selective 5-HT_{2B}-receptor antagonists. Conversely, chronic stimulation of 5-HT_{2B} receptors by selective agonists mimicked chronic SSRI actions on behavior and hippocampal neurogenesis, which were abolished in *Htr2b*$^{-/-}$ mice [3]. Comparable lack of SSRI effects was recently reported in mice knockout for 5-HT_{2B} receptors only in serotonergic neurons (*Htr2b*$^{5\text{-}HTKO}$ mice) in which dorsal raphe serotonin neurons displayed a reduced firing frequency, and a stronger hypothermic effect following 5-HT_{1A}-autoreceptor stimulation [4]. Cell autonomous effects were confirmed by the increased excitability of serotonergic neurons observed upon raphe-selective 5-HT_{2B}-receptor overexpression. Correlative findings have been described in humans, in which expression of 5-HT_{2B} receptors can be found in brain stem and a loss-of-function polymorphism of 5-HT_{2B} receptors has been associated with serotonin-dependent phenotypes, including increased impulsivity and suicidality [5].

Serotonin released within raphe nuclei is known to induce feedback inhibition of serotonergic neuron firing activity by stimulating dendritic 5-HT_{1A} negative autoreceptors. Unlike soma and terminals, the dendritic serotonin release is independent of action potentials, relies on L-type Ca2+ channels, can be induced by NMDA, and displays distinct sensitivity to the SSRI antidepressants [6]. Dendritic serotonin release, and hence 5-HT_{1A} receptor-mediated autoinhibition, is thus engaged by excitatory glutamatergic inputs to the dorsal raphe, via locally triggered calcium influx, rather than by neuronal firing. The unique control of dendritic serotonin release has important implications for the antidepressant action of SSRIs. The lack of 5-HT_{2B} receptor in serotonergic neurons is associated with a higher 5-HT_{1A}-autoreceptor reactivity and thus a lower activity of these neurons [4]. The excess of inhibitory control exerted by 5-HT_{1A} receptors in *Htr2b*$^{5\text{-}HTKO}$ mice may thus explain the lack of response to chronic SSRI in these mice.

The serotonergic tone of raphe neurons and thus the SSRI therapeutic effects likely results from the opposite control exerted by 5-HT_{1A} and 5-HT_{2B} receptors via a mechanism that remains to be described.

ACKNOWLEGMENT

This work has been supported by funds from the Centre National de la Recherche Scientifique, the Institut National de la Santé et de la Recherche Médicale, the Sorbonne Universités, and by grants from the Fondation pour la Recherche sur le Cerveau, the Fondation de France, the Région Ile-de-France, the Fondation pour la

[1]INSERM U 839, Paris 75005, France; [2]UMR-S839 Sorbonne Université, Paris 75005, France; [3]Institut du Fer à Moulin, Paris 75005, France and [4]Translational Research Institute, Queensland University of Technology, Brisbane, QLD 4059, Australia
Correspondence: Luc Maroteaux (luc.maroteaux@upmc.fr)

Published online: 25 September 2018

Recherche Médicale "Equipe FRM DEQ2014039529", the French Ministry of Research (Agence Nationale pour la Recherche ANR-17-CE16-0008 and the Investissements d'Avenir programme ANR-11-IDEX-0004-02) and the DIM Cerveau et Pensée région Ile-de-France (PME2012). L.M.'s team is part of the École des Neurosciences de Paris Ile-de-France network and of the Bio-Psy Labex and as such this work was supported by French state funds managed by the ANR within the Investissements d'Avenir programme under reference ANR-11-IDEX-0004-02.Competing interests: The authors declare no competing interests.

REFERENCES

1. Richardson-Jones JW, Craige CP, Guiard BP, Stephen A, Metzger KL, Kung HF, et al. 5-HT1A autoreceptor levels determine vulnerability to stress and response to antidepressants. Neuron. 2010;65:40–52.
2. Doly S, Valjent E, Setola V, Callebert J, Herve D, Launay JM, et al. Serotonin 5-HT2B receptors are required for 3,4-methylenedioxymethamphetamine-induced hyperlocomotion and 5-HT release in vivo and in vitro. J Neurosci. 2008;28:2933–40.
3. Diaz SL, Doly S, Narboux-Nême N, Fernandez S, Mazot P, Banas S, et al. 5-HT2B receptors are required for serotonin-selective antidepressant actions. Mol Psychiatry. 2012;17:154–63.
4. Belmer A, Quentin E, Diaz SL, Guiard BP, Fernandez SP, Doly S, et al. Positive regulation of raphe serotonin neurons by serotonin 2B receptors. Neuropsychopharmacology. 2018;43:1623–32.
5. Bevilacqua L, Doly S, Kaprio J, Yuan Q, Tikkanen R, Paunio T, et al. A population-specific HTR2B stop codon predisposes to severe impulsivity. Nature. 2010;468:1061–6.
6. Colgan LA, Cavolo SL, Commons KG, Levitan ES. Action potential-independent and pharmacologically unique vesicular serotonin release from dendrites. J Neurosci. 2012;32:15737–46.

Dynamic network targeting for closed-loop deep brain stimulation

Alexander B. Herman[1] and Alik S. Widge[1]

Neuropsychopharmacology (2019) 44:219–220; https://doi.org/10.1038/s41386-018-0210-x

Deep brain stimulation (DBS) has gained wide use in movement disorders and remains an area of active research in psychiatric disorders. Recent clinical trial setbacks may reflect clinicians' trial-and-error approach to selecting stimulation parameters [1]. Newer studies focus on "closed-loop" approaches, where DBS settings are adjusted based on an objective, brain-based readout. Those studies divide roughly into "anatomical" approaches based on targeting stimulation to specific white matter (WM) bundles and "physiologic" approaches that focus on changing pathologic signatures in brain electrical activity. We argue that success in psychiatric applications may require a synthesis of both approaches: individualized anatomically guided electrode placement coupled with biomarker-responsive targeting of network dynamics.

The anatomical approach optimizes clinical response by tailoring electrode placement relative to individual brain anatomy. In subcallosal cingulate (SCC) DBS for depression, an open-label study prospectively targeted the intersection of four different tracts in peri-SCC WM using individualized probabilistic tractography. Out of 11, 9 patients responded, a substantial improvement over the same group's prior results [2]. The same approach is now being expanded beyond SCC WM to optimize DBS placement in the ventral striatum/ventral capsule and medial forebrain bundle [1].

In comparison, the physiology-based closed-loop DBS approach is making strides in neurological disorders. Clinical outcomes improve in Parkinson disease when DBS is targeted to suppress specific cortical electrical oscillations or is locked to the phase of those oscillations [3]. A similar oscillatory feature was successfully used as a control signal in responsive DBS for Tourette syndrome [4]. Closed-loop DBS-like stimulation has also enhanced human memory. Recordings from sites across the brain can predict periods of poor memory encoding, and lateral temporal stimulation at those timepoints rescues memory performance [5]. If similar biomarkers can be identified for psychiatric symptoms, an analogous responsive stimulation approach should be possible in mental disorders. Preliminary evidence suggests that such biomarkers can be identified through a focus on cross-diagnostic domains of function, and that those markers can in turn be used for closed-loop control of psychiatrically relevant functions such as emotion regulation [6].

Psychiatric disorders likely involve dysfunction across multi-scale neural networks [1, 7], and effective DBS appears to require modulation of multiple circuits [2]. These results suggest the potential power of a multinode, network approach to sensing and stimulating in DBS. Delivering stimulation in response to features on multiple time scales (for instance, both amplitude and phase) may increase symptom relief while reducing side effects [3]. In conditions with distributed pathology, recording from and stimulating multiple areas simultaneously may better control network interactions. The ability to sense multiple network nodes might allow a better assessment of stimulation's effects on network connectivity/activity. Conversely, network activity might best be modulated by multisite stimulation. DBS and related technologies are believed to act by de-synchronizing brain networks, but this depends on stimulation efficiently propagating within those networks. In cases where single-site stimulation fails to

[1]Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA
Correspondence: Alik S. Widge (awidge@umn.edu)

Received: 28 July 2018 Revised: 26 August 2018 Accepted: 28 August 2018
Published online: 18 September 2018