and 20-Hz stimuli. The tetanic stimulation elicited asynchronous neurotransmitter release, observed as miniature EPSPs (mEPSPs) during and after stimulation, which permitted a quantitative assessment of postganglionic, cholinergic receptor sensitivity. Post-tetanic mEPSP amplitudes (recorded at −60 mV) were reduced by 25% in STZ, but were unaffected in BKS-db$^{+/+}$ mice. Intriguingly, the number of post-tetanic mEPSPs was substantially greater in BKS-db$^{+/+}$ mice. The increased post-tetanic mEPSP frequency was observed as early as 6 wks of age in the BKS-db$^{+/+}$ mice. Post-tetanic mEPSP frequency increased with $[Ca^{2+}]_o$ and with depolarization of mitochondria with CCCP. Commonly, in CCCP, mEPSP frequency increased to a similar extent in both BKS control and BKS-db$^{+/+}$ mice. The results indicate that diabetes does not suppress ganglionic neurotransmission at parasympathetic MPG neurons. Ongoing experiments test the hypothesis that impaired intraterminal Ca^{2+} homeostasis with type 2 diabetes, potentially associated with altered mitochondrial function, may disrupt presynaptic regulation of neurotransmitter release.

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Abstract 19.4

Vagus nerve stimulation and the cholinergic anti-inflammatory pathway: A potential new therapeutic approach in inflammatory bowel diseases

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Background: The brain and the gut communicate through the autonomic nervous system (ANS), represented by the sympathetic and parasympathetic nervous systems. The vagus nerve (VN), a major component of the ANS, plays a key role in the neuroendocrine-immune axis to maintain homeostasis through its afferents (via modulation of the hypothalamic pituitary adrenal axis; HPA) and efferents (via modulation of the cholinergic anti-inflammatory pathway; CAP). High frequency VN stimulation (VNS) of afferents is used for the treatment of drug-resistant epilepsy and depression in humans. In rats, low frequency (5 Hz) VNS of efferents can activate the CAP and decrease the secretion of TNFα, a pro-inflammatory cytokine which plays a key role in inflammatory bowel diseases (IBD: Crohn's disease and ulcerative colitis). Our group explores how this anti-inflammatory effect of VNS could be used for the treatment of IBD.

Team results: The ANS is imbalanced in irritable bowel syndrome and in IBD patients; thus VNS could restore the ANS equilibrium. We have previously reported that a chronic 5-Hz VNS performed in a rat model of colitis reduced body weight loss (a classical inflammatory parameter in IBD patients) and decreased TNFα and myeloperoxidase (a marker of leukocyte infiltration) in the colonic mucosa. We performed the first fMRI study of acute VNS in rodents showing that even low-frequency VNS at 5 Hz, known to theoretically activate vagal efferents, was also able to have central effects through afferents. Low-frequency VNS could thus both have peripheral (CAP) and central effects (vago-vagal positive loop; HPA axis activation; modification of the central ANS), modulating the sympatho-vagal balance and thus inflammation.

Conclusion: Our data argue for an anti-inflammatory role of chronic VNS and provide potential therapeutic applications for IBD patients. We are currently running a pilot study of VNS in patients with moderate to severe Crohn's disease (ClinicalTrials.gov id: NCT01569503).

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Poster 1.6

Cholinergic sympathetic neurons present in embryonic mouse stellate ganglion become noradrenergic neurons in adults

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In mature rodents, sympathetic cholinergic neurons innervate sweat glands and periosteum. The neurons arise postnatally from noradrenergic neurons that convert to cholinergic neurons in the first few days of postnatal life under the influence of target-derived signals. Hence, sympathetic cholinergic neurons should not be present in embryonic ganglia. However, a number of reports confirm that cholinergic neurons are present prior to birth in sympathetic ganglia in rodents. We have used Cre-loxP technology to trace the fate of the early-appearing cholinergic neurons. Mice in which the promoter for choline acetyltransferase drives Cre recombinase (ChAT-cre mice) were crossed with ROSA EYFP animals where Cre expression removed a floxed stop codon to permanently activate EYFP expression. EYFP-immunoreactive (-IR) neurons were present from E11.5 and consistently made up around 2–3% of the total cells in the ganglion into adult life. EYFP-IR terminals were also present in brown fat and around blood vessels, targets which are not innervated by sympathetic cholinergic neurons in the adult. EYFP-IR neurons showed a range of chemical phenotypes, including some with expression of tyrosine hydroxylase and neuropeptide Y, a combination characteristic of noradrenergic, but not cholinergic sympathetic neurons. Finally, retrograde tracing from a range of targets normally innervated by noradrenergic sympathetic neurons showed that in every case, around 2% of all labelled sympathetic neurons were EYFP-IR and included many cells expressing NPY in addition to tyrosine hydroxylase. We hypothesise that a proportion of sympathetic neurons initially develop a cholinergic phenotype in embryonic ganglia but convert to a noradrenergic phenotype when they contact targets. This implies that all autonomically innervated targets provide signals that regulate the phenotype of the innervating sympathetic postganglionic neuron and that some targets can direct both noradrenergic to cholinergic phenotype switches (sweat glands and periosteum) and others a cholinergic to noradrenergic switch.

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Poster 1.7

Special AT-rich sequence-binding protein-2 (Satb2) — Independent initiation of cholinergic sweat gland innervation in rat in vivo

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