enhanced? This paper provides exciting new findings identifying an essential part of the molecular mechanism of PHP that delays symptoms in MND mouse models and prompts research that will enhance our understanding of, and the treatment of, neurodegenerative disease.

REFERENCES

Davis, G.W. (2013). Homeostatic signaling and the stabilization of neural function. Neuron *80*, 718–728.

Lo, S.C., Wang, Y., Weber, M., Larson, J.L., Scearce-Levie, K., and Sheng, M. (2015). Caspase-3 deficiency results in disrupted synaptic homeostasis and impaired attention control. J. Neurosci. *35*, 2118–2132.

Logroscino, G., Piccininni, M., Marin, B., Nichols, E., Abd-Allah, F., Abdelalim, A., Alahdab, F., Asgedom, S.W., Awasthi, A., Chaiah, Y., et al.; GBD 2016 Motor Neuron Disease Collaborators (2018). Global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. *17*, 1083–1097.

Mathis, S., Goizet, C., Soulages, A., Vallat, J.-M., and Masson, G.L. (2019). Genetics of amyotrophic lateral sclerosis: A review. J. Neurol. Sci. *399*, 217–226.

Orr, B.O., Hauswirth, A.G., Celona, B., Fetter, R.D., Zunino, G., Kvon, E.Z., Zhu, Y., Pennacchio, L.A., Black, B.L., and Davis, G.W. (2020). Presynaptic Homeostasis Opposes Disease Progression in Mouse Models of ALS-Like Degeneration: Evidence for Homeostatic Neuroprotection. Neuron *107*, this issue, 95–111.

Turrigiano, G.G., and Nelson, S.B. (2004). Homeostatic plasticity in the developing nervous system. Nat. Rev. Neurosci. *5*, 97–107.

Younger, M.A., Müller, M., Tong, A., Pym, E.C., and Davis, G.W. (2013). A presynaptic ENaC channel drives homeostatic plasticity. Neuron *79*, 1183–1196.

From Synapse to Supper: A Food Preference Recipe with Olfactory Synaptic Ingredients

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C1ql3 protein and its receptor Bai3 are involved in synaptic organization and function. In this issue of *Neuron*, Wang et al. (2020) report that both are essential for synaptic function between the anterior olfactory nucleus and the olfactory bulb and for the generation, but not recall, of associative olfactory memories determining food preference in mice.

The smell of food! No doubt this is a stimulus charged with tremendous emotional load, capable of evoking powerful memories and of driving our actions. Certain foods immediately arouse our senses, while others repel us in disgust, and a complex interplay between physiological, psychological, social, and cultural factors is known to influence our meal preferences (Shepherd and Raats, 2006). This was no secret to the late chef Anthony Bourdain, who in his travels around the world interacted with locals, colorfully highlighting cultural aspects that make us prefer certain foods. He unraveled nuances of regional cuisine and people's predilections, eventually developing his own taste for the novel dishes he tried.

Humans are not alone when it comes to social influences on food preference. Animals are also able to socially learn which foods to prefer or reject (Galef et al., 1984; Hikami et al., 1990), an evolutionarily adaptive ability. But what are the biological underpinnings of such a remarkable phenomenon? Strikingly, the mammalian brain seems to be genetically pre-programmed to associate food and circumstance. Among the gargantuan amount of synapses in a large number of neural circuits, some located in the olfactory system control food preference (Liu et al., 2017), a fact easy to understand given the intimate relationship between the sense of smell and eating behavior.

In this issue of *Neuron*, Wang and collaborators in Thomas Südhof's group describe the workings of synapses between the anterior olfactory nucleus (AON) and the olfactory bulb (OB) and how olfaction-mediated learning of food preference is controlled by signaling molecules that help organize those neural connections (Wang et al., 2020). They investigated C1ql3, a secreted protein in the tumor necrosis factor (TNF) superfamily, hypothesized to act as a synaptic organizer. In previous work by the group, C1ql3 was shown to be involved in associative memories of emotionally salient stimuli (Martinelli et al., 2016).

In the olfactory system, C1ql3 is expressed in the AON and in the piriform cortex (Martinelli et al., 2016). Wang and colleagues suspected that *C1ql3*-expressing neurons reach the OB but did

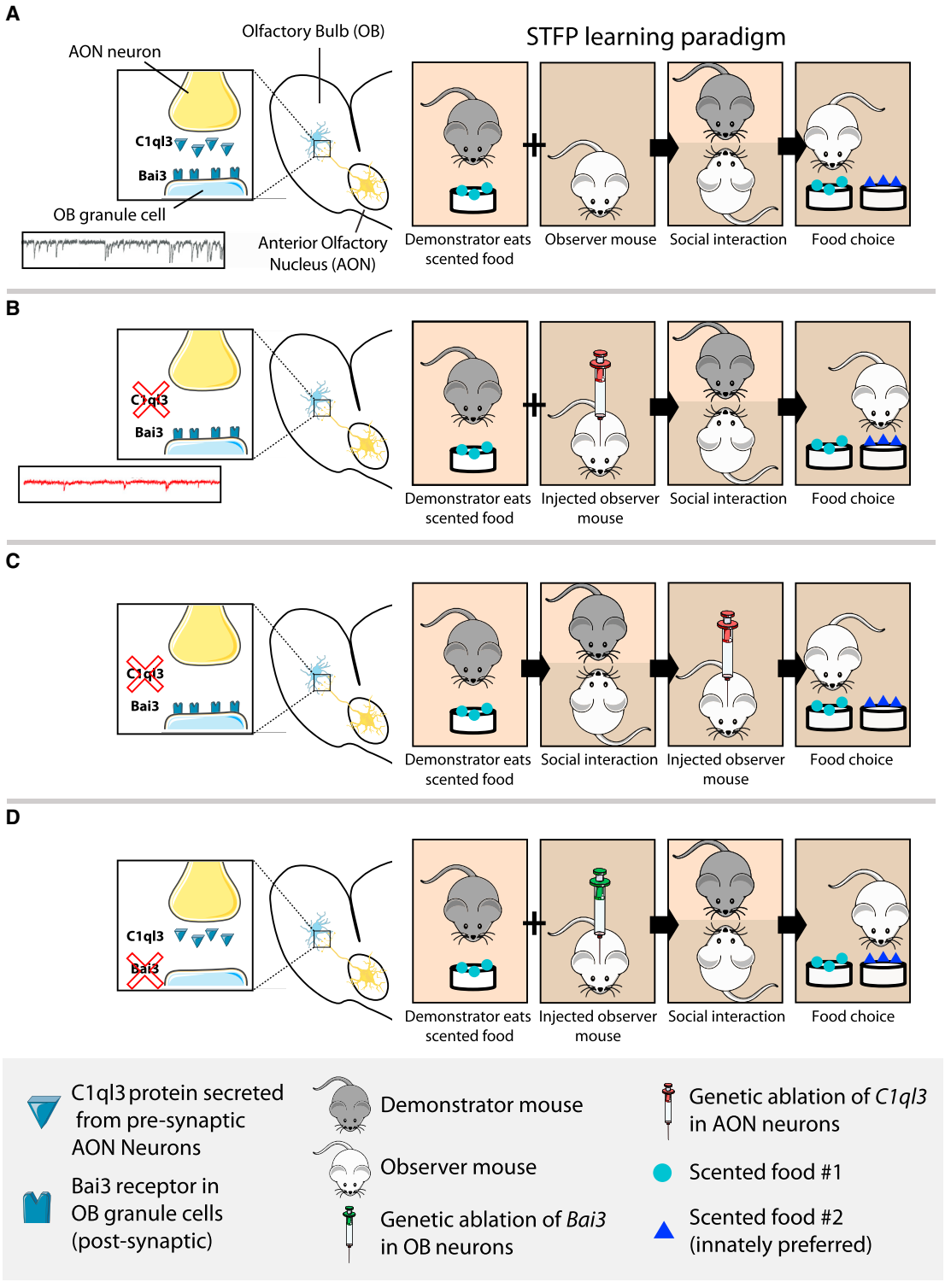

Figure 1. Genetic Manipulation of Synaptic Organizers in the Olfactory System

(A) Observer mice learn to prefer food previously consumed by a demonstrator.

(B and C) *C1ql3* genetic ablation in the anterior olfactory nucleus before (B), but not after (C), interaction between mice disrupts social transmission of food preference (STFP).

(D) *Bai3* deletion in the olfactory bulb phenocopies *C1ql3* ablation.

Graphic elements adapted from Smart Servier Medical Art.

not know whether these projections come from the AON or from the piriform. In the current paper's first experiments, they used retrograde tracing to determine that AON neurons projecting to the OB are mostly *C1ql3* positive, in contrast to piriform cells connected to the OB, which are only in part *C1ql3* positive.

The rest of the study delved deeper into investigating the AON→OB connections and the role played by C1ql3. Fortunately, several tools that allow the analysis and manipulation of one type of synapse in isolation are now available. The authors injected Cre-expressing viruses into the AON of floxed mice to conditionally knockout *C1ql3* in this nucleus. What effect could such specific genetic ablation have on AON synapses and therefore on olfaction-related behaviors? The authors systematically tested several aspects of olfaction in *C1ql3*-ablated animals but could not find any changes in olfactory sensitivity and olfaction-related sociability.

Olfaction also influences several aspects of appetitive behavior. Wang et al. (2020) found that food consumption in *C1ql3*-ablated animals was unaltered, implying that olfactory loss, if any, did not significantly affect the animal's general drive to find food and eat. Just like humans, mice innately exhibit preference for certain types of food and tend to eat more often from meals scented with their favorite odors and less often from food odorized with disfavored ones. Alas, *C1ql3* ablation in the AON was found not to affect such innate preference behavior.

In a decisive plot twist, Wang et al. (2020) focused on a curious kind of olfactory memory related to social interaction: when a demonstrator mouse interacts with an observer mouse (much like Bourdain interacting with natives in his food voyages), the observer identifies olfactory stimuli in the demonstrator's breath, resulting in the formation of an associative memory that allows the observer to later develop preference for the types of food ingested by the demonstrator prior to social interaction (Figure 1A). Several animal species exhibit this bizarre behavior, known as social transmission of food preference (STFP), which persists for several weeks in mice (Galef, 2003; Galef et al., 1984; Liu et al., 2017).

Lo and behold, Wang et al. (2020) found that STFP learning was impaired in mice with genetic ablation of *C1ql3* in the AON (Figure 1B). Importantly, the behavior was lost only when *C1ql3* was ablated in the observer mouse prior to its social interaction with the demonstrator. When ablation was performed after social interaction, STFP learning was still present (Figure 1C), implying that C1ql3 and its associated synaptic components are functionally needed for the acquisition, but not for the retrieval, of that olfactory memory.

The authors showed that AON *C1ql3*-positive neurons project not only to the OB but also to the piriform, such that the AON manipulation experiments described above could not parse out the contribution of AON→OB versus AON→piriform connections. These possibilities were explored in two subsequent experiments. In one group of mice, *C1ql3* was knocked out specifically in AON neurons projecting to the OB, while in another cohort the knockout targeted AON neurons connecting with the piriform. Interestingly, STFP learning was spoiled only in the first group, which targeted AON→OB connections (Wang et al., 2020).

In trying to unravel the underlying mechanisms of C1ql3's role in STFP, Wang et al. (2020) showed that the number of AON→OB synapses was diminished after *C1ql3* ablation. More significantly, *C1ql3* ablation in the AON caused changes in several electrical properties of OB granule cells, including reduction in frequency and amplitude of spontaneous excitatory postsynaptic currents (sEPSCs) (traces in Figure 1). Therefore, genetic ablation of *C1ql3* leads to impairment of AON→OB synaptic transmission, in keeping with the idea that C1ql3 is important for synapse organization and function.

Up to this point, Wang et al. (2020) genetically manipulated *C1ql3*-positive AON neurons connecting to the bulb (presynaptic). An important complementary approach is to investigate C1ql3's receptor in the postsynaptic neuron. Bai3 is a GPCR known to bind C1ql3 in other brain regions (Bolliger et al., 2011). The authors observed that after *Bai3* ablation in the OB, synaptic density and function were affected, as seen when *C1ql3* was knocked out in the AON. Importantly, these defects were accompanied by loss of STFP memory acquisition (Figure 1D), but not of other olfactory or appetitive behaviors (Wang et al., 2020).

Although it remains to be demonstrated that C1ql3 is released by AON projection neurons and that C1ql3 physically interacts with Bai3 receptors on OB granule cells, the work by Wang and colleagues is a beautiful (and rare) example of investigation of behavior after manipulation of specific synapses between defined brain sites. Several routes of investigation stem from this study. What intracellular events connect Bai3 detection of its C1ql3 secreted ligand to alterations in granule cell synapse function? Because granule cells are continuously formed in adult animals, at which stage is the C1ql3-Bai3 interaction critical? Is it necessary for the formation of novel synapses between the incoming granule cells and their AON presynaptic liaisons or for already established AON-OB synapses?

Perhaps the most exciting question is: how and by which processes do AON functional inputs to the OB contribute to the formation of olfactory memories? Does it involve any aspect of the lateral inhibition promoted by granule cells onto mitral/tufted cells in the OB? Additionally, what is the interplay among all brain sites—OB and hippocampus included—shown to regulate different aspects of STFP?

Molecular neuroscience is a rich stew of knowledge that enables us to understand human and animal behavior. Our current ability to finely peel through neural circuits provides the opportunity to reveal the intricate contributions of various molecular and cellular ingredients. Not surprisingly, the course that emerges is one in which social remembrances are crucial. Bourdain once said: "Context and memory play powerful roles in all the truly great meals in one's life." He knew it all too well. Mice do too.

REFERENCES

Bolliger, M.F., Martinelli, D.C., and Südhof, T.C. (2011). The cell-adhesion G protein-coupled receptor BAI3 is a high-affinity receptor for C1q-like proteins. Proc. Natl. Acad. Sci. USA *108*, 2534–2539.

Galef, B.G., Jr. (2003). Social learning of food preferences in rodents: rapid appetitive learning. Curr. Protoc. Neurosci. *Chapter 8*, 5D.

Galef, B.G., Kennett, D.J., and Wigmore, S.W. (1984). Transfer of information concerning distant foods in rats: A robust phenomenon. Anim. Learn. Behav. *12*, 292–296.

Hikami, K., Hasegawa, Y., and Matsuzawa, T. (1990). Social transmission of food preferences in Japanese monkeys (Macaca fuscata) after mere exposure or aversion training. J. Comp. Psychol. *104*, 233–237.

Liu, Z., Chen, Z., Shang, C., Yan, F., Shi, Y., Zhang, J., Qu, B., Han, H., Wang, Y., Li, D., et al. (2017). IGF1-Dependent Synaptic Plasticity of Mitral Cells in Olfactory Memory during Social Learning. Neuron *95*, 106–122.e5.

Martinelli, D.C., Chew, K.S., Rohlmann, A., Lum, M.Y., Ressl, S., Hattar, S., Brunger, A.T., Missler, M., and Südhof, T.C. (2016). Expression of C1ql3 in Discrete Neuronal Populations Controls Efferent Synapse Numbers and Diverse Behaviors. Neuron *91*, 1034–1051.

Shepherd, R., and Raats, M. (2006). The Psychology of Food Choice (CABI Publishing).

Wang, C.Y., Liu, Z., Ng, Y.H., and Südhof, T.C. (2020). A Synaptic Circuit Required for Acquisition but Not Recall of Social Transmission of Food Preference. Neuron *107*, this issue, 144–157.

Understanding the Munchies

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In this issue of *Neuron*, Thoeni et al. (2020) demonstrate that both food restriction and a high-fat diet cause an endocannabinoid-dependent inhibition of D1 medium spiny neuron terminals in the lateral hypothalamus that promotes overeating.

Sporadic munchies leading to a third slice of pizza after a long workday or a midnight chocolate snack during a movie break are delicious treats but, if unregulated, can degrade one's health and lifespan. Acute overeating elicited by prior food restriction is an adaptive behavioral strategy conserved across species that serves to refill depleted energy stores after periods of food restriction. However, chronic overeating triggered by ready availability of hyperpalatable food (i.e., high fat, high sugar) is a risk factor for obesity and is maladaptive (Coccurello and Maccarrone, 2018). The human brain is poorly armed against the constant food seductions that first emerged in western societies, and in many societies, the high prevalence, accessibility, and affordability of hyperpalatable foods as compared to healthy alternatives have caused an obesity epidemic. A better understanding of the brain pathways involved in the development of pathological eating behaviors is important to inform public health strategies against obesity.

The lateral hypothalamus (LH) is interconnected with the brain reward and homeostatic systems, which places the LH at a circuitry control nexus for the regulation of feeding behavior and modulating the hedonic value of food (Coccurello and Maccarrone, 2018). Using optogenetic circuit manipulation, it was recently shown that GABAergic neurons in the bed nucleus of the stria terminalis project to and inhibit glutamatergic neurons in the LH to disinhibit feeding behavior (Jennings et al., 2013). Conversely, GABAergic D1 medium spiny neurons (D1-MSNs) from the nucleus accumbens shell (NAcShell) project to and inhibit LH GABAergic neurons to stop feeding behavior (Connor et al., 2015).

Chronic exposure to high-fat foods that are rich in saturated fatty acids can lead to adaptations in the brain reward system that could further amplify maladaptive eating behavior (Lafourcade et al., 2011).

Although previous optogenetic studies have revealed the importance of LH microcircuits in the real-time control of feeding behaviors, it remained to be discovered which adaptations in these LH circuits could contribute to chronic dysregulation of eating behaviors. In the new study by Thoeni et al. (2020), the authors set out to investigate whether changes in food intake (i.e., overeating after food restriction or overeating due to hyperpalatable food) induce neuroadaptations at the NAcShell D1-MSN-to-LH synapses that induce overeating. To this aim, the authors elegantly combined *in vitro* and *in vivo* optogenetics, whole-cell patch-clamp recordings, tracing studies, and *in vitro* and *in vivo* pharmacology to examine the role of synaptic plasticity at the D1-MSN-to-LH synapses in the regulation of feeding behavior.

In the first set of experiments, Thoeni et al. (2020) probed the capacity of NAcShell D1-MSN-to-LH synapses to undergo long-term potentiation of GABA transmission (i-LTP). D1cre mice were injected with floxed-ChR2 into the NAcShell and whole-cell patch-clamp recordings were performed. Surprisingly, the application of the adenylyl cyclase activator forskolin (FSK) that is known to induce i-LTP at other D1-MSN terminals (Creed et al., 2016) did not induce i-LTP in brain slices from *ad libitum*-fed mice. Since LH neurons are comprised of subpopulations of GABAergic and glutamatergic neurons that maintain opponent control over feeding behavior (Connor et al., 2015; Jennings et al., 2013), the authors speculated that the i-LTP might be only expressed in one of those