Nephropathy and Other Topics

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Nephropathy and blood pressure

Burrows et al. (abstract 266) analyzed the incidence of end-stage renal disease (ESRD) in individuals with diabetes, using data from the U.S. Renal Data System and estimates of the U.S. population with diabetes from the National Health Interview Survey, and found that although the number of diabetic individuals beginning treatment for ESRD increased from 17,728 in 1990 to 45,951 in 2005, the age-adjusted incidences were 299, 343, and 201 per 100,000 diabetic population in 1990, 1996, and 2005, respectively, with decreases in incidence consistently seen in 2005 among diabetic individuals aged <45, 45–64, 65–74, and >75 years—perhaps an indication that ESRD is being successfully prevented. There remain important areas for intervention. Kim et al. (abstract 748) studied 3,239 Pima Indians aged 5–19 years. Microalbuminuria and macroalbuminuria were found in 7 and 1% of nondiabetic and in 29 and 2% of diabetic children, respectively. Regression to normoalbuminuria was found in 76% of nondiabetic but only 20% of diabetic youth, whereas progression to macroalbuminuria was seen at annual rates <1% in nondiabetic youth with microalbuminuria but 4 and 12% in diabetic patients with albumin-to-creatinine ratios 30–100 and 100–300 mg/g, respectively. Orchard and Costa cou (abstract 973) compared 208 type 1 diabetic patients with intermittent versus persistent microalbuminuria and found the latter group to be 14 times more likely to progress to macroalbuminuria. Persistent microalbuminuria was associated with higher A1C, systolic blood pressure, and pulse. Cignarelli et al. (abstract 734) reported that among 407 type 2 diabetic patients, there were 55 subjects with glomerular filtration rate (GFR) <60 ml/min of whom 76% were normoalbuminuric. Although A1C, lipids, statin use, and glycemic treatment were similar in those with GFR <60 vs. >60 ml/min, the former were older with body weight 67 vs. 82 kg and diabetes duration 14 vs. 10 years. An et al. (abstract 743) studied 562 diabetic patients and reported that 151 had Modification of Diet in Renal Disease (MDRD) GFR <60 ml/min of whom 44 had normalalbuminuria. Similarly, of those not treated with renin-angiotensin system inhibitors, 18 of 51 with GFR <60 ml/min had normalalbuminuria. Given this frequency, the investigators suggested normalalbuminuria to be an early stage of diabetic nephropathy, although it might also indicate renal disease. In a study of 2,099 Pima Indian type 2 diabetic patients, Pavkov et al. (abstract 736) reported that among those with MDRD GFR <60 ml/min per 1.73m² in 1982–1988 vs. 2001–2006, the proportion of subjects with normalalbuminuria increased from 9 to 18%. Improved antihypertensive therapies might be in part responsible.

Katayama et al. (abstract 721) followed 1,558 type 2 diabetic patients with urine albumin <150 mg/g creatinine for 8 years. Progression to macroalbuminuria was 2.7- and 5.8-fold more likely in those with A1C 7–9 and >9%, respectively, compared with A1C <7%. Those with systolic blood pressure 120–140 and >140 mmHg had 2.3- and 3.6-fold greater likelihood of progression than those with systolic blood pressure <120 mmHg. Cigarette use was an additional risk factor. Of those with microalbuminuria, 30% became normoalbuminuric, suggesting benefits of early and intensive blood pressure- and glucose-lowering treatment.

Genes and nephropathy

Kankova et al. (abstract 369) determined polymorphisms in genes of the pentose phosphate pathway, transaldolase, glucose-6-phosphate dehydrogenase, and transketolase (TKT) as well as levels of the TKT cofactor thiamine in 623 diabetic patients with versus without nephropathy, finding a specific TKT haplotype to be associated with more rapid nephropathy progression and with a lower thiamine level. A study of thiamine supplementation in diabetic patients with this haplotype would be of great interest. Marcovecchio et al. (abstract 370) reported that levels of albuminuria among 933 diabetic patients aged 10–18 years were associated with a polymorphism of the gene encoding ELF1, a transcription factor regulating the expression of immune system and vascular genes.

Advanced glycation end products

Uribarri et al. (abstracts 255 and 371) found that in vitro expression of the advanced glycation end product receptor 1 (AGER1)—involved in advanced glycation end product (AGE) removal and prevention of AGE-induced inflammation and oxidative stress—increased with 2-day but decreased with 14-day AGE exposure, particularly to methylglyoxal. In diabetic patients and in nondiabetic patients with chronic kidney disease, monoclonal cell AGER1 levels were also decreased. AGER1 correlated with serum AGE levels in normal individuals, but patients with diabetic or nondiabetic chronic kidney disease had lower monocytic AGER1 despite higher AGE levels, suggesting a potential therapeutic target. Cai et al. (abstract 256) from this group showed an association between mitochondrial oxidant stress and AGEs in vitro and that oxidant stress was decreased in aortic endothelial cells overexpressing AGER1. Zheng et al. (abstract 745) and Zhang et al. (abstract 706) from this group overexpressed AGER1 in nondiabetic and streptozotocin-induced diabetic mice, showing reduced AGE and 8-isoprostane levels in the nondiabetic and reduced serum with increased urinary AGE levels in the diabetic animals overexpressing the receptor, with lessening of both histological evidence of diabetic nephropathy and renal cortical transforming growth factor-β.

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a potential mediator of glycemia-related renal disease. Mice overexpressing AGER1 were resistant to renal tubular injury and endoplasmic reticulum stress caused by the antibiotic and glycoprotein biosynthesis inhibitor tunicamycin and, interestingly, required a higher dose of streptozotocin to cause diabetes, suggesting that AGER1 induction may be a promising target for pharmacological research.

Coughlan et al. (abstract 763) measured carboxymethyllysine in 263 diabetic patients, finding those with micro- and macroalbuminuria to have urinary levels ~30–300 and 200–1,000 times higher than those with normoalbuminuria, respectively, whereas serum levels did not correlate with the degree of renal dysfunction.

Kennedy et al. (abstract 728) administered GLY-230 (Glycadia Pharmaceuticals), an inhibitor of nonenzymatic glycation of albumin, to 21 diabetic and 21 nondiabetic subjects, reducing glycated albumin without changing A1C in the diabetic patients. Among diabetic patients with albuminuria, urine albumin excretion decreased from 69 to 30 mg/g creatinine and excretion of the transmembrane podocyte protein nephrin, which reflects damage to the filtration barrier, decreased 41%.

Other markers
Schernthaner et al. (abstract 372) compared 138 type 2 diabetic patients with normo-, micro-, and macroalbuminuria and with similar age, duration of diabetes, A1C, BMI, blood pressure, creatinine, and lipids, finding reduction in peripheral blood endothelial progenitor cells by 29 and 73%, respectively, in the latter two groups, without change in total circulating progenitor cells. In multivariate analysis, diabetes duration, cardiovascular disease, and particularly the degree of albuminuria were independently associated with endothelial progenitor cell number.

Kimura et al. (abstract 764) studied serum cystatin C as a diagnostic marker for renal insufficiency in Japanese type 2 diabetic patients. The correlation coefficient was 0.85 of cystatin C with GFR calculated using the MDRD formula, whereas there was no significant correlation with serum parathyroid hormone. Receiver operating characteristic curves showed considerably greater sensitivity and specificity of cystatin C than of parathyroid hormone for stage 2 and stage 3 chronic kidney disease. Satoh et al. (abstract 717) followed 50 hypertensive and 50 normotensive type 2 diabetic patients with microalbuminuria for 2 years and found that cystatin increased gradually while there was no significant change in serum creatinine, suggesting the former to be useful in longitudinal follow-up as well as in cross-sectional studies. The relationships may be complex, however, as Naour et al. (abstract 1762) reported that cystatin C mRNA is highly expressed in adipose tissue with doubling of expression in obese versus lean patients’ subcutaneous fat. Cystatin C levels increased with increasing obesity and correlated with carotid intima-media thickness (IMT) in obese adults and children. LeCaire et al. (abstract 919) reported that cystatin C was inversely associated with MDRD GFR. Cystatin C but neither GFR nor creatinine was associated with albuminuria and with carotid IMT in this study, although Jimenez-Corona et al. (abstract 918) did find an association between carotid IMT and creatinine clearance. Evidence that cystatin C may not be ideal for renal function estimation was reported by Costacou et al. (abstract 733). Factors associated with progression to renal failure or transplantation over 16-year follow-up in 35% of 118 type 1 diabetic patients with microalbuminuria were as follows: longer diabetes duration, greater prevalence of hypertension, lower creatinine clearance, and higher non–HDL cholesterol, cystatin C, albuminuria, adiponectin, and C-reactive protein. At years ~14 through ~10, there were, however, no differences in cystatin C, whereas the creatinine clearance was lower in the group ultimately developing renal failure, suggesting that the latter measure may have greater clinical utility.

Joh et al. (abstract 711) administered α-lipoic acid and the aldose reductase inhibitor fideresta to streptozotocin-induced diabetic rats and found reduction in albuminuria and in vascular endothelial growth factor expression. Kume et al. (abstract 705) administered exenatide versus control treatment to db/db mice and reported reduction in obesity, glycemia, and hypertension, as well as attenuation of the development of albuminuria and renal mesangial expansion and macrophage infiltration. Tong et al. (abstract 724) followed 6,004 type 2 diabetic patients for a median of 5 years. In multivariate analysis, statin use was associated with a 25% reduction in likelihood of a decrease in MDRD GFR to <60 ml/min, whereas there were no protective effects of fibrate treatment, controlling for age, sex, smoking status, diabetes duration, blood pressure, BMI, A1C, LDL and HDL cholesterol, albuminuria, use of insulin, angiotensin-directed treatment, and other microvascular and macrovascular complications.

De Galan et al. (abstract 752) studied whether effects of perindopril-indapamide versus placebo on renal outcomes vary according to baseline blood pressure and investigated the association between achieved follow-up blood pressure and risk of renal events in the Action in Diabetes and Vascular disease: preterAx and diamicron-MR Controlled Evaluation (ADVANCE) study of 11,140 type 2 diabetic participants. Blood pressure decreased from 145/81 to 140/77 vs. 135/75 mmHg in the control versus intervention groups, the latter having a 21% reduction in the composite of new-onset microalbuminuria, new-onset macroalbuminuria, doubling of creatinine >200 μmol/l, ESRD, or renal death, with similar benefit for the components of the end point and similar benefit of treatment in subgroups ranging from baseline systolic/diastolic <120/<70 to >90/160 mmHg. With achieved blood pressure as low as 106/62 mmHg, there was a linear relationship between the logarithm of achieved blood pressure and renal events, suggesting benefit at levels below current recommended targets. Emanuele et al. (abstract 742) studied baseline associations with nephropathy among the 1,792 participants in the Veterans Affairs Diabetes Trial (VADT), which excluded subjects with baseline serum creatinine >1.6 mg/dl. Lower GFR was associated with age, diabetes duration, higher C-peptide levels, higher BMI (but lower waist-to-hip ratio), a history of cerebrovascular disease, and retinopathy. Greater degrees of albuminuria were associated with higher A1C, systolic blood pressure, total cholesterol, and fibrinogen; lower HDL cholesterol; and retinopathy and coronary disease.

Lipid treatment
Drexel et al. (abstract 878) studied 491 statin-treated patients with stable coronary heart disease, of whom 116 had type 2 diabetes. Presumably because all patients were intensively treated, LDL cholesterol and apolipoprotein B were not predictors of events, but low HDL cholesterol and apolipoprotein A1, small LDL particle diameter, and high triglyceride levels were associated with events, sug-
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...gesting the potential importance of new lipid treatment targets. Devaraj and Jialal (abstract 258) isolated HDL from fasting blood from six type 1 diabetic and six non-diabetic subjects and found that the former had decreased capacity to efflux cholesterol from macrophages, increased lipid peroxides, and decreased paraoxonase activity (a mediator of enzymatic protection of LDL against oxidative modification). Type 1 diabetic HDL increased monocyte chemotaxis, failed to protect against adhesion molecule activity, and contained increased levels of serum amyloid A, suggesting that HDL from type 1 diabetic patients may be dysfunctional and proinflammatory, explaining the often observed paradox of high HDL cholesterol in these patients despite development of cardiovascular disease. Richards et al. (abstract 866) analyzed the information value of fasting versus nonfasting lipids in 22 type 2 diabetic and 25 non-diabetic patients and reported that nonfasting LDL cholesterol was 9 mg/dl lower than fasting, whereas nonfasting triglyceride levels were higher. Four patients had nonfasting and two had fasting triglyceride levels >400 mg/dl. Nonfasting results failed to identify one patient requiring additional treatment (a false negative) but misidentified no patients (no false positives), suggesting high sensitivity and a reasonable alternative to fasting lipid determination, particularly when testing would otherwise be omitted as a result of nonfasting status.

Statins

Foody et al. (abstract 263) used claims data from 92 U.S.-managed care plans to identify cardiovascular events in 46,076 diabetic patients without cardiovascular disease who newly initiated atorvastatin (10 or 20 mg) versus simvastatin (20 or 40 mg). Over a 1.5-year follow-up, reported cardiovascular event rates were 3.35 versus 4.45 per 100 person-years with a significant 12% lower event rate, adjusting for age, sex, type of health plan, payer type, geographic region, calendar year of statin initiation, physician specialty, comorbidities, concomitant therapies, and prior health care cost. Of course, such epidemiological studies should only be regarded as hypothesis generating because the apparent better outcome with atorvastatin could reflect differences in patients (those choosing brand versus generic or those more versus less influenced by direct-to-consumer marketing) or in physician choices (using simvastatin for somewhat more sick patients).

Niacin

Bays et al. (abstract 86) reported effects of the combination of extended release niacin (2 g daily) with or without laropiprant to reduce flushing versus placebo, in 600 subjects with versus 787 without metabolic syndrome—the combination showing 18 vs. 20% reduction in LDL cholesterol, 22 vs. 17% increase in HDL cholesterol, and 28 vs. 17% reduction in triglyceride levels, with 2−4 mg/dl increase in fasting glucose level (without increasing or reducing the lipid effects of niacin by adding laropiprant). The overall study has been published and reported that 10.2% of patients stopped niacin with laropiprant versus 22.2% with niacin monotherapy (1). Plaisance and Judd (abstract 1395) administered niacin versus placebo to rats and found elevation in adiponectin levels, with increased adiponectin secretion from adipocytes incubated with niacin for 24 h in vitro—suggesting a potential mechanism of benefit, although not concordant with the glucose-raising effect of the agent.

Fibrates

Li et al. (abstract 475) studied 45 hypertriglyceridemic individuals with type 2 diabetes or impaired glucose tolerance. Fenofibrate (200 mg daily) decreased fasting insulin 30% with a 30% increase in the acute insulin response to intravenous glucose, with deterioration in both indexes in a placebo group. Jones et al. (abstract 85) treated 276 type 2 diabetic patients who had LDL cholesterol >130 mg/dl, triglyceride levels >150 mg/dl, and HDL cholesterol <40 mg/dl (50 mg/dl for female subjects) with the fenofibrate preparation ABT-335, rosvastatin (10–40 mg), or the combination for 12 weeks. ABT-335 increased HDL cholesterol by 15% and reduced triglyceride levels by 34% and HDL cholesterol by 6%; rosvastatin (10 and 20 mg) increased HDL cholesterol by 7 and 12%, reduced triglyceride levels by 28 and 27%, and reduced LDL cholesterol by 44 and 45%; however, the combination had a less than additive effect at the rosvastatin 10- and 20-mg doses in increasing HDL cholesterol by 21 and 18% and reducing triglyceride levels 45 and 42%, with LDL reductions of 37% at both doses (less than the effect of rosvastatin alone), suggesting that the use of the combination in diabetic patients should be highly selective.

Calorie restriction

Andrew Dillin (La Jolla, CA) noted that lifelong calorie restriction by half (without malnutrition) improves longevity in every animal model studied, from worms to rodents to nonhuman primates. The DAuer Formation (daf-16) insulin/IGF-1 analog gene is not required for diet restriction in worms and flies. Diet restriction-mediated longevity in the roundworm Caenorhabditis elegans is independent of FOXO1, with a transcriptional coregulator smk-1, a mitogen-activated protein kinase homolog that specifically regulates longevity and stress resistance (2). Smk-1 has effects analogous to those of peroxisome proliferator–activated receptor-γ coactivator (PGC)-1 and appears to partner with daf-16 in insulin signaling as well as in mediating effects of dietary restriction, perhaps involving an alternate forkhead-like transcription factor to FOXO1, pha-4—the worm ortholog of the Foxa gene. In mammals, Foxa1 binds and activates genes expressed in foregut endoderm-derived lineages and is required for fetal development, but gene deletion in adulthood shows that Foxa1 function later in life is to regulate glucose homeostasis. Pha-4 similarly has developmental function early in the C. elegans life cycle; during adult life, it mediates the longevity effect of dietary restriction in a fashion specific to dietary restriction, whereas daf-16 is more specific to the response for insulin/IGF-1. Pha-4 expression increases with diet restriction, although its subcellular localization does not change, and overexpression of pha-4 extends life span on ad libitum diet, particularly with deletion of daf-16 (3).

Anne Brunet (Palo Alto, CA) discussed FOXO transcription factors in insulin and nutrient signaling as components of molecular mechanisms of longevity and noted the progressive increase in life span of a variety of species with reductions in calorie intake by 25 to 65% (4) and with reduction in risk of cancer, increased performance in learning and memory, and a variety of additional effects suggesting delay in aging and age-related traits. Given that insulin levels decrease with dietary restriction and because reducing insulin action extends life span in worms, flies, mice, and perhaps humans, studies of the insulin signaling pathway have been important. Insulin and IGF-1 act via the FOXO family of forkhead transcription factors (with pyruvate dehydrogenase kinase phosphorlylating FOXO), blocking its translocation to the nucleus and leading...
to target gene inactivation. FOX0 in the nonphosphorylated state enters the nucleus and may lead to transcription of antiaging genes. FOX0 interacts with SIRT1—the mammalian homolog of the sirtuin (silent information regulator) enzymes—a histone/protein deacetylase that has been linked to the prolongation of life span caused by caloric restriction. There are seven mammalian sirtuins: SIRT1 and SIRT2 expressed mainly in the brain; SIRT3, SIRT4, and SIRT5 active in mitochondria; SIRT6 active in the nucleus; and SIRT7 active in the nucleolus and activating RNA polymerase I transcription. SIRT1 levels increase with dietary restriction, potentially activating target genes leading to stress resistance and longevity. The genes mediating the effect of dietary restriction may involve AMP-activated protein kinases (AMPKs) that may be a cellular energy sensor activated by low leptin, low energy, low glucose, exercise, and biguanides. AMPK can integrate a wide variety of stimuli by its exquisite ability to sense the AMP/ATP ratio, with increase in AMP triggering change in the α catalytic subunit of AMPK, activating acetyl-CoA carboxylase, with multiple effects on lipid and protein synthesis. In C. elegans, with reduced nutrition there is extended life span and amelioration of the decline in physical activity with age, associated with increased AMP/ATP ratio, requiring AMPK. Overexpression of AMPK in C. elegans leads to increased life span and stress resistance. AMPK may directly phosphorylate daf-16 in C. elegans and FOXO1 in mammals, extending longevity. Another forkhead transcription factor FOXO3 is also phosphorylated with increases in AMPK and may have roles in stress resistance and energy metabolism. AMPK activators such as metformin then may be beneficial for nondiabetic life span (5).

A number of reports at the ADA meeting provided information on effects of caloric restriction. Zheng et al. (abstract 1263) reported that 40% caloric restriction of obese Zucker rats improved hepatic insulin sensitivity in association with reduction in extracellular signal-regulated kinase activity. Jing et al. (abstract 145) studied Sirt3 expression of which is decreased in skeletal muscle of streptozotocin-induced diabetic mice, showing decreased hepatic and skeletal muscle expression on a high-fat diet. Small interfering RNA administration to decrease Sirt3 in vitro in myoblasts reduced insulin-stimulated phosphorylation of Akt and mitogen-activated protein kinase because of decreased insulin receptor substrate (IRS)-1 tyrosine phosphorylation; oxygen consumption induced by mitochondrial uncoupling was significantly decreased, AMPK activity was inhibited, and PGC-1 and other stress markers were increased. Suchankova et al. (abstract 1492) studied hepatocytes overexpressing PGC-1α (a SIRT1 target gene) and found reduction in SIRT1 activity with high glucose concentrations increasing acetylated PGC-1α, as did the SIRT1 inhibitor nicotinamide that also decreased the phosphorylated form of AMPK, implying that SIRT1 may regulate AMPK and that the activity of SIRT1 may be decreased by hyperglycemia. Banks et al. (abstract 1387) studied mice overexpressing SIRT1 and reported improved glucose tolerance with increased adiponectin and reduced metabolic rate as well as decreased food intake to maintain body weight. Milne et al. (abstract 1907) and Perni et al. (abstract 540) studied effects of small molecule SIRT1 activators, ozapolypyriones, and isoazahiazoles (IATs) and found inhibition of inflammation in vitro in human monocytes and improved insulin sensitivity, with reduced inflammatory gene expression in a high-fat diet–induced obesity model with the agents SRT2183 and SRT1720. The IAT SIRT1 activator SRT2104 demonstrated significant glucose-lowering activity in both the db/db and dietary obesity mouse models.

Resveratrol—a plant chemical produced under attack by bacteria or fungi, present in wine—extends the life span of several invertebrates and vertebrates and counteracts high-fat diet–induced insulin resistance in mice, perhaps by activating SIRT1 and PGC-1α. Knight et al. (abstract 1321) extended studies showing that hypothalamic resveratrol suppressed hepatic glucose production and increased insulin sensitivity by central SIRT1 activation. Systemic resveratrol administration increased insulin sensitivity by reducing hepatic glucose production without increasing peripheral glucose utilization. Inhibition of hypothalamic Sirt1 activity reduced the effect of systemic resveratrol by increasing hepatic glycogenolysis. Sanli et al. (abstract 572) reported that resveratrol reduced free fatty acid–induced insulin resistance in vitro; Donadon et al. (abstract 346) administered resveratrol (100 mg daily) versus placebo to 16 healthy normal-weight subjects, reducing monocyte inflammatory and mitogenic gene expression while increasing IRS-1 expression; and Kitada et al. (abstract 753) found that db/db mice showed reduction in hyperglycemia and in albuminuria and mesangial expansion, although Kasinath et al. (abstract 738) reported that resveratrol improved renal injury in streptozotocin-induced diabetic rats by stimulating AMPK rather than by affecting SIRT1 activity.

Polsky et al. (abstract 102) analyzed the effect of alcohol consumption in 3,175 participants in the Diabetes Prevention Program followed for 3.2 years and found that those receiving metformin or the intensive lifestyle intervention had lower rates of diabetes development with ingestion of one or more alcoholic beverages daily, controlling for age, sex, weight, ethnicity, C-reactive protein, exercise, caloric intake, insulin sensitivity and secretion, and fasting glucose. Kim and Reaven (abstract 354), however, administered 20–30 g of alcohol (red wine or vodka) daily for 1 month to 20 insulin-resistant subjects and reported only modest and nonsignificant increase in insulin sensitivity, with a 9% increase in HDL cholesterol.

Biology of taste and taste receptors
Charles Zuker (La Jolla, CA) discussed the biology of taste and taste receptors (6). To understand the signaling and coding mechanisms by which the brain encodes and decodes taste stimuli, we need to understand “how the tongue knows” what it has just tasted and, next, “how the brain knows what the tongue knows.” The main tastes are sweet, sour, bitter, salty, and umami (the taste of monosodium glutamate). Taste contributes to the overall enjoyment and pleasure of a meal in humans but plays more basic roles in other species mediating behaviors, with sweet acting as a measure of calories, salt electrolyte balance, umami amino acids, sour as key to preventing ingestion of spoiled foods, and bitter preventing ingestion of toxins. Nearly every plant toxin tastes bitter to humans. The basic units of taste are taste receptor cells, which are organized in taste buds and in turn organized in the tongue in taste papillae of various types. Every taste bud in all areas of the tongue contains receptors for all basic tastes, with the posterior tongue enriched with bitter receptors, which trigger the gag reflex.

The attractive taste modalities are sweet and umami, mediated by combinations of three G-protein–coupled receptor units T1R1, T1R2, and T1R3, with umami as a combination of T1R1 + T1R3
and sweet T1R2 + T1R3, whereas bitter taste recognition involves the type 2 G-protein–coupled taste receptor. Salty taste may involve epithelial Na channels similar to those in the kidney, and sour taste may involve intracellular acidification acting on specific membrane proteins (7). Electrophysiological measurement after taste challenge assays increase in action potential response to one or another of the five basic tastes. Deletion of T1R1 or T1R3 eliminates the umami response, T1R3 also sweet, and T1R2 eliminates sweet taste providing evidence of the G-protein–coupled receptor selectivity of receptor rearrangements. Bitter is related to the rhodopsin light receptor; there are 24 human and 33 rodent bitter receptors, functioning to give information about specific bitter tastes. Sequence differences in taste receptors underlie taste selectivity and sensitivity differences between species. Rodents, for example, do not taste aspartame and intensively sweet proteins, whereas introduction of the human receptor into a mouse can give rise to recognition of these as specific taste signals. Taste cells are segregated by type at the periphery of the tongue, with specific cells dedicated to specific taste qualities. Animals lacking entire taste qualities can detect, recognize, and respond normally to the remaining modalities, and experiments introducing another receptor into a cell type will lead to activation of the typical stereotyped behavior of that cell type–specific activation.

After taste signals are generated, neurotransmitters are secreted acting both on neighboring taste cells, suggesting local information processing, and on sensory afferent fibers. Cells for sweet, bitter, and umami taste stimuli secrete ATP that acts as a neurotransmitter, whereas sour and salt taste cells release other neurotransmitters including serotonin. At the brain level, understanding of taste recognition is more preliminary; however, there is evidence of selective distribution of unique receptors from specific tastes in specific cortical areas, with mixtures of several tastes activating certain groups and inactivating other groups of cortical cells. This is not, Zuker commented, the full story of how the brain “knows” specific signals, but it is a beginning.

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