Preface to the Special Issue: 
Brief review of plant hormones and their utilization in agriculture

A hormone is generally defined as a class of signaling molecules that are secreted from glands in organisms and transported by the circulatory system to target organs to regulate physiology and behavior. However, the term "hormone" is sometimes extended to include chemicals produced by cells that affect the same cell or nearby cells. In the target cells, hormones bind to specific receptor proteins, resulting in a change in cell function and the activation of a signal transduction pathway. Unlike in animals, there is no specific hormone-secretion gland in plants, but small signal molecules are produced within the plant in extremely low concentrations. These are called plant hormones, which regulate cellular processes in certain targeted cells near that they are produced or moved to other organs where they function. To date, auxins, gibberellins (GAs), cytokinins (CKs), abscisic acid (ABA), ethylene, brassinosteroids (BRs), jasmonic acid (JA), salicylic acid (SA), florigen, and strigolactones (SLs) have been reported as plant hormones (Fig. 1). Some plant hormone-like compounds are registered as pesticides. An auxin-like compound, 2,4-dichlorophenoxyacetic acid (2,4-D), was successfully developed as an herbicide in the USA in 1945, which is the earliest plant growth regulatory pesticide, and is still available in the agricultural market. GAs, CKs, and ethylene are also available in the agricultural market as plant growth regulators (PGRs). BR- and SL-like compounds have received a lot of attention in recent years because they can be candidates for new PGRs in agriculture. In this review, we briefly introduce each hormone with its discovery, biosynthesis, and receptor-related action, as well as chemicals that are used as agrochemicals presently and those that may be developed. Representative plant hormone structures are shown in Fig. 1. Readers can refer to the comprehensive review of plant hormones (Jiang and Asami, Biosci. Biotechnol. Biochem. 2018/10.1080/09168451.2018.1462693).

1. Auxin

In 1880, Charles Darwin and his son Francis proposed that an "influence" moved from the site of light perception to the site of differential growth and resulted in curvature of the phototropism. Later, it was revealed that the "influence" was auxin. Auxin is the first plant hormone to play a cardinal role in coordinating many growth and behavior processes in the plant’s life cycle, and it is essential for plant body development. Th-
mann first isolated indole-3-acetic acid (IAA) in 1937. In the 1930s, Kögle and Thimann isolated compounds that stimulate plant growth using the avena curvature test from human urine, yeast, and fungi. They named those growth-stimulating substances auxin. IAA was first isolated from a plant in 1946. Auxin is synthesized from l-tryptophan via indole-3-pyruvate by the tryptophan aminotransferase of Arabidopsis and YUCCA flavin-containing monoxygenase families. Non-specific auxin biosynthesis inhibitors such as amino-oxybenzylglycine (AVG), an inhibitor of ACC synthase, and 1-aminoxyphytlenopropionic acid (1-AOPP), targeting the Trp aminotransferase, were reported. PVM1169 and PVM2031 were more specific inhibitors than AVG and 1-AOPP. Auxin binding to the auxin receptor TIR1 and a part of the Skp-Cullin-F-box (SCF) ubiquitin ligase complex initiates the proteolysis of Aux/IAA proteins that repress the functions of auxin. This process is inhibited by auxin receptor inhibitor α-(phenylethyl-2-oxo)-IAA (PEO-IAA). Auxin distribution within tissues is mediated by several classes of auxin transporters, including pin-formed proteins (PINs), auxin transporter 1 and auxin transporter-like (AUX1/LAX), and p-glycoproteins belonging to the ATP-binding cassette (ABC) family (PGP/ABCB). Multiple auxin signal inhibitors such as N-naphthylphthalamic acid (NPA), 1-pyrenoylbenzoic acid (PBA), and 2,3,5-triodobenzoic acid (TIBA) have been confirmed as polar auxin transport inhibitors. NPA and PBA target PINs and PGP, while TIBA might target AGR1/PINs. 2,4-D, 4-chloro-2-methylphenoxyacetic acid (MCPA), and dicamba are used as herbicides.

2. Gibberellin (GA)

GAs regulate various developmental processes, including stem elongation, germination, vegetative growth, flowering, and reproduction. GAs were found in the study on bakanae (foolish seedling) disease in rice. Japanese scientist Eiichi Kurosawa showed that a substance produced by Gibberella fujikuroi triggered the symptoms of foolish seedling disease. Later, this substance was named "gibberellin." GAs were first isolated by Kurosawa, and GA1 was first crystallized in 1938 by Yabuta and Sumiki. To date, more than 130 GAs have been reported, but only a few compounds (GA1, GA3, and GA4) are biologically active. GAs are synthesized from geranylgeranyl diphosphate (GGDP) by a series of enzymes. Hydroxylation of the 3β position is necessary for the bioactivity of GAs. Bioactive GAs undergo hydroxylation at the 2β position by a 2-oxoglutarate-dependent dioxygenase, GA2-oxidase (GA2ox), which leads to their deactivation. In 2005, GA-insensitive dwarf1 (GID1) was identified as a GA receptor in rice, and the signaling pathway has now been established. The binding of GAs to the GID1 receptor induces conformational changes in the lid of GID1 to facilitate its interaction with SLR1, a rice DELLA protein. GID1 receptors have also been identified in Arabidopsis.

It is well known that GAs have potential for use on various commercially important plants. They are widely used in the grape-growing industry as a hormone to induce the production of larger bundles and bigger grapes, especially Thompson seedless grapes. Although it is not practical to synthetically produce a large amount of GAs, this fermentation technique can be used. GA biosynthesis inhibitors inhibit growth and induce early fruit-set as well as seed-set. Several types of plant growth retardants have been developed and confirmed to act as GA biosynthesis inhibitors. Paclobutrazol and uniconazole inhibit the oxidation of ent-kaurene to ent-kaurenoic acid, and prohexadione inhibits 3β-oxidation to suppress GA production. These inhibitors are used to suppress plant height, thus increasing plant compactness and preventing lodging.

3. Cytokin (CK)

CKs promote cell division in plant roots and shoots, but they also affect apical dominance, axillary bud growth, and leaf senescence. CKs were discovered by Folke Skoog in the 1940s. There are two types of CKs, adenine (kinetin, zeatin, and 6-benzylaminopurine) and phenylurea CKs (diphenyleura and thidiazuron). No phenylurea CKs have been found in plants. trans-Zeatin (tZ), a major CK, is synthesized from dimethylallyl diphosphate and ADP/ATP by isopentenyltransferase that produces isopentenyladenine (iP) nucleotide. The iP nucleotide is then catalyzed by cytochrome P450. Phosphoribohydrolase converts the iP nucleotide to active tZ.

CK signaling is mediated by a two-component system. CRE1/AHK5, a histidine kinase, is a CK receptor in Arabidopsis and transfers the phosphoryl group to a histidine phosphotransferase to initiate CK signaling. CKs participate in local and long-distance signaling using the same transport mechanisms as purine and nucleotides. Typically, CKs are transported in the xylem. CKs are used to increase crop production: CK treatment led to a 5–10% yield increase from cotton seedlings under drought conditions. CKs act in concert with auxin, and they are complementary, having generally opposite effects. CKs are used in agriculture. Benzyladenine is used to produce healthy rice seedlings due to its anti-aging effect, and phenylureas such as thidiazuron are used as defoliants before harvesting the cotton.

4. Abscisic acid (ABA)

ABA was first isolated from cotton and characterized by Liu and Carns during their study of fruit abscission, which accounts for its name. The structure of ABA was proposed by Okuma and Addicott. ABA functions in developmental processes, including seed and bud dormancy, cell division and elongation, floral transition, the control of organ size, and stomatal closure. It is especially important for plant response to environmental stresses, including drought, soil salinity, cold or freezing temperatures, heat, and heavy metal ions. ABA was biosynthesized from carotenoids by several enzymes. Zeaxanthin epoxidase (ZEP), which is encoded by ABA1 in Arabidopsis, converts zeaxanthin to violaxanthin in chloroplast. Then nine cis-epoxycarotenoid dioxygenases (NCEDs) cleave the cis isomers of violaxanthin and neoxanthin to xanthoxin. Finally, cis-xanthoxin is converted to active ABA through sequential reactions catalyzed by short-
chain dehydrogenase/reductase 1 (SDR1) encoded by ABA2 and abscisic-aldehyde:oxygen oxidoreductase (AAO3). Fluridone, an aquatic herbicide, inhibits carotenoid accumulation and ABA biosynthesis, and abamectin inhibits NCEDs.

The ABA signaling pathway was established by the identification of PYR/PYL/RCAR proteins (PYLs), a group of soluble ABA receptors. ABA binds to PYL and promotes conformational changes in the gate and latch loops in PYL, which facilitates its interaction with the 2C protein phosphatase (PP2C) that interacts with and inactivates sucrone non-fermenting 1-related protein kinase 2 (SnRK2) through dephosphorylation. The catalytic site of PPC2 is sealed by its interaction with the ABA–PYL complex, and PP2C subsequently loses its SnRK2-inhibitory effect. When released from the inhibition by PPC2, SnRK2s phosphorylate themselves and their targets to induce ABA responses. Pyrabactin was used to screen for resistant mutants, which led to the identification of a pyrabactin-resistant (PYR1) loss-of-function mutant. PYR1 and 14 homologs were subsequently identified as ABA receptors. Pyrabactin, which is a selective agonist for PYL, overcomes the redundancy of the 14 ABA receptor homologs. Recently, sulfonamide (dihydroquinoline, quinabactin/AM1) was reported to be an agonist of PYL. Quinabactin/AM1 promotes the interaction between PYL and PP2C, inhibits seed germination, and prevents leaf water loss. The crystal structure of PYL–ABA–PP2C complex was elucidated by four groups, including Miyazono et al. and Nishimura et al. in 2009.

5. Ethylene

In 1864, ethylene was discovered as the main active component in gas leaks from street lights that led to stunting of growth, twisting of plants, and abnormal thickening of stems. Sarah Doubt discovered in 1917 that ethylene stimulated abscission. Farmers in Florida would commonly get their crops to ripen in sheds by lighting kerosene lamps, the heat from which was originally thought to induce ripening. In 1924, Frank E. Denny discovered that the molecule ethylene emitted by kerosene lamps induced ripening. Gane reported in 1934 that plants synthesize ethylene, and Crocker proposed in 1935 that ethylene was the plant hormone responsible for fruit ripening as well as the senescence of vegetative tissues. Ethylene is synthesized from S-adenosylmethionine (SAM) by two enzymes, aminocyclopropene-1-carboxylic acid (ACC) synthase (ACS) and ACC oxidase (ACO). Ethylene receptors localize to the endoplasmic reticulum (ER) system, and five receptor genes have been identified: ethylene response 1 (ETR1), ETR2, ethylene response sensor 1 (ERS1), ethylene-insensitive 4 (EIN4), and ERS2. [Note: Is the phrase “ethylene-insensitive 4” appropriate? Usually the adjective “insensitive” must modify a noun.] The ethylene responsive gene is activated via signal transduction [ETR1→CTR1→EIN2→EIN3→ethylene response factor 1 (ERF1)].

Ethylene is used to ripen bananas and inhibit potato germination, both of which are performed in a closed same container. Ethephon, which produces ethylene in plants, is used in the agricultural field. Aminoxyacetic acid (AOA), a general inhibitor of the pyridoxal phosphate-dependent enzyme, also inhibits ethylene biosynthesis by targeting ACS. α-Aminoacylbutyric acid (AIB) acts as a competitive inhibitor of ACO. 2-Amino-oxygenobutyric acid (AOI) inhibits ACS and ACO. As ethylene induced the seed germination of some root parasitic weeds, it was used in the USA to stimulate the germination of Striga spp. without host plants. As germinated seeds cannot survive without host plants, this method is referred to as suicidal germination.

6. Brassinosteroid (BR)

Brassinolide (BL) was found to be the sixth plant hormone. Before the discovery of BL-deficient or BR-insensitive Arabidopsis mutants, it had been thought that BL was the secondary metabolite. Mitchell and coworkers published “Brassins—A New Family of Plant Hormones from Rape Pollen” in 1970. The response of brassins was histologically different from the response induced by GAs. Mandava and his group purified the compound using silica gel and C18 reversed-phase HPLC chromatography and obtained 4 mg of BL from 40 kg of pollen. The structure of BL was revealed via X-ray crystal structure analysis. In Japan, scientists at Nagoya University had been trying to isolate and determine the structure of new auxin-like substances that were active in the rice lamina inclination (RLI) assay. This RLI assay was originally designed by Maeda in 1965 to detect synthetic auxins. The scientists at Nagoya University published the Distylium factors existing in insect galls in the aphid-infested leaves of Distylium racemosum, which had far higher activity than the IAA in Maeda’s bioassay system. Distylium factors were also found in healthy D. racemosum leaves. Marumo and co-workers isolated three Distylium factors (A1, A2, and B) that were detected as single spots on a TLC in 1968, but their structures could not be determined due to the low sensitivity of the NMR and MS instruments. Later, Yokota and co-workers isolated castasterone from chestnut insect gall and dolicholide from immature seeds of Dolichos lablab. These BL-like compounds are grouped as brassinosteroids (BRs).

BRs are synthesized from campesterol via various cytochrome P450 enzymes (CYPs). The biosynthesis of BRs is fully reviewed by Ohnishi in this special issue (J. Pestic. Sci., Vol. 43, No. 3). The receptor of BL is BR11, with an extracellular domain containing a leucine-rich repeat (LRR), and BL binds to LRR. BRs bind to BR11 and its co-receptor, BAK1 (SERK3), and the intracellular domain of BR11/BAK1 is phosphorylated to start the signal transduction. Finally, transcription factors BES1 and BZR1 move into the nucleus and activate the target genes.

BL and its modified compounds increase fruit-setting and fruit size, but the application of BRs in agriculture is hampered by the high synthetic cost of BRs. Therefore, simple non-steroidal BL mimics are needed for the development of practicable compounds. Characterization of the three-dimensional structure of the BL-receptor and advanced computer technology opened the door of in silico screening to find non-steroidal BL-like compounds. NSBR1 was discovered as the first non-steroi-
dal brassinolide-like compound by Sugiura et al. in 2017. Another BR mimic was also reported by Lei et al. in 2017. Inhibitors of BL biosynthesis, such as Brz, Brz2001, and Brz2202, have also been developed and used as tools in biology and biochemistry research.

7. Jasmonic acid (JA)

Jasmine is a well-known aromatic flower, and in 1962, methyl jasmonate (MeJA) was discovered as the main ingredient of that aroma. In 1971, jasmonic acid (JA) was identified from the broth of Lasiodiplodia theobromae as an inhibitor of plant growth. MeJA was isolated from plants as a plant growth regulator in 1980. JA and its derivatives are lipid-based plant hormones that regulate a wide range of processes in plants. JA and its derivatives can also be released as volatile organic compounds (VOCs) to permit communication between plants and microorganisms.

JA biosynthesis begins when α-linolenic acid is released from a chloroplast membrane. Lipoxygenase (LOX) inserts an oxygen into the C-13 position of α-linolenic acid to produce 13-hydroperoxyoctadecatrienoic acid (13-HPOT). Fatty acid hydroperoxides are cyclized by the allene oxide synthase (AOS) to produce 12-oxophytodienoic acid (OPDA). OPDA reductases (OPRs) construct a cyclopentanone ring to derive (+)-7-iso-JA, which is converted to MeJA by the JA carboxymethyltransferase (JMT). Conversion to the bioactive jasmonate, (+)-7-iso-JA-Ile, is catalyzed by the JA-amino acid synthase (JAR1). Jasmonate response inhibitor-1 (jarin-1) was found to inhibit the JA signals induced by MeJA. JARIN-1 prevents the biosynthesis of JA-Ile by targeting JAR1.

The physiological roles of a phytotoxin coronatine (COR) were isolated from the pathogen Pseudomonas syringae pv. atropurpurea and are similar to those of JA, and the structure of COR is similar to that of JA-Ile. Turner et al. isolated an Arabidopsis mutant that is insensitive to COR, and Xie et al. characterized this loss-of-function mutant and identified its causal gene. This gene encodes an F-box protein belonging to the E3 ubiquitin ligase complex, named coronatine insensitive 1 (COI1). Later, MYC2 was identified as a basic helix-loop-helix transcription factor that regulates JA-responsive genes. The jasmonate ZIM domain (JAZ) represses the transcription of jasmonate-responsive genes through interaction with MYC2. JA-Ile, a bioactive JA, binds to the COI1 receptor and promotes the interaction of COI1 with JAZ, leading to the polyubiquitination and subsequent degradation of JAZ by the 26S proteasome. The COI1–JAZ complex was crystallized to provide the mechanism view on JA-Ile perception. The keto group of JA and the COOH of Ile in JA-Ile interact with the JAZ domain, explaining the reason (+)-7-iso-JA-Ile is the most bioactive ligand for COI1. Based on this analysis, JA O-methylxime (JA-MO), JA-Ile-MO, and COR-MO were rationally designed. COR-MO was confirmed to be an antagonist of COI1, which impedes the interaction between COI1 and JAZ, JAZ degradation, and the physiological roles of JA-Ile and COR in Arabidopsis. Prohydrojasmon, a simple derivative of JA, is now available on the market to improve the color of apples.

JA signaling is important for plant defense against insects. Hijacking of the COI1 receptor by certain pathogens increases plant susceptibility, as confirmed by the construction of a genetic modification of the COI1 receptor that specifically perceives JA-Ile but not COR. Structural modeling based on the crystal structure of COI1–JAZ was used to direct the modification. The substitution of Ala with Val at the 384 position of COI1 decreased the affinity of COR by 100 times.

8. Salicylic acid (SA)

A large amount of SA accumulates in infected plants. SA is a phenolic phytohormone and plays a role in growth/development, photosynthesis, transpiration, ion uptake, and transport. Salicin, a glucoside of SA, was first isolated in Salix bark extract in 1828 and has been used as a pain reliever. In 1890, aspirin (acetylsalicylic acid) was introduced by Bayer as a commercial drug for the treatment of pain, fever, and inflammation. SA is involved in endogenous signaling, mediating in plant defense against pathogens. It plays a role in the resistance to pathogens by inducing the production of pathogenesis-related proteins. It is involved in the systemic acquired resistance (SAR) in which a pathogenic attack on one part of the plant induces resistance in other parts. The pathogenesis-related (PR) genes encode small secreted or vacuole-targeting proteins with antimicrobial properties. PR1 gene expression is promoted by SA and can be used as a molecular marker of the onset of SAR. The signal can also move to nearby plants when SA is converted to the volatile ester methyl SA. SA has also been extensively studied in medicinal research.

It is thought that SA is synthesized from chorismate and phe nylalanine via two pathways, although there are several gaps in the pathways. Chorismate is converted to isochorismate by isochorismate synthase (ICS). Isochorismate is subsequently converted to SA by isochorismate pyruvate lyase (IPL) or by isochorismate mutase. Phenylalanine is converted to trans-cinnamic acid by phenylalanine ammonia lyase (PAL), which is then decarboxylated to benzoic acid. Benzoic acid is hydroxylated to SA by benzoic acid 2-hydroxylase (BA2H). 2-Aminoindan-2-phosphonic acid (AIP), which is known as a PAL inhibitor, suppressed pathogen-induced SA accumulation in tobacco, cucumber, and Arabidopsis.

A non-expressor of pathogenesis-related gene1 (NPR1) is a master regulator and resides in the cytoplasm. NPR1 paralogs, NPR3 and NPR4, are SA receptors that target NPR1 for degradation in an SA-concentration-dependent manner. It is also reported that NPR1 could bind to SA and function as an SA receptor. Synthetic agonists and antagonists that are selective for specific receptors can provide further insight into the signal pathway. Benzo(1,2,3)-thiadiazole-7-carbothioic acid S-methyl ester (BTH) induces disease resistance without causing SA ac-
cumulation. 3-Allyloxy-1,2-benzothiazole 1,1-dioxide (probena-
zole) and 1,2-benzoisothiazol-3-(2H)-one 1,1-dioxide (BIT) were reported to stimulate the SA/NPR1-mediated defense sig-
naling pathway upstream of SA. BTH and 2,6-dichloroisonicotin-
ic acid (NIA) are used as SA analogs to induce SAR responses in plants. N-Cyanomethyl-2-chloroisonicotinamide (NCI) in-
duces disease resistance in an NPR1-dependent manner without SA accumulation. NCI functions between SA and NPR1 in the signal transduction pathway. 4-Phenyl-2-[(3-trifluoromethyl]-
aniline)methylidene]-cyclohexane-1,3-dione (PAMD) was found to be the strongest inhibitor for SA-induced-β-glucuro-
nidase (GUS) expression, but it has adverse effects on plant growth. A structure–activity study of PAMD analogs led to a compound with fewer side effects on plant growth.

9. Strigolactones (SLs)

SLs are group of chemical compounds produced by plant roots (Xie et al., 2016). SLs promote the germination of parasitic plants that grow in the host plant's root, such as Striga lutea and other plants of the genus Striga. SLs play an essential role in rec-
ognition of the plant by symbiotic fungi because they establish a mutualistic association with these plants and provide phosphate and other soil nutrients. SLs inhibit shoot branching in plants and play roles in enhancing lateral root formation and root hair elongation. The structure of natural canonical SLs is based on a tricyclic lactone linked to a hydroxymethyl butanolide (D-ring). SL was first isolated in 1966 (Cook et al.) from cotton plants as the germination stimulant for the root parasite witchweed, but the role of the SL was unclear. Akiyama et al. demonstrated that 5-deoxyxtrigol (SDS), a natural stereoisomer of SLs, acts as a branching factor to promote the hyphal branching of arbuscular mycorrhizal (AM) fungi, which in turn help plants to capture nutrients. SLs were finally recognized as plant hormones fol-
lowing the finding that SL inhibits shoot branching in rice and Arabidopsis. Due to their fruitful roles, SLs can be expected to contribute to agriculture. In sub-Saharan Africa and the Medi-
terranean region, crops are often severely damaged by the para-
sitic weeds Striga and Orobanche, which are difficult to control because of large quantity and small size of their seeds. Suicide germination could be an effective approach for controlling dam-
age by these parasitic weeds.

SLs are derived from β-carotenoid by sequential enzyme catalyzation. D27 catalyzes the isomerization of all-trans-
β-carotene to 9-cis-β-carotene, which is oxidized to carlac-
tone (CL) by CCD7/CCD8. CL is converted to carlactonic acid (CLA) in Arabidopsis by MAX1 and to 4-deoxyorobanchol (4DO) and orobanchol in rice. Although some compounds such as abamine, which targets CCD, tebuconazole, TIS13 and its derivative (TIS108), which target P450, are reported to be SL biosynthesis inhibitors. However, none of them were specific inhibitors of SL biosynthesis. New inhibitors of CCD based on abamine could be found.

Studies investigating the SL signaling pathway have made fast progress. DWARF14 (D14) is a member of the α/β hydrolase superfamily and was the first to be identified as a tiller regula-
tor in rice. Computational homology modeling suggested that D14 might be an SL receptor, because it is similar to several α/β hydrolase-like proteins, such as GA receptors, as reported by Mashita et al. in 2016. D14 perceived SLs and hydrolyzed SLs to yield D-OH, a butenolide ring with a hydroxyl group. D14 is now recognized as both an SL receptor and an enzyme that hydrolyzes SLs. Many groups are developing SL agonists and an-
tagonts to reduce the damage from root parasitic weeds or to regulate plant architecture to improve crop productivity.

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