Original article

Cannabis points to the synaptic pathology of mental disorders: how aberrant synaptic components disrupt the highest psychological functions

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Cannabis can elicit an acute psychotic reaction, and its long-term use is a risk factor for schizophrenia. The main active psychoactive ingredient Δ^9-tetrahydrocannabinol (Δ^9-THC) activates cannabinoid 1 (CB1) receptors, which are localized to the terminals of glutamate and GABA neurons in the brain. The endogenous cannabinoids are involved in information processing and plasticity at synapses in the hippocampus, basal ganglia, and cerebral cortex. Exogenously applied CB_1 receptor agonists disrupt neuronal dynamics and synaptic plasticity, resulting in cognitive deficits and impairment of the highest psychological functions. Various other pro-psychotic drugs, such as ketamine and methamphetamine, exert their effects in the same microdomain of synaptic spines as Δ^9-THC. Additionally, many of the most robust findings in psychiatric genetics include components that localize to dendritic spines and have important roles in information processing and plasticity.

Dialogues Clin Neurosci. 2020;22(3):251-258. doi:10.31887/DCNS.2020.22.3/pmorrison

Keywords: bipolar; cannabis; cognition; connectome; dendritic spine; ketamine; plasticity; psychosis; schizophrenia; Δ^9-tetrahydrocannabinol

Introduction: the phenomenology of endocannabinoid CB1 receptor agonists

It is well known that persistent heavy use of cannabis increases the risk of schizophrenia-like psychoses. There are numerous reviews of the topic,[1,2] so we will not present the evidence yet again. Rather, we will discuss the possible molecular mechanisms underlying the psychotogenic effects of cannabis and its effects on cognitive functions such as memory. The main psychoactive component of cannabis is Δ^9-tetrahydrocannabinol (Δ^9-THC) which is an agonist at the endocannabinoid cannabinoid 1 (CB_1) receptor. Agonists at the CB_1 receptor can have a major effect on the higher faculties, including the induction of an acute psychotic reaction.[3] Synthetic CB_1 receptor agonists appear to produce a more florid psychotic reaction than Δ^9-THC.[4,5]

The phenomenology of endocannabinoid CB_1 receptor agonists

The acute psychosis resulting from exogenous cannabinoid effects on CB_1 receptors is polymorphic, with features that can be categorized as positive, negative, and disorganized.[6] Thinking can be grandiose, "a feeling of great insight… I must write down this fantastic theory," or have a more sinister, paranoid flavor, "every occurrence, cough, object,

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test, has deeper and connected meaning…it was all deliberate, planned…some sort of prank, to make a fool of people."[7]

There can also be an apparent disconnect in the unity of the highest faculties. In normal consciousness, the will to move, the movement itself, and the recognition that one has just moved are part of a coherent whole, which is taken for granted. Under CB_1 receptor agonists, there can be an apparent fragmentation, for instance "…there was a dissociation between movement and the will to move." The same effect can also occur in the domain of language, for example "There's an incredible disconnection between thinking and saying something" and "The key theme in hallucinations… you do not realize if you are saying these words out loud or just thinking it."[7] So-called first-rank symptoms of schizophrenia, in which there are abnormalities in selfhood, can occur with CB_1 receptor agonists, such as "It feels like my legs are being controlled by strings from the ceiling. Yes… actual strings."[7] These reports indicate that CB_1 receptor agonists can have a marked effect on neuronal dynamics, which manifest as a transformation of the experience of lived reality.

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Effects of CB_1 receptor agonists on hippocampal functioning

It is well established that cognitive functioning can be impaired under CB_1 receptor agonists. The deficits are apparent over the range of cognitive domains, including executive functioning and delayed recall.[3,7]

Delayed recall of new information depends on the proper functioning of the hippocampus. The hippocampus acts as a buffer, which stores information in the background, obviating the need to continuously circulate information in consciousness.[8] Hippocampal functioning is easily tested by the recall of a list of words, some 15 to 20 minutes after the initial presentation of the list. In laboratory studies, delayed recall is invariably disrupted under Δ^9-THC conditions.[3,7] Essentially, Δ^9-THC and other endocannabinoid CB_1 receptor agonists disrupt the proper neurophysiological functioning of the hippocampus.

The circuitry of the hippocampus is reasonably well understood. This is the case both at the gross anatomical level and at the micrometer level of individual synapses.[9] The intrinsic circuitry of the hippocampus follows a regular and well-demarcated pattern, a characteristic made use of by cellular electrophysiologists deciphering the general rules of synaptic plasticity. The most well-known form of plasticity, long-term potentiation (LTP), was discovered at excitatory synapses within the hippocampal complex in 1973.[10,11] Ten years later, it was demonstrated that the potentiated synapse uses glutamate as a neurotransmitter, and that transmission via the postsynaptic N-methyl-D-aspartate (NMDA) receptor is essential for the induction of LTP.[11] This form of plasticity, NMDA-receptor–dependent LTP, has been found throughout the central nervous system, reflecting the role of glutamate as the main excitatory transmitter in the brain. Through LTP, glutamate synapses can be strengthened. The NMDA receptor acts as a coincidence detector, with channel opening in response to presynaptic activity ("sensed" at the glutamate binding site of the receptor) and concurrent postsynaptic activity (the voltage sensor in the receptor). Essentially, the NMDA receptor functions as a logical "AND gate."[12] The influx of Ca^{2+} through the NMDA channel pore is the primary event, eliciting an array of downstream changes, which make the postsynaptic neuron more sensitive to glutamate.[11] Short-lived strengthening appears to be essential for holding information for minutes to hours.[11] Long-lived strengthening is believed to underlie the inscription of relatively permanent memory traces into the nervous system. The latter process necessitates the synthesis of new components and structural alterations at the synapse.[13]

In the years since the discovery of NMDA-dependent LTP, numerous forms of synaptic plasticity have been discovered throughout the brain.[14] Plasticity can be expressed through presynaptic as well as postsynaptic mechanisms. Typically, the amount of glutamate released from the presynaptic terminal, in response to an action potential, can be enhanced or diminished, over various time frames.[15]

The hippocampus was again the locus for the discovery and elucidation of a novel form of plasticity, which was found to

be mediated by endogenous cannabinoid molecules.[16] The mechanisms turned out to be highly unorthodox. Normally, synapses are conceptualized as transferring information in a presynaptic to postsynaptic direction. Endogenous cannabinoid signaling in the hippocampus is very different. The transmitter, in this case a small lipid molecule called 2-arachidonoylglycerol (2-AG) is produced postsynaptically in dendritic spines, whereas the receptor for 2-AG, the CB_1 receptor is found on the presynaptic terminal. Thus, endocannabinoid signaling in the hippocampus constitutes retrograde transmission, in that the flow of information is in the postsynaptic to presynaptic direction.[17] When activated by 2-AG, CB_1 receptors evoke a decrease in presynaptic neurotransmitter release. This decrease can be short-term or prolonged. The latter case is referred to as long-term depression (LTD).[17]

LTD, mediated via endocannabinoid transmission, would soon be discovered at additional loci in the brain, especially in those structures where learning and the inscription of new memory traces is intrinsic to their function; the amygdala (fear memory) the striatum (habit learning), the cerebellum (psychomotor learning), and the cerebral cortex.[17] An emergent generality was that the main output neurons in the amygdala, striatum (medium spiny neurons), cerebellum (Purkinje neurons), and cerebral cortex (pyramidal neurons), are able to synthesize and release endocannabinoids from their dendritic spines, and in doing so have the ability to fine-tune their synaptic inputs.[17] It also became apparent that CB_1 receptors are found, not just on glutamate terminals, but also on GABA terminals. Thus, principal neurons can fine-tune their incoming excitatory (glutamate) and inhibitory (GABA) signals. This fine-tuning can be short-term or relatively permanent.[17]

Endocannabinoid signaling is essential for the proper functioning of the hippocampus as a memory buffer. In normal physiology, the synthesis and subsequent metabolism of 2-AG is under precise control.[18] However, exogenously applied CB_1 receptor agonists cannot replicate the subtleties of endogenous cannabinoid signaling. For example, whereas 2-AG pushes the balance in hippocampal circuits toward LTP and associative learning, exogenously applied cannabinoids inhibit LTP.[19,20] Exogenous cannabinoids also disrupt theta rhythms, which are known to be fundamental for the proper orchestration of hippocampal functioning, and for LTP in the hippocampus.[20] Finally, exogenous cannabinoids disrupt the synchronized firing of individual hippocampal neurons.[20] At the behavioral level, endocannabinoid signaling in the hippocampus is important for learning and memory, whereas in stark contrast, exogenously administered CB_1 receptor agonists impair hippocampal-dependent memory performance.

In the last decade, our knowledge of endocannabinoid signaling and endocannabinoid-mediated plasticity in the hippocampus has reached new heights of unorthodoxy.[21] For instance, it has become apparent that hippocampal astrocytes express CB_1 receptor. Upon CB_1 receptor stim-

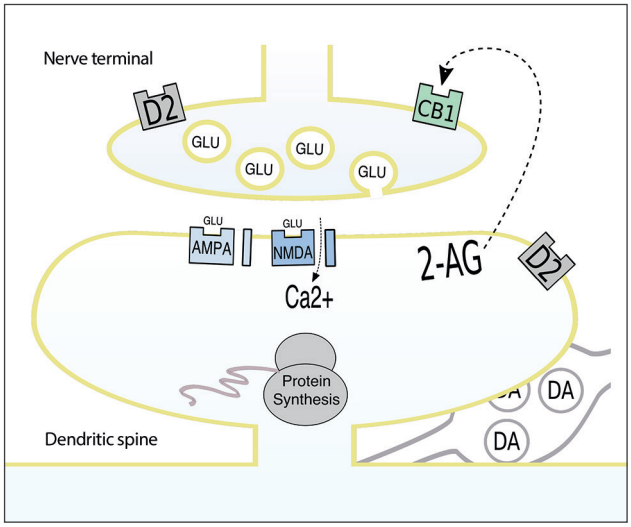

Figure 1. A nerve fiber from the cerebral cortex is shown forming an excitatory synapse at the dendritic spine of a principal striatal neuron. Glutamate (GLU) released from the terminal activates postsynaptic receptors of the AMPA and NMDA class. A dopamine (DA) fiber and varicosity is shown at the spine neck. The synapse can be strengthened through the mechanism of long-term potentiation (LTP) by opening of the NMDA channel and the influx of calcium. Sustained LTP requires protein synthesis and morphological changes in the dendritic spine. The endocannabinoid molecule 2-AG is produced "on demand" in the dendritic spine and functions as a retrograde transmitter at CB_1 receptors on the presynaptic terminal. Endocannabinoids reduce presynaptic transmitter release and elicit a form of synaptic plasticity, which is expressed presynaptically, called long-term depression (LTD). Endocannabinoid synthesis in the dendritic spine requires the action of dopamine at D_2 receptors. The pro-psychotic drug Δ^9-tetrahydrocannabinol acts at the CB_1 receptor; ketamine, at the NMDA channel; and methamphetamine, on dopamine varicosity. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; NMDA, N-Methyl-D-aspartate; 2-AG, 2-arachidonoylglycerol

ulation, astrocytes release glutamate, which acts at receptors on neighboring neurons (gliotransmission). In one scenario, astrocytic-derived glutamate evokes presynaptic LTP in the hippocampus by activating metabotropic glutamate (mGlu) receptors on nerve terminals.[21] Additional complexity will no doubt emerge, further emphasizing the gulf between the effects of endogenous and exogenous cannabinoids. To summarize, endocannabinoids are important components in how the hippocampal networks hold information in memory. In contrast, Δ^9-THC and other exogenous cannabinoids disrupt information processing in the hippocampus.

Psychosis and pro-psychotic drugs

Unlike the case with deficits in episodic memory, psychosis cannot be mapped onto a specific brain structure as easily. Psychosis is a less defined concept. Over time, there have been attempts to localize psychosis within various brain structures, including the hippocampus, the basal ganglia, dopamine neurons, and the cerebral cortex; others have conceptualized a more generalized, widespread deficit in information processing.[22-25] Currently, there is no firm ground on which to base an answer. Another difficulty is that it is possible to be psychotic in various ways. In some cases, persecutory delusions are the dominant theme, in others, a profound breakdown in the normal sense of selfhood and agency. Finally, psychosis is also much more difficult to measure than episodic memory performance. Indeed, it is not at all clear if it makes sense, or constitutes scientific progress, to put numbers on psychosis and to then search for statistical correlations between psychosis scores and a selected biological variable.

One solution is to return to the synaptic level, and thereafter to consider the effects of pro-psychotic drugs. The higher faculties—thinking, planning, selfhood, etc—do not reside in a single neuron, but are assumed to emerge from a network of neurons.[26] Nervous tissue is immensely powerful because of the rich, dynamic, temporally coherent, and highly plastic interconnectivity between neurons.[27] For example, a 1-mm voxel of cerebral cortex (a standard functional magnetic resonance imaging [fMRI] unit) contains a sobering, ~300 million local synaptic connections.

Just as was the case for cannabis-induced impairments in hippocampal-dependent memory, acute cannabinoid psychoses are probably the result of disrupted information processing in neuronal networks at the synaptic scale. An important observation is that other pro-psychotic molecules act in the same microdomain as Δ^9-THC (*Figure 1*).

Repeated, heavy use of stimulant drugs such as crystal methamphetamine and crack cocaine can elicit a classic paranoid psychosis. The psychomotor effects of stimulants can be blocked by dopamine D_2 antagonists, standard antipsychotic drugs used in psychiatry.[28] Dopamine plays an important role in synaptic plasticity within the hippocampus and in the striatum.[29] Whereas the effects of dopamine on hippocampal synapses are mediated via the D_1 receptor class, the effects of dopamine on striatal synapses are mediated by both D_1 and by D_2 receptors.[29,30] Dopamine D_2 receptors are located at dendritic spines, where they can elicit endocannabinoid synthesis and downstream LTD at cortical inputs to the striatum.[30]

Ketamine can elicit a profound transformation in the experience of lived reality, in which insight is absent. Healthy subjects describe phenomena that go beyond the realms of a paranoid psychosis.[31] Ketamine can induce a euphoric, dream-like oneiroid state with bizarre posturing on the surface. Reports are of time stopping, dissolution of the ego, being dead, meeting (or being) God, and travel through fractal geometries.[31] The psychedelic effects of ketamine appear to stem from blockade of the NMDA-receptor channel and inhibition of short- and long-term potentiation (STP and LTP) at glutamate synapses.[32] Lysergic acid diethylamide (LSD) elicits a marked transformation in conscious experience with absence of insight via stimulation of serotonergic 5-HT_{2A} receptors.[33]

Any enterprise that proposes a detailed, unifying theory for the various pro-psychotic drugs risks being outmoded, in a fairly short time frame, as our knowledge of the microanatomy and physiology of synaptic networks reaches new heights of complexity. For instance, it now appears that a joint dopamine D_2 and endocannabinoid CB_1 mechanism can evoke LTP at cortical inputs to the striatum, rather than the canonical LTD, which dominated the literature for a decade.[34] Technically, it means that bidirectional plasticity is the new order at corticostriatal synapses. Ongoing efforts are elucidating the precise spatiotemporal circumstances at the synaptic level, which determine whether the direction of plasticity is toward LTP or toward LTD.[34]

As is the case for the effects of Δ^9-THC on the hippocampus and memory described above, some tentative conclusions can be drawn for the effects of pro-psychotic drugs. The basic assumption of course, as was stated in the beginning of this section, is that the higher faculties emerge from the rich, dynamic, temporally coherent and highly plastic interconnectivity between neurons. The pro-psychotic drugs Δ^9-THC, ketamine, and methamphetamine, all share the ability to disrupt synaptic signaling within the same microdomain. It is likely that the pro-psychotics exert their dramatic and bizarre effects on the highest human faculties of thought, knowledge, and selfhood by disrupting information processing in neuronal networks at the synaptic level. Whether the essential disruption for psychosis can be localized to the striatum, the hippocampus, the cortex, a combination of these structures, or the long-range signaling between structures remains unknown but is perhaps not that critical. The pivotal events in psychosis, at least as far as pro-psychotic drugs go, appear to occur at the submicrometer scale in axon terminals and dendritic spines.

Pro-psychotic drugs as pointers to endogenous mental illness: the dendritic spine

Compounds such as Δ^9-THC may act as pointers toward the abnormal neurophysiology of endogenous mental illness.[35] Pro-psychotic drugs can be thought of as eliciting a "lesion" at the protein level, which is translated via altered synaptic dynamics, and ultimately manifests as altered conscious experience. Progress in molecular neuroscience has revealed that the hitherto unknown cause of many developmental disorders is abnormal protein components, which regulate structural plasticity. The dendritic spine, in particular, has emerged as a key locus for synaptic pathology. Dendritic spines are highly dynamic structures that undergo morphological change as part of learning and memory.[36] Pro-psychotic drugs, including Δ^9-THC, impact upon the structural plasticity of dendritic spines.[26,37-40]

Spines can appear, change shape, enlarge, and disappear throughout the lifespan in an activity-dependent manner.[41] Essential processes for spine rearrangement include motility, protein synthesis, stabilization, and pruning. Spine size is highly correlated with synaptic strength (the magnitude of excitatory postsynaptic potentials) and spine stability.[36] There are critical periods of development during which plasticity is intense, followed by a decrease with age.[36] The central idea is that neuronal networks are sculpted by experience during development and that with age, network stability takes priority over new learning.[36] A window also applies for the peak expression of genes involved in synaptic plasticity and schizophrenia.[42] Notably, the risk-increasing effect of cannabis for schizophrenia[43] and neuropsychological impairment[44] appears to be greatest following exposure during the adolescent phase of brain development. A similar window of vulnerability exists in animal models, in which exposure to CB_1 receptor agonists in adolescence results in persistently reduced social interaction and impaired cognitive functioning.[45-47]

Many neuropsychiatric and intellectual disorders are associated with abnormalities in synaptic components[36,48,49] (*Figure 2*).[50] These components often have a fundamental role in structural plasticity.[36,49,50] There are proteins that span the synaptic cleft, tethering and stabilizing the presynaptic terminal to the adjacent dendritic spine. Deletions in these cell-adhesion molecules, such as neurexin-1, are associated with autism and schizophrenia.[36,49,51] For example, deletions that disrupt neurexin-1 exons confer a ten-times-greater risk for schizophrenia.[52]

Variation in the *CACNA1C* gene has been consistently associated with bipolar disorder, schizophrenia, major depression, autism, and attention-deficit hyperactivity disorder (ADHD).[53] *CACNA1C* codes for an alpha subunit of a postsynaptic, voltage-dependent, L-type Ca^{2+} channel ($Ca_v1.2$). The $Ca_v1.2$ channel is found in dendritic spines and shafts, where it has a key role in synaptic plasticity.[54,55] In the striatum for example, the coincidence of presynaptic activity (sensed by mGlu receptors), postsynaptic activity (sensed by L-type Ca^{2+} channels), and dopamine release (sensed by D_2 receptors) evokes endocannabinoid synthesis and release from dendritic spines.[56] The released endocannabinoid elicits plastic adaptations at the presynaptic cortical input.[56]

Persistent memory traces and ingrained psychomotor habits require relatively permanent structural changes at synapses.[13] The prolonged form of LTP requires the local synthesis of new proteins.[57] The machinery for protein synthesis (and protein degradation) is found locally within dendritic spines.[58] Regulatory pathways include brain-derived neurotrophic factor (BDNF) receptor and tropomyosin receptor kinase B (TrkB), and intracellular mediators such

as AKT (also known as protein kinase B) and mammalian target of rapamycin (mTOR).[36] Several conditions, including tuberous sclerosis and fragile X syndrome, are a result of genetic abnormalities within the signaling components that regulate protein synthesis, giving rise to intellectual and psychiatric symptoms.[36,49] Fragile X results in abnormalities in plasticity (eg, LTD), and can present as autism, ADHD, and intellectual disability.[59] Variants in AKT are reported to show an interaction with cannabis for the risk of developing a psychotic disorder.[60]

Actin filaments give spines their structural dynamism.[61,62] Variation in numerous proteins of the RHO GTPase signaling pathway, which control actin filaments, are a cause of intellectual disability and autism.[36,49] Translocation or mutation affecting the protein disrupted in schizophrenia 1 (DISC-1) reportedly confers a risk for multiple psychiatric disorders, including schizophrenia, and bipolar and major depression.[63] DISC-1 is localized to dendritic spines, where it regulates actin and spine morphology via kalirin-7 and Rac1.[63,64]

Finally, synapses that are destined for elimination express complement C4, a tag that is recognized by microglia, which engulf and clear the redundant synaptic elements.[65] In the early stages of Alzheimer disease, before amyloid deposition and tangle formation, there is an upregulation of complement proteins, microglial phagocytosis, and the loss of synapses.[66] Thus, Alzheimer disease appears to be a disorder of runaway synaptic loss. Schizophrenia has been conceptualized as a disorder of impoverished connectivity.[67] Variation in the complement C4 gene is strongly associated with schizophrenia, and it has been hypothesized that excessive synaptic pruning by phagocytic microglia induced by variants in complement C4 during adolescence is responsible for the onset of the disorder in some cases.[68]

In summary, our mental health is obviously dependent on the health of synapses and neuronal networks. A range of psychiatric disorders and intellectual disabilities are associated with synaptic pathology. The ability of a neuronal network to learn from experience confers survival advantage. There are mechanisms for short-term and relatively persistent change at individual synaptic connections; strengthening, weakening, growth, stabilization, and pruning. Learning mechanisms at synapses are elaborate, consisting of a vast array of components in dynamic flux. Molecular neuroscience will continue to add detail, but it is already apparent that the long-sought-for pathophysiology of major mental illness is not as distant as is sometimes portrayed. What we are learning about the molecular mechanisms underlying the psychotogenic effects of drugs like cannabis may hasten the day of understanding.

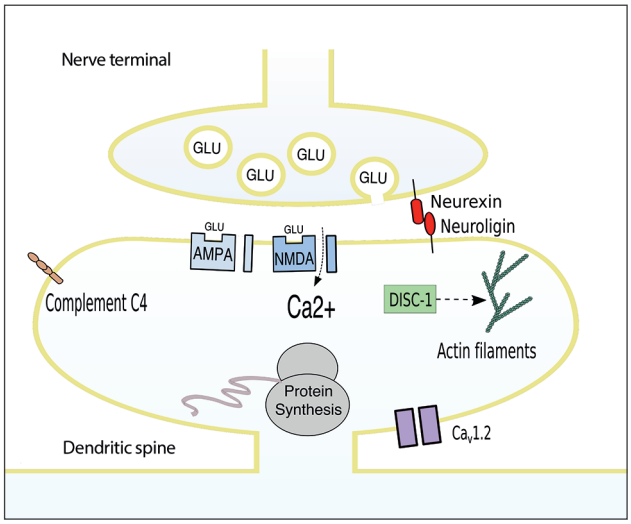

Figure 2. A glutamate nerve terminal is shown synapsing on a dendritic spine. Glutamate (GLU) released from the terminal activates postsynaptic receptors of the AMPA and NMDA class. Activation of the NMDA receptor and the resultant influx of Ca^{2+} is the prime mover in long-term potentiation (LTP), the process by which the synapse becomes stronger. In the short term, the AMPA receptor is sensitized to glutamate, and more AMPA receptors are shuttled to the postsynaptic membrane. Sustained LTP requires local protein synthesis and the incorporation of new components into the postsynaptic machinery. Training and new learning changes the morphology of the spine and stabilizes the synaptic connection. Filamentous actin provides motility, and cell-adhesion molecules such as neurexin and neuroligin bridge the synaptic cleft. Synapses can also express a tag, complement C4, which is recognized by phagocytic microglia, which function to prune redundant connections, particularly during adolescence. A large number of psychiatric and intellectual disability disorders are associated with abnormalities in local protein synthesis (eg, fragile X syndrome), actin dynamics (learning disability and schizophrenia), cell adhesion molecules (autism and schizophrenia) and complement C4 (dementia of Alzheimer's type and schizophrenia). The post-synaptic L-type Ca^{2+} channel ($Ca_v1.2$) is involved in dendritic spine plasticity (LTP, long-term depression, and protein synthesis). Robust genetic findings have demonstrated that variation in the *CACNA1C* gene, which codes for an alpha subunit of $Ca_v1.2$, confers a risk for bipolar disorder, schizophrenia, major depression, autism, and ADHD. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DISC-1, disrupted in schizophrenia 1; NMDA, N-Methyl-D-aspartate; 2-AG, 2-arachidonoylglycerol

Conclusions and future directions

There has been considerable progress in identifying the genetic and environmental factors that predispose to mental disorders, and cellular neuroscience continues to reveal the workings of nervous tissue at a highly resolved level of detail. Psychotropic molecules such as Δ^9-THC, the main psychoactive constituent of cannabis, have been useful in showing how a precise, molecular manipulation that elicits mental and intellectual disorder disrupts neuronal processing at the synaptic scale. It is perhaps unsurprising that other pro-psychotic molecules also work at the same level, disrupting synaptic dynamics, but less so that a whole host of psychiatric disorders and intellectual disabilities are associated with disruptions in synaptic physiology. Dendritic spines in particular appear to be implicated, which may be a consequence of their importance in learning and memory. The timing of extraneous effects on the brain such as adolescent cannabis use is important, as critical windows appear within time; in the small scale, oscillations such as theta waves permit LTP; but also over a longer scale, windows of gene expression facilitate marked network reorganization. Further developments will enhance our knowledge of the effect of temporality on the emergence of synaptic pathology and mental illness. It is already apparent from the emergence of genetic pleiotropy that the traditional diagnostic systems in psychiatry are largely redundant. Additionally, whole-brain imaging methods in humans look increasingly blunt and remote from real progress, which is clearly at the synaptic scale. Continued progress at the synaptic scale will inevitably usher in personalized psychiatry, not yet perhaps in terms of therapeutics, but in terms of precise formulation. Psychiatric formulations will eventually be on a footing as robust as those in medicine and neurology. ■

Acknowledgments/Disclosures: Dr P. D. Morrison has had no conflicts of interest in the last 3 years.

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