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Current Neuropharmacology, **2021**, *19*, **925-938**

REVIEW ARTICLE

Cholecystokinin-Mediated Neuromodulation of Anxiety and Schizophrenia: A "Dimmer-Switch" Hypothesis

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ARTICLE HISTORY

Received: August 07, 2020
Revised: October 08, 2020
Accepted: November 10, 2020

DOI:
10.2174/1570159X18666201113145143

Abstract: Cholecystokinin (CCK), the most abundant brain neuropeptide, is involved in relevant behavioral functions like memory, cognition, and reward through its interactions with the opioid and dopaminergic systems in the limbic system. CCK excites neurons by binding two receptors, CCK_1 and CCK_2, expressed at low and high levels in the brain, respectively. Historically, CCK_2 receptors have been related to the induction of panic attacks in humans. Disturbances in brain CCK expression also underlie the physiopathology of schizophrenia, which is attributed to the modulation by CCK_1 receptors of the dopamine flux in the basal striatum. Despite this evidence, neither CCK_2 receptor antagonists ameliorate human anxiety nor CCK agonists have consistently shown neuroleptic effects in clinical trials. A neglected aspect of the function of brain CCK is its neuromodulatory role in mental disorders. Interestingly, CCK is expressed in pivotal inhibitory interneurons that sculpt cortical dynamics and the flux of nerve impulses across corticolimbic areas and the excitatory projections to mesolimbic pathways. At the basal striatum, CCK modulates the excitability of glutamate, the release of inhibitory GABA, and the discharge of dopamine. Here we focus on how CCK may reduce rather than trigger anxiety by regulating its cognitive component. Adequate levels of CCK release in the basal striatum may control the interplay between cognition and reward circuitry, which is critical in schizophrenia. Hence, it is proposed that disturbances in the excitatory/inhibitory interplay modulated by CCK may contribute to the imbalanced interaction between corticolimbic and mesolimbic neural activity found in anxiety and schizophrenia.

Keywords: Anxiety, cholecystokinin, dopamine, gamma-aminobutyric acid, glutamic acid, schizophrenia.

1. INTRODUCTION

Cholecystokinin (CCK) is a member of a sulfated peptide family originally thought to be confined to the gastrointestinal tract but whose small form CCK8 is the most widely distributed neurotransmitter in the mammal brain [1]. It binds two receptor subtypes, namely CCK_1 and CCK_2, expressed at relatively low and high levels in the brain [2]. Relevant behavioral functions attributed to CCK are memory and cognition [3-6], reward-related behaviors [7-9], and more importantly, anxiety [10-16]. Yet systemic administration of selective CCK_2 agonists like CCK4 and pentagastrin triggers panic in humans [10,17,18], CCK_2 antagonists have never been proven to ameliorate human anxiety [19-21].

Despite the failed clinical trials, CCK continues to be a valid therapeutic target in psychiatry [22] due to its intermingled functional interplays with dopamine (DA) [23, 24], opioids [5], γ-aminobutyric acid (GABA) [25], and glutamate [6]. Accordingly, it has been proposed to have a neuromodulatory function in a range of abnormal behaviors, from social isolation-induced aggression in Drosophila [26] to human anxiety [9] and schizophrenia [27]. Also, as a result of its neuromodulatory role, significant inter-individual differences have been found in response to the panicogenic CCK4 challenge [28-33]. In schizophrenics, rapidity of antipsychotic response to haloperidol and the Scale for the Assessment of the Negative Symptom was found negatively correlated with the levels of CCK in cerebrospinal fluid [34] and peripheral blood mononuclear cells [35], respectively. The role of CCK in mental health could be indirect.

The neurobiology of anxiety and shizophrenia is interwoven in some points [36]. CCK is interspersed in the excitatory-inhibitory neurons of corticolimbic areas [37] and mesolimbic pathways [38, 39] that malfunction in both panic disorder [40, 41] and schizophrenia [42-47]. CCK has coevolved with GABA and glutamate [48] to colocalize in the interneurons that sculpt cortical dynamics [49]. CCK is likely to corelease with glutamate within the corticofugal projections to the basal striatum [50]. Starting from this body

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1570-159X/21 $65.00+.00

of evidence and using the analogy to a *dimmer-switch*, the premise of this review was to posit the neuromodulatory role of CCK in anxiety and schizophrenia.

2. PHYSIOLOGICAL ROLES OF CCK IN CORTICO-LIMBIC AREAS AND MESOLIMBIC PATHWAYS

2.1. CCK Function in Cortical Micro-circuitry Dynamics

CCK is widely distributed in GABAergic basket cells (CCK^+-GABA BCs) of the isocortex [51, 52]. These interneurons are concentrated in layers IV and VI of the human cortex [53], and layers II and III, deep layer V, and layer VI in the rodent cortex [54]. In these areas, pyramidal neurons are the primary target of CCK [55]. CCK colocalizes with glutamate neurons and controls glutamatergic excitatory projections and local GABAergic BCs that gate signal flow and sculpt network dynamics [56]. CCK^+-GABA BCs receive information from distinct sources and multiple modulatory systems, by mostly inhibitory [57] and to a lesser extent from glutamatergic afferents [58], thus integrating these inputs over longer time windows to shape and respond to subtleties of principal cell outputs [25, 59]. Cortical CCK is also expressed in the somatostatin Martinotti interneurons of the somatosensory cortex [60] which exerts inhibitory actions regulating the balance between bottom-up and top-down inputs across layers [61].

An important feature of the transmission at CCK^+-GABA BCs and their downstream targets compared to their fast spiking parvalbumin immune-positive GABAergic BC counterparts (PV^+-GABA BCs) is the accommodation of firing patterns from largely synchronous neurotransmitter release to an asynchronous mode during repetitive activation [37, 62, 63]. This strategic innervation enables both networks of GABAergic BCs, CCK^+ and PV^+ interneurons, to effectively control the gain of summated synaptic potentials and the action potential discharge of the target (pyramidal) cells. Such adapting discharge may enhance temporal integrative capacity of CCK^+-GABA BCs [64], thereby making them responsive to combined input from temporally and physically more separated inputs [65]. A balance between CCK^+-GABA and PV^+-GABA BCs in a given cortical region is related to the type of processing that area performs. Inhibitory networks in the secondary cortex tend to favor the inclusion of CCK^+-GABA BCs more than networks in the primary cortex [66]. CCK is likely to regulate the relationships between both BC interneurons [67], which may have an impact on anxiety [68].

In the basolateral amygdala (BLA), subpopulations of CCK^+-GABA BCs are responsible for the anxiogenic effects of CCK [69, 70]. Glutamate-responsive GABAergic neurons rich in CCK_2 receptors control the trafficking of nerve impulses from the cerebral cortex to the central amygdala to produce its disinhibition and to trigger anxiety-like behaviors [71]. The efferents of the principal (pyramidal) neurons of the BLA are under the influence of perisomatic CCK^+-GABA BCs [72, 73] and the inhibition of basal forebrain cholinergic neurons [74] to modulate the cognitive component of anxiety and fear [75].

Finally, a body of evidence demonstrates that CCK is a potent anticonvulsant neuropeptide [76-78]. There is a loss of CCK^+-GABA BCs synapses in animal models of epilepsy [79-82]. In humans, the content of CCK decreases in the tissue of the active focus of epileptic spiking [83]. CCK consistently modulates neuronal inhibitory projections in the cortex.

2.2. CCK and Hippocampal Electrical Oscillations

CCK is largely expressed in inhibitory interneurons BCs, the major subclass of GABA interneurons in the hippocampus [52, 63, 84-87], and the dentate gyrus or DG [88]. Except for a minority that innervates other CCKergic interneurons, most CCK^+-GABA BCs of the hippocampus possess axons that cross considerable distances to synapse onto the somata and proximal dendrites of the pyramidal neurons [37]. They do so in parallel with the second inhibitory PV^+-GABA BC network [86]. CCK might directly excite PV^+-GABA BCs by activating CCK_2 receptors [89] and efficiently interfere with action potential generation of PV^+-GABA BCs [90]. CCK excitates PV^+-GABA BCs and indirectly suppresses GABA release from CCK^+-GABA BCs in neuronal microcircuits to gate, like a molecular switch, the different sources of perisomatic inhibition for pyramidal cells [91].

CCK released endogenously from hippocampal interneurons facilitates glutamatergic transmission [92]. This is of special relevance to the CA3 subfield, a key region of the hippocampus for the generation of behaviorally relevant synchronous activity patterns, where CCK^+-GABA BCs underlie information processing [93, 94], schizophrenia [63], and the modulation of anxiety [95]. CCK is also present in efferent or afferent pathways originating from CCK^+-pyramidal cells of the hippocampal formation and/or from the hippocampal subcortical nuclei, the supramammillary nuclei, and the dorsomedial nucleus of the hypothalamus [96]. Finally, CCK^+ -GABA BCs are also modulators of neuronal circuits [91, 97] and assist in the maturation of glutamatergic synapses, *i.e*. activation of N-methyl -D-aspartate (NMDA) receptors, *via* GABAergic depolarization of the dendrites of the principal cells [98].

As to the DG, CCK^+-GABA BCs release GABA in a highly asynchronous manner to generate long-lasting inhibition of the brain [62]. The inhibitory control in the hilar region is qualitatively different from other cortical areas [99]. CCK^+-GABA BC somas almost exclusively reside at the subgranular hilar border and polymorphic layer [88]. Synaptic inhibitory interactions exist between CCK^+ hilar commissural, associational path cells [88], among CCK^+ Schaffer collateral associated interneurons in the stratum radiatum [100]; and between homologous pairs of CCK^+-GABA BCs [101]. Certain essential cognitive processes require the precise temporal interplay between excitatory pyramidal cells and inhibitory interneurons in the hippocampus [102]. CCK^+-GABA BCs may play a role in the generation and information processing of theta (4-10 Hz) oscillations [103]. The numerous GABAergic inputs to CCK^+-GABA BCs do undergo long-term potentiation (LTP) during theta burst stimulation of the hippocampus, presumably leading to disinhibition of pyramidal cells during theta rhythm-associated behavioral states [64]. CCK occupies a privileged position to control the function of the first region where all sensory modalities merge together to build unique representations and memories that bind stimuli together.

2.3. CCK Role in Learning and Memory

Of relevance, CCK^+-GABA BCs release glutamate in their efferents to principal cells [49, 52, 104, 105], being their activity critical for working memory retrieval [6]. The glutamate released under the control of these interneurons activates NMDA receptors, which subsequently stimulates cortical CCK expression [106]. In the hippocampus, CCK expression enhances glutamate [107], modulates NMDA receptors [108], and enhances long-term potentiation *via* CCK_2 receptors [109]. There is evidence that CCK participates in both associative [106] and social memories [3]. Because CCK^+-GABA BCs are critical for a correct behavioral function [110], CCK disturbances may underlie the learning deficits that are associated with anxiety disorders [111] and schizophrenia [44,112].

2.4. Cortical Modulation of Striatal DA Neurotransmission by CCK and Glutamate

Glutamatergic cortifugal pathways from wide areas of the cortex converge the striatum [113] and the ventral tegmental area (VTA) to enhance the discharge of dopamine (DA) in the nucleus accumbens [114]. CCK colocalizes with DA in the pathways ascending from the VTA to the nucleus accumbens [23], where it intimately modulates DA release at the presynaptic terminals through CCK_1 and CCK_2 receptors [7]. Crossed corticostriatal projections containing releasable CCK and glutamate project onto the terminal fields of the striatal/accumbens neurons [50]. Of special interest are the CCK projections arising from the mPFC [115], which control DA release in the nucleus accumbens [116]. Corticostriatal CCK neurons, which probably have glutamate as their co-transmitter, might promote goal-directed behaviors [39]. Therefore, dysfunction of CCK [8, 117-121] and glutamate transmission [46] in these pathways may provoke adaptational deficits, impulsive behaviors, and schizophrenia.

In the striatum, cortical glutamate projections establish complex interactions with DA *via* NMDA and D_2D receptors to tonically regulate CCK expression [122]. In turn, CCK released in the striatum may modulate the excitability of glutamate *via* CCK_1 and CCK_2 receptors [123], as well as of other amino acids and opioids also released by neostriatal neurons [124]. In addition, activation of CCK_2 receptors in striatal neurons stimulates GABA neurotransmission [38], the main output toward the thalamus and a putative site of pharmacological intervention in the treatment of schizophrenia [125]. In agreement with this hypothesis, some evidence suggests that CCK_2 antagonists inhibit the activity of DA neurons [126]. How exactly CCK is coreleased with glutamate to impact on accumbal DA turnover is not known and should be considered in future research since disturbances of the basal striatum are the cause of cognitive symptoms of schizophrenia [46, 127].

3. PHARMACOLOGY OF CCK^+-GABA BCs

3.1. CCK_1 and CCK_2 Receptors

The activation of G protein-coupled CCK_2 receptors facilitates the excitability of pyramidal neurons [128, 129] and control GABA released by CCK^+ BCs [130]. CCK can signal not only through the CCK^+-GABA BCs, but even within the PV^+-GABA BCs to provide divergence and specificity to its effects [89]. Despite the high density of CCK_2 receptors in the cortex, the role of CCK_1 receptors in anxiety cannot be overlooked even if the absence of specific ligands for the CCK_1 receptor has complicated its study [131]. At this point, it should be considered that CCK-induced anxiety implies the activation of both CCK_1 and CCK_2 receptors in the cortex [132], that stress-induced fear conditioning upregulates the expression of both CCK_1 and CCK_2 receptors in the BLA [133], and also that highly specific CCK_1 antagonists may have some anxiolytic-like effects in animal models [134].

3.2. Retrograde Inhibition of CCK^+-GABA BCs by Endocannabinoids

CCK^+-GABA BCs are downstream the activation of cannabinoid 1 (CB_1) receptors in rodents [91, 135-139] and in the monkey [140]. The release of GABA from CCK^+ interneurons is under the homosynaptic tonic inhibition of endocannabinoids (eCBs) [141] *via* CB_1 activation [142]. In hippocampal networks, cannabinoid-mediated modulation largely operates *via* presynaptic receptors located on CCK^+-GABA BC terminals [143, 144]. GABA released by these interneurons is also subjected to both direct and indirect modulation of acetylcholine and glutamate [141]. Synaptic facilitation between CCK^+-Shaffer collateral afferent interneurons is likely to modify the onset of CB_1-mediated retrograde inhibition to affect spike timing and the expression of anxiety [100].

In the cortex, CB_1 and CCK_2 receptors modulate cortical GABAergic neurotransmission and anxiety in opposite directions [145]. eCB-signaling machinery controls the excitability of BLA pyramidal neurons [146, 147], as well as the dynamic regulation of perisomatic inhibition [148], through the retrograde activation of CB_1 receptors [139, 149]. Also, in the BLA, the eCB-CCK interplay is required for the extinction of aversive memories [150]. CB_1 receptors are located in the amygdala projection CCK^+-glutamatergic neurons to the nucleus accumbens that control mood stability [151]. A cooperation between glutamate and CCK *via* CCK_2 occurs during the induction and regulation of the eCB-mediated retrograde signaling in cortical and amygdaloid regions [152]. Because CB_1 receptors widely mediate endocannabinoid effects on glutamatergic and GABAergic transmission to modulate cortical networks and the expression of anxiety and fear [153], the role of CCK-CB_1-glutamate interactions in fear-related psychiatric diseases [154, 155] awaits further research.

3.3. Excitatory and Inhibitory Synapsis in CCK^+-GABA BCs

The dendrites of the CCK^+-GABA BCs receive both glutamatergic afferents and GABAergic [56]. While glutamate activates NMDA receptors to release CCK [156], GABA activates $GABA_B$ receptors in the dendritic terminals of CCK^+-GABA BCs, which are present at higher densities than in PV^+-GABA BCs [157]. In the hippocampus, dendritic inhibition is also induced by somatostatin to modulate the activity pattern of CCK^+-GABA BCs and the flow of information toward the DG circuitry [88]. As to CCK^+-GABA BC terminals, $GABA_B$ auto-receptors reduce periso-

matic inhibition of pyramidal cells in hippocampal networks [158], while glutamate released by these terminals [49] activates metabotropic and kainate receptors [52]. Postsynaptically, $GABA_B$ receptors mediate the long-term depression induced by the GABA released from CCK^+-GABA BCs [159], whereas $GABA_A$ mediates the neuronal inhibition induced by PV^+-GABA BCs on principal neurons [37]. The activation of $GABA_B$ receptors attenuates the anxiogenic effects of CCK in the hippocampus [160, 161], suggesting that $GABA_B$ agonists might be useful in the treatment of alcohol withdrawal [162].

Where GABA attenuates excitability, the vasoactive intestinal polypeptide (VIP) and neuropeptide Y (NPY) neurons provide network disinhibition in the hippocampal formation. VIP coexists with CCK in the subset of GABA BCs that control the activity of GABAergic granule cells *via* perisomatic inhibition [85, 163, 164]. VIP interneurons are specialized in synchronized pyramidal neuron ensembles along the hippocampal-subicular axis that may be necessary for memory consolidation [165] and in modulating emotional processes and adaptive responses to stressful stimuli [166]. VIP interneurons regulate the information flow across hippocampus-prefrontal networks to drive avoidance behavior [167]. VIP [168] and CCK [169] mediates neurogenesis in the dentate gyrus, a process critical for mood homeostasis [170]. NPY locally affects the activity of CCK^+-GABA BCs to change the way these interneurons process extrahippocampal afferent information, influencing hippocampal function and its network excitability during normal and pathological oscillatory activities. [171]. Dysfunctional NPY^+ interneurons trigger anxiety [110, 172-175] and schizophrenia [176] *via* CCK^+-GABA BCs.

4. CCK-MEDIATED NEUROMODULATION OF ANXIETY AND SCHIZOPHRENIA

4.1. The CCK Dichotomy in Anxiety-related Pain and Fear

CCK interacts with endogenous opioids [5] to reduce anxiety in animal models [177] and to modulate the affective component of pain in humans [178]. Nevertheless, the precise nature of their interactive influence remains elusive. While antagonistic CCK-opioid interactions trigger anxiety-induced hyperalgesia [5, 178-180], activation of CCK_2 receptors [181] and eCB [182] may even produce stress-induced analgesia. This dichotomy points to the PAG, which works like a *dimmer-switch* of fear-motivated behaviors [183]. The PAG is where the administration of CCK may either elicit or inhibit anxiety-like responses [184], where CCK both opposes and reinforces the anxiolytic effects of opioids and eCBs [185], and where CCK elicits either defense/avoidance [186] or aggression behaviors [187]. Finally, neuromodulation of anxiety extends to the amygdala and the nucleus accumbens, where CCK increases arousal and enhances fear extinction, respectively [188].

4.2. CCK_2 Receptors and the Adaptation to Stress

Some evidence casts a shadow of doubt over whether the activation of CCK_2 receptors triggers anxiety [14]. For instance, CCK_2-KO mice do not consistently behave less anxious than their wild-type littermates [189-191] and have problems adapting to the environment [192]. Also, CCK-KO mice exhibit an anxious trait [193], suggesting that CCK may not generate anxiety directly. CCK_2 receptors modulate the CCK tone, which in turn contributes to anxiety expression [194]. In this situation, the release of CCK anticipates the occurrence of stress [195] and provides relief both during and after stress [196, 197]. Moreover, CCK signaling in the lateral amygdala is required for the recovery from fear [198]. Thus, it is not surprising that in one clinical trial, the baseline of panic attack frequency in panic disorder patients under chronic treatment with CCK_2 receptor antagonist was greater than in the placebo group [20]. In this vein, the panic challenge with CCK4, the gold standard CCK_2 agonist, inhibits the HPA axis and produces a reduction of anxiety [199]. The association between CCK gene expression and post-traumatic stress disorder [133, 200] supports the notion that certain levels of CCK_2 receptor activity might be necessary to restore the normal levels of anxiety [201].

4.3. CCK and the Fine Tuning of DA Turnover

The colocalization of CCK and DA in the mesolimbic pathways [23] justified the interest of CCK as a pharmacological target of schizophrenia [202, 203]. Given the influence of CCK on accumbal DA [7, 187, 204, 205], it was believed that CCK agonists may be a promising treatment of those mental disorders that resulted from excessive DA release [206, 207]. Neither the CCK agonism therapy [202] nor the altered DAergic predictions in schizophrenia [208] were accurate.

CCK neurotransmission mediates DA turnover [7,209]. As a result of schizophrenia, CCK gene expression is reduced in the entorhinal cortex [210], limbic lobe [211,212], frontal and temporal lobes [213], while the concentration of CCK decreases in cerebrospinal fluid [34,214]. Moreover, there is a loss of CCK binding sites in the cortex and the hippocampus [215,216] and reduced CCK neurotransmission in the frontal cortex [217]. In contrast, CCK expression is enhanced in the midbrain DA cells of schizophrenic brains [218]. Similar to CCK, there is a co-occurrence of high and low DA activities in mesolimbic DA neurons and preprontal cortex, respectively, in schizophrenia [208].

Frontal cortico-accumbens glutamatergic and mesolimbic dopaminergic afferent interactions [47] along with disturbances in the cell firing within the basal striatum participate in the physiopathology of schizophrenia [219-221]. CCK_1 receptors occupy a pivotal position at this interface due to their localization in the somatodendritic region of DA neurons of the VTA in rodents [222] and monkeys [223] as well as in the DAergic terminals of the caudal nucleus accumbens [7], and striatal spiny neurons [123] from where they modulate DA release [224, 225] to enhance reward-related behaviors [8, 9, 177, 226]. Interestingly, strong genetic evicence connects CCK_1 receptors to schizophrenia [177, 227]. It is also hypothesized that the CCK_1 receptor may be a potential link of the comorbidity of schizophrenia and substance of abuse [228], since it may kindle DA release in the accumbens to the detriment of DA neurotransmission in the cortex.

5. THE *DIMMER-SWITCH*-LIKE NEUROMODULATION OF CCK IN ANXIETY AND SCHIZOPHRENIA

The puzzling role of CCK in anxiety and schizophrenia could be explained using the analogy of a *dimmer switch* that simultaneously turns up and down the levels of both cognitive processing and motivation to adjust behavioral states (Fig. **1**). The first node point of this model may operate through the GABA-glutamate interplay in corticolimbic areas, including the hippocampus [37, 52] to shift cortical dynamics from synchronous to asynchronous when appropriate and thus facilitate information processing and behavioral performance [67,229]. Failure in CCK_2 receptors, and perhaps in CCK_1 receptors in corticolimbic areas [132, 133, 194], may lead to maladaptive learning and anxiety [117, 230]. A second *dimmer swicht* may consist of the interface of cortico-accumbal and mesolimbic pathways, *i.e.* the nucleus accumbens, which dims the salience of stimuli signaled by patterns of DAergic discharge [220].

Although anxiety is inextricably related to the first episode of psychosis, or acute relapses [231], this temporal precedence is not equivalent to causality. It better suggests that anxiety may be the catalyst that triggers distressing experiences of psychosis in more vulnerable individuals [36]. Psychosis and anxiety are triggered by a common cause, the imbalances in the DA innervation, both in terms of phasic activation and attenuation of tonic DA [232]. A sustained deficiency in mesocortical DA function [208, 233] is likely to alter the fronto–striato–thalamic pathway [234] during the early stages of schizophrenia. The prefrontal cortex, a structure critically involved in both the vulnerability to stress and the cognitive deficits in schizophrenia [235], is influenced by the release of DA from the midbrain. In turn, a deficit in glutamatergic projection from the dorsolateral prefrontal cortex to midbrain DAergic neurons might alter some cognitive circuitries [236], thus affecting working memory in schizophrenia [237]. Given the direct control of striatal DA release by glutamatergic corticostriatal afferents [238], an increment of the CCK tone may compensate a deficitary working memory [6] at the expense of increasing the occurrence of anxiety at the beginning of schizophrenia [36]. As schizophrenia progresses, the overstimulation of CCK may lead to

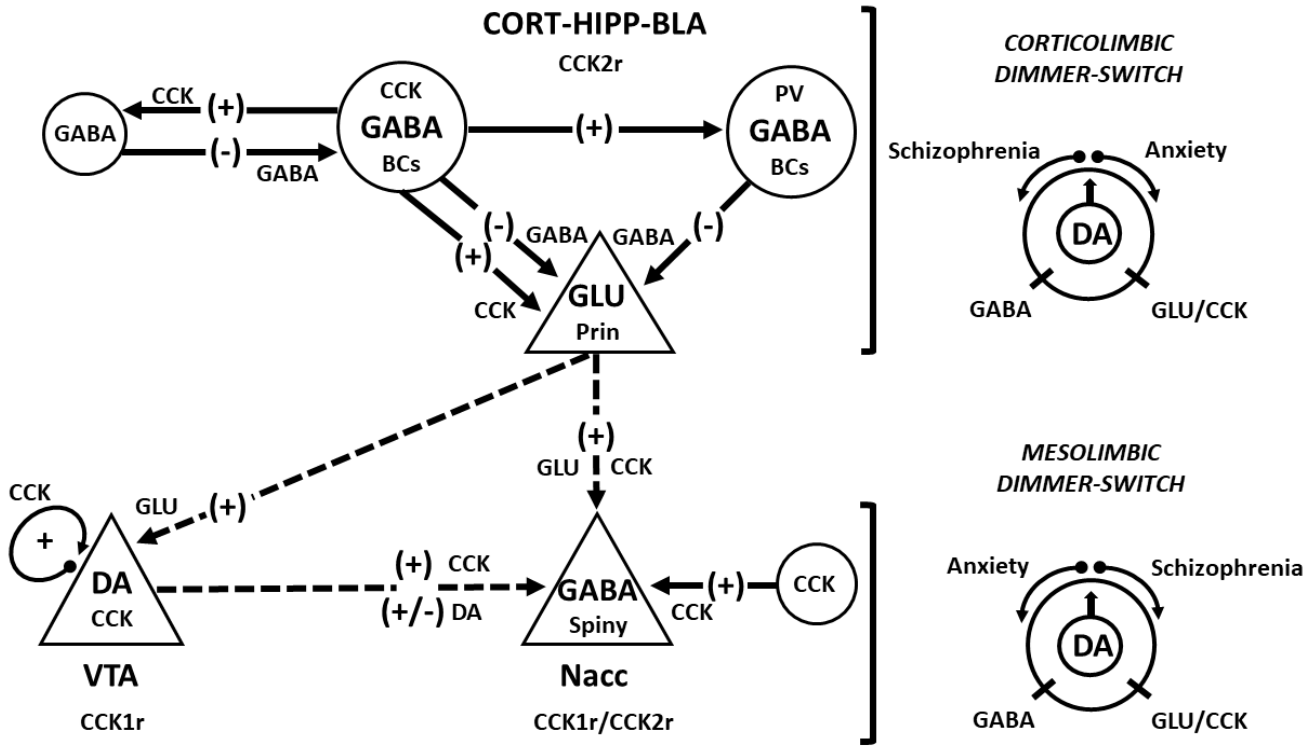

Fig. (1). Diagram of the *dimmer-switch* hypothesis regarding the role of CCK in anxiety and schizophrenia. The diagram shows the main circuitry of the corticomesolimbic system: (1) interneurons (circles) forming microcircuitries connected by solid-arrow lines and (2) projection neurons (triangles) with their efferents like dashed-arrow lines. Inhibition (negative signs) is produced by GABA, which interacts with $GABA_A$ and $GABA_B$ receptors located in principal glutamatergic cells (not shown). Excitatory (positive signs) impulses are transmitted by CCK and glutamate (GLU). The CCK_2 receptor (CCK2r) predominates in corticolimbic areas, while the CCK_1 receptor (CCK1r) is more abundant in the VTA. Both CCK1r and CCK2r are present presynaptically in DAergic terminals and postsynaptically in striatal neurons. CCK is co-released with DA, which has both excitatory (*via* D_1D receptors) and inhibitory (*via* D_2D receptors) effects on accumbal GABAergic (spiny) neurons. The putative disequilibriums in corticomesolimbic pathways are represented by *dimmer-switch*es. The hypothesis posits hyperactivity of corticolimbic areas (excessive GLU by dysregulated CCK) is detrimental to the mesolimbic pathways in the development of anxiety. In contrast, if the activity of the mesolimbic pathways was unusually higher (fast DA turnover) than in corticolimbic areas (excess of GABA), it may progress to schizophrenia. **Abbreviations:** basket cells (BCs); basolateral amygdala (BLA), cortex (Cort), hippocampus (Hypp), principal/pyramidal neurons (Prin); parvalbumin (PV), nucleus accumbens (Nacc), and ventral tegmental area (VTA).

an internalization of the CCK_2 receptor [239], which would account for the reduction of CCK_2 binding sites observed in post-mortem schizophrenic brains [216, 217].

CCK is not only a *dimmer-switch* of GABA, but also of DA (see the graphical abstract). The interplay between cognition and reward circuitries in schizophrenia [221] depends on how CCK modulates accumbal DA turnover [9], which is either enhanced by cortical glutamate and likely CCK *via* CCK_1 receptors [224, 225] or dimed by striatal GABA through CCK_2 receptors [38]. Cognitive performance in mental health and disease relies on the adequate levels of CCK expression in both cortical areas [240], and in mesolimbic pathways [188], which is likely to be the cornerstone of the excitatory-inhibitory dynamics in limbic neural networks. Given its multi-functional molecular switch role in neuronal circuits [91], CCK could work as the universal dimmer of many neurotransmitters during the adjustments at the onset of mental illnesses.

CONCLUSION

In sum, the neuromodulatory role of CCK may be compared to the work of a *dimmer-switch* that may turn up (*via* glutamate plus CCK), and down (*via* GABA), the flux of DA-mediated neurotransmission across corticomesolimbic neural formations. That could explain the anxiety linked to the withdrawal of drugs, including alcohol. This hypothesis would strongly support the development of new partial CCK_1 and CCK_2 receptor agonists with varied grades of CCK receptor selectivity for the treatment of anxiety and schizophrenia.

LIST OF ABBREVIATIONS

BCs = Basket cells

PV = Parvalbumin

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors thank Prof. Margery Beinfeld from Tufts University for the proofreading of the manuscript.

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