Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia

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Abstract

Substantial evidence suggests that psychosis in schizophrenia is associated with a dysregulation of subcortical dopamine system function. Here we examine evidence that this dysregulation is secondary to hyperactivity within hippocampal subfields. Enhanced hippocampal activity has been reported in both preclinical models and in schizophrenia patients. Moreover, this hippocampal hyperactivity is correlated with enhanced dopamine neuron activity and positive symptoms, respectively. Thus, restoration of hippocampal function could provide a more effective therapeutic approach than current therapeutics based on dopamine D2 receptor blockade. Indeed, initial studies demonstrate that allosteric modulation of the $\alpha 5 GABA_A$ receptor can decrease aberrant dopamine signaling and associated behaviors in a verified rodent model of psychosis.

Schizophrenia

Schizophrenia is a disease with a prevalence of approximately 0.8% of the population and a lifetime prevalence of about 1% [1]. It is characterized by three classes of signs and symptoms; positive, negative and cognitive, which are initially reported based on whether the sign or symptom was in addition to (positive), or absent from (negative), normal behavior [2]. Thus, positive symptoms of the disease include hallucinations, delusions and disorganized thoughts, whereas negative signs consist of anhedonia and social withdrawal [2]. Cognitive deficits are also a hallmark of the disease and are typically associated with deficits in attention and executive function [3]. It has been postulated that different symptoms are associated with aberrant activity of distinct brain regions and/or neurotransmitters.

The dopamine hypothesis of schizophrenia

The neurotransmitter system that has been most commonly associated with schizophrenia is the dopamine system. This 'dopamine hypothesis' is one of the longest standing hypotheses of schizophrenia and is based on multiple observations linking dopamine dysregulation to the pathophysiology of the disease. This includes the finding that enhanced activity within

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the subcortical dopamine system is associated with the positive symptoms of schizophrenia [4, 5] and the fact that all antipsychotic medications are dopamine D2 receptor antagonists [6, 7]. Moreover, changes in dopamine D2 receptor density are consistently observed in schizophrenia patients (for review see: [8]). Further evidence in support of the dopamine hypothesis has been obtained from imaging studies in human schizophrenia patients that demonstrate significantly increased release of dopamine in the striatum in response to amphetamine administration [4, 9, 10] with the amplitude of increased dopamine release corresponding to the exacerbation of positive symptoms. More recently, studies have shown that the region of the striatum that shows the largest increase in dopamine release in patients with schizophrenia is related to associative information processing [11]. In addition, dopamine-enhancing drugs (such as amphetamine) precipitate psychotic episodes in normal individuals that are virtually indistinguishable from the acute psychotic episode observed in schizophrenia patients [12]. Taken collectively, these findings lend much evidence and support for the dopamine hypothesis.

However, it is important to note that there has been no substantial pathology reported within the mesolimbic dopamine system of schizophrenia patients. This has led to the suggestion that the pathology might actually be upstream in the systems that regulate the dopamine system, and that the aberrant dopamine transmission and associated symptoms may actually be secondary to dysfunction in cortical and hippocampal regions, which are known to display progressive structural and neurochemical alterations in schizophrenia. Interestingly, this would suggest that the current treatments for schizophrenia (D2 receptor antagonists) might not be the most effective therapeutic approach. Antipsychotic medications, although effective at treating positive symptoms in a subset of patients, do not show a high level of efficacy -- especially across symptom classes -- and exhibit significant side effects [13]. In addition, there is a dramatically high rate (reported at >74%) of patients discontinuing treatment, which demonstrates an urgent need for improved therapies [13]. Here we review recent advances in the understanding of the afferent regions that regulate dopamine system function and provide evidence that targeting afferent regions, specifically the ventral (anterior) hippocampus may be a more effective therapeutic strategy. It should be noted that this hypothesis does not preclude current direct treatments of positive symptoms, but rather, suggests an additional therapeutic strategy for the treatment of schizophrenia.

Altered hippocampal function in schizophrenia

The hippocampus is a temporal lobe structure essential for the consolidation of long-term memories. Deficits in hippocampal structure and function are a consistent observation in imaging and postmortem studies from schizophrenia patients [14]. Specifically, one of the more constant findings from imaging studies is that patients show an inability to recruit the hippocampus during a task (i.e. memory recall) [15, 16]. Further evidence for a hippocampal dysfunction came from structural imaging and *post mortem* analyses that demonstrated consistent anatomical differences, such as a decrease in hippocampal volume, in the brains of schizophrenia patients [17–19]. Thus, several lines of evidence show a decrease in hippocampal function associated with schizophrenia; however, it is important to note that a decrease in function does not necessarily connote a decrease in activity within this structure. Indeed, there is now a significant literature demonstrating that activity within distinct hippocampal subfields is actually increased, at rest, in schizophrenia patients [14, 16, 20–24]. Specifically, techniques with high spatial resolution have provided evidence for increased regional cerebral blood flow ($H_2 0^{15}$-PET: [22, 25]) and increased regional cerebral blood volume (dynamic susceptibility contrast MRI: [20]) at rest in schizophrenia patients. Importantly, these increases in activity have been directly correlated with clinical measures of psychosis [20, 24]. Given that the positive symptoms of the disease are associated with increases in mesolimbic dopamine transmission, one would predict that a

disruption within the hippocampus could be the source of dopamine system dysregulation in schizophrenia.

Hippocampal regulation of dopamine system function

The consequence of the purported hippocampal hyperactivity in schizophrenia patients is not entirely known. However, activation of the ventral hippocampus (vHipp) increases dopamine efflux throughout the nucleus accumbens (NAc) of anesthetized rats [26, 27]. Thus, chemical or electrical stimulation of the vHipp produces sustained increases in extrasynaptic dopamine throughout the NAc, a principle target of dopamine neurons [26, 27]. The mechanisms underlying these effects were not immediately apparent because the hippocampus does not directly innervate the dopamine neurons of the ventral tegmental area (VTA). The vHipp could augment dopamine release either via a direct effect on presynaptic dopamine terminals or via the modulation of dopamine neuron activity by means of a polysynaptic pathway. It has now been demonstrated that NMDA activation of the vHipp dramatically increases dopamine neuron activity in the VTA in a dose-dependent manner [28–30]. More specifically, the vHipp modulates dopamine neuron population activity (i.e. the number of neurons tonically active – see Box 1) and this is correlated with an altered dopamine efflux in the NAc [29] and an increased behavioral response to amphetamine [31–33]. This increase is dependent on the activation of the NAc by the vHipp because microinfusion of the glutamate antagonist kynurinic acid directly into the NAc blocks vHipp NMDA-induced increases in population activity [28]. Furthermore, the effects of NMDA can be produced by mimicking the effects of NAc excitation-induced increases in GABA receptor activation in the ventral pallidum (VP) [29]. Taken together, these results suggest that the vHipp modulates dopamine neuron population activity via a polysynaptic projection involving a glutamatergic input to the NAc that increases GABAergic activity to the ventral pallidum. This increase in GABA activity decreases tonic VP activity resulting in a disinhibition of dopamine neuron activity in the VTA (Figure 1).

Increases in dopamine neuron population activity not only result in an increase in tonic dopamine efflux in the NAc, but can also regulate the phasic, synaptic dopamine response to stimuli [30]. Specifically, it has been demonstrated that glutamatergic afferents to the VTA can induce burst firing of dopamine neurons *in vivo* [34]. Furthermore, increases in dopamine neuron burst firing are correlated with increases in dopamine efflux that are localized to the synapse and rapidly curtailed by perisynaptic dopamine transporters [29]. Increases in burst firing are therefore thought to provide the physiologically relevant signal that encodes error prediction or motivational salience. It is important to note that activation of glutamatergic afferents will only induce burst firing in those neurons that are spontaneously active [30]. In neurons that are hyperpolarized by tonic GABAergic inputs from the VP, glutamate will not elicit burst firing due to magnesium blockade of the NMDA receptor. Thus, by regulating the number of dopamine neurons that are spontaneously active, the number of neurons conveying the phasic signal is altered. In this way, the vHipp can dramatically influence dopamine transmission by setting the gain of the system [30]. Disorders of vHipp function will, therefore, result in alteration of this critical gain function.

Such a condition has been modeled using a rat developmental model of schizophrenia. This model involves the administration of a mitotoxin methylazoxymethanol acetate (MAM) to pregnant female rats, specifically on gestational day 17, which results in a range of anatomical, behavioral and neurochemical deficits that are consistent with those observed in schizophrenia patients (for review see [35]). It should be noted that administration of MAM at earlier time points produces a more widespread histopathology that does not accurately reflect that observed in patients [36]. Consistent with recent human imaging data, MAM-treated rats display baseline hyperactivity of the vHipp [31], and this is associated with a

significantly higher number of spontaneously active VTA dopamine neurons compared to control rats [31]. This increase in dopamine neuron activity was attributed to hyperactivity within the vHipp because inactivation of the vHipp normalized the augmented dopamine neuron activity, as well as reversed the behavioral hyper-responsivity to amphetamine administration [31]. Therefore, it appears that the hippocampal hyperactivity observed in rodent models as well as in human schizophrenia patients might contribute to the dopamine hyperfunction and associated psychosis (Figure 1). As a result, the gain of the system would be set to maximal (i.e., all of the dopamine neurons are spontaneously firing), causing any stimulus to trigger phasic firing across the entire population of dopamine neurons.

What is the consequence of loss of modulation within the vHipp? Studies suggest that the vHipp is involved specifically in context-dependent processing; i.e., modulating the behavioral response based on the setting. Thus, in settings that are highly activating, such as a dangerous environment or one with potential high rewards (e.g., hunting for food), the vHipp would increase activation of the dopamine system to allow a stimulus to cause a large dopamine response. In contrast, in a benign environment in which stimuli are not likely to have strong survival implications, the vHipp would tone down the dopamine response. However, if the vHipp is pathologically in a constant high-activity state, the dopamine system would always be driven to respond maximally to all stimuli the organism encounters (Figure 2). Such a situation could lead to the attribution of strong behavioral importance to stimuli that otherwise would be safely ignored. This has been termed aberrant salience, and is suggested to potentially underlie delusional or hallucinatory states in schizophrenia [37].

The depolarization block hypothesis of antipsychotic medications

All current antipsychotic medications have antagonist actions at the dopamine D2 receptor; however, it is evident that antipsychotic drugs achieve their effects via mechanisms that are more complex than the simple blockade of dopamine receptors. Thus, although the maximum rate of improvement occurs early in treatment [38–41], patients also require several weeks of treatment to reach maximum therapeutic responses [38] without evidence of tolerance, as one would expect from simple receptor blockade. Understanding the mechanisms that underlie the therapeutic response to antipsychotic drugs is obviously of fundamental importance both to the understanding of the pathophysiology of schizophrenia and in developing more effective treatments.

Electrophysiological experiments performed in the 1970s provided crucial information regarding the mechanism of action of antipsychotic medications [42, 43]. Although the acute systemic administration of D2 antagonists to anesthetized rats increases dopamine neuron activity (firing rate and burst firing) potentially via blockade of inhibitory autoreceptors in the VTA, the chronic administration (21 days) of classical antipsychotic drugs produces a dramatic decrease in the number of spontaneously active dopamine neurons [42, 43]. It was demonstrated that this decrease in population activity was attributable to a phenomena known as depolarization block, whereby a substantially depolarized membrane potential results in the inability of the dopamine neurons to generate action potentials [42, 43]. It has been suggested that the induction of depolarization block may be attributable to an interaction between the neuroleptic and anesthetic [44]; however, given that we have previously demonstrated that antipsychotics produce depolarization block in paralyzed rats, this appears unlikely [42, 45]. Given that paralyzed rats can be easily stressed if not handled appropriately, this likely underlies the differences between these studies. Collectively, studies showing the induction of depolarization block provide important information regarding the clinical efficacy of antipsychotic medications that might explain, in part, the delayed maximal efficacy and lack of tolerance during antipsychotic drug treatment.

However, recent clinical studies have questioned this hypothesis, largely based on the observation that clinical improvements are not delayed, *per se*, but rather are gradual, taking weeks to reach maximum effect [38]. The initial electrophysiological studies examining antipsychotic induced depolarization block reported that three weeks of administration is required to produce a decrease in dopamine neuron activity in normal rats. It is important to note, however, that studies in untreated rats might not necessarily reflect results obtained in a pathological condition. Indeed, MAM-treated rats (and presumably schizophrenia patients) display augmented dopamine system function that begins around puberty and persists throughout adulthood. Thus, it is likely that this chronic increase in dopamine transmission results in adaptive changes in dopamine receptor and transporter function. We have recently demonstrated that MAM-treated rats display a significant increase in postsynaptic D2 receptor function throughout both the VTA and NAc [46]. Specifically, the inhibitory effects of the D2 agonist, quinpirole, on dopamine neuron activity are significantly enhanced in MAM-treated rats [46]. Furthermore, the locomotor response to quinpirole is also significantly augmented in this model, suggesting a significant increase in D2 receptor function [46]. Moreover, the initial response of control rats to antipsychotic drugs is a compensatory increase in dopamine neuron population activity; a state that is already present in the MAM-treated rat. Given the significant changes in D2 receptor function and the already-present high level of dopamine neuron firing, we posit that the temporal effects of antipsychotic drug administration might be augmented in MAM-treated rats. Indeed, whereas three weeks of treatment are required to produce depolarization block in control animals, MAM-treated rats display a decrease in population activity upon acute administration of antipsychotic drugs [47]. Therefore, depolarization block is effectively reversing the increase in dopamine neuron population activity in the MAM-treated rat and, unlike control rats, achieves this effect soon after initiation of antipsychotic drug treatment.

The hippocampus as a novel therapeutic target

Although conventional antipsychotic medications might effectively decrease the positive symptoms of schizophrenia, they are not particularly effective at treating negative signs and cognitive symptoms. This largely reflects the mechanism of action of the D2 antagonists. A decrease in dopamine neuron population activity, due to depolarization block, will reduce the ascribed salience of the dopamine signal; however, it achieves this not by reversing the proposed vHipp overdrive, but instead by inducing an offsetting deficit of depolarization block. Thus, there is still a loss of function whereby the vHipp cannot regulate the gain of the dopamine system (Figure 2). This limits the effectiveness of current antipsychotic treatment,[13]. Antipsychotic medications are not treating the pathology of the disease, but rather produce an abnormal state that offsets the downstream dopamine dysfunction associated with the positive symptoms. Based on the increasing evidence for pathology within the hippocampus underlying the dopamine dysfunction, we posit that restoration of hippocampal function could provide a novel therapeutic approach.

The hyperactivity within hippocampal subfields observed in schizophrenia is likely attributable to a decrease in GABAergic signaling within this region [48, 49]. These GABA deficits, observed postmortem in schizophrenia patient brains, are largely restricted to the class of GABAergic interneurons containing the calcium binding protein parvalbumin [49]. Similarly, we have recently demonstrated a regionally selective decrease in parvalbumin interneuron staining throughout the vHipp of MAM-treated rats [50]. This reduced expression of PV-containing interneurons correlated with a reduction in coordinated neuronal activity during task performance in freely moving rats [50]. A more effective therapeutic strategy might lie in the restoration of GABA interneuron regulation of patterned activity within ventral hippocampal circuits. Interestingly, the use of the GABA modulatory drugs known as benzodiazepines, either alone or as an adjunct to conventional

antipsychotics, have been extensively studied in schizophrenia patients. Although patient response varies, around one-third of patients improve upon treatment with benzodiazepines [51]. Those who do respond to treatment improve quickly, but the benefits diminish over time. High doses seem to be more beneficial than lower doses, but serious side effects have thus far hampered the feasibility of this treatment. Benzodiazepines act on $GABA_A$ receptors, which are found throughout the neuraxis. Therefore, it is not surprising that side effects associated with benzodiazepines (sedation, ataxia and cognitive impairment) limit the usefulness of these compounds [51]. By contrast, a benzodiazepine with selectivity for the hippocampus would provide a more effective therapeutic tool.

The $GABA_A$ receptor is a pentameric structure made from at least eighteen distinct subunits ($\alpha1-6,\beta1-3,\gamma1-3,\delta,\varepsilon,\theta,\rho1-3$) [52]. It is the α subunit that provides the allosteric benzodiazepine binding site, and the molecular diversity of this subunit results in distinct functional and anatomical distributions [52]. The $\alpha1$-containing receptors are the most abundant (~60%) and are thought to underlie the sedative properties of benzodiazepines. In contrast, the $\alpha5$ subunit is much more discretely distributed, with high levels of expression limited to the hippocampus. These receptors are primarily extrasynaptic, localized to the base of the dendritic spines of pyramidal neurons [53]. Thus, the $\alpha5$-$GABA_A$ receptor is positioned to be activated by synaptic GABA as well as 'spillover' from adjacent synapses to provide an inhibitory input to glutamatergic hippocampal projection neurons [53, 54].

Given the specific localization of these receptors to the hippocampus and their purported inhibitory control over hippocampal output, these receptors make an ideal candidate as a potential target to selectively decrease hippocampal activity (Figure 3). Moreover, as this is an allosteric site, drugs acting here would modify GABAergic transmission while preserving the temporal structure necessary for ensembles of neurons to guide behavior [55]. Similarly, the use of allosteric modulators is advantageous from a therapeutic perspective given their decreased potential for toxic effects over conventional agonist drugs. One such compound is SH-053-2′F-R-CH$_3$, a positive allosteric modulator of GABA that displays selectivity and enhanced efficacy at the $\alpha5$ receptor [56]. The systemic administration of this compound selectively attenuates evoked hippocampal activity in anesthetized rats [57]. Moreover, we have recently demonstrated that this compound can normalize the pathological increase in dopamine neuron population activity in the MAM-model of schizophrenia. In addition, SH-053-2′F-R-CH$_3$, also reduced to associated hyperlocomotor response to psychomotor stimulants in MAM-treated rats [57].

Concluding remarks

There is increasing evidence from preclinical and human imaging studies suggesting that augmented hippocampal function, secondary to a loss of interneuron function, underlies the dopamine hyperfunction associated with psychosis in schizophrenia. Thus, a restoration of hippocampal function might provide a novel therapeutic target for the treatment of the disease. Indeed, our recent data demonstrate that a positive allosteric modulator of the $\alpha5GABA_A$ receptor can reverse aberrant dopamine system function and, thus, could be effective in treating the dopamine-mediated psychosis. In addition, given that the hippocampus also modulates rhythmic activity that coordinates function across cortical regions implicated in the negative and cognitive symptoms of the disease (such as the prefrontal cortex), restoration of vHipp function may provide a more complete therapeutic profile devoid of the deleterious side effects associated with conventional antipsychotic medications.

Acknowledgments

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BOX 1

Dopamine Neuron Activity States
Dopamine neurons in the mesencephalon can be routinely identified *in vivo* and distinguished from non-dopaminergic neurons by standard electrophysiological criteria [58, 59]. These neurons typically display a bi-phasic (positive/negative), long duration action potentials that, when measured by extracellular techniques, are greater than 2ms in duration [58, 59]. Dopamine neurons recorded *in vivo* display three distinct patterns of activity. The first is a 'silent' mode whereby the membrane potential is significantly hyperpolarized and the dopamine neuron is not spontaneously active [58, 59]. Given that dopamine neurons are autonomous pacemakers *in vitro* [60], this activity state is likely attributable to afferent-mediated inhibition. Non-firing dopamine neurons recorded intracellularly *in vivo* are consistently bombarded by GABAergic inputs, likely originating from the ventral pallidum [61]. The second activity state is an irregular, single spike firing pattern that is generated intrinsically by pacemaker potentials and regulated by local and remote afferent activity [62]. The third activity pattern consistently observed in dopamine neurons are periods of high frequency activity known as burst firing. High frequency bursts of activity are considered the functionally relevant signal sent to post-synaptic targets to indicate reward or to encode an error prediction signal [63].
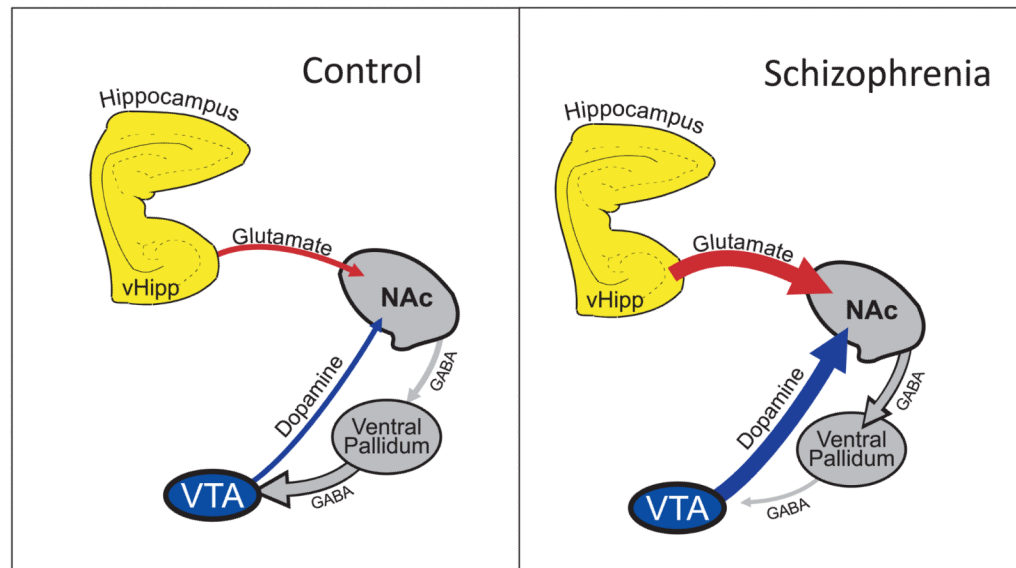
Figure 1.
The ventral hippocampus (vHipp) regulates dopamine neuron activity via a polysynaptic projection. Thus, the vHipp excites neurons in the nucleus accumbens that, in turn, inhibit ventral pallidal (VP) activity. Given that the VP provides an inhibitory tone to the dopamine neurons of the VTA, activation of the vHipp will result in an increase dopamine neuron activity. In schizophrenia, hippocampal activity is pathologically enhanced which leads to an enduring increase in dopamine system function. Adapted from [64].
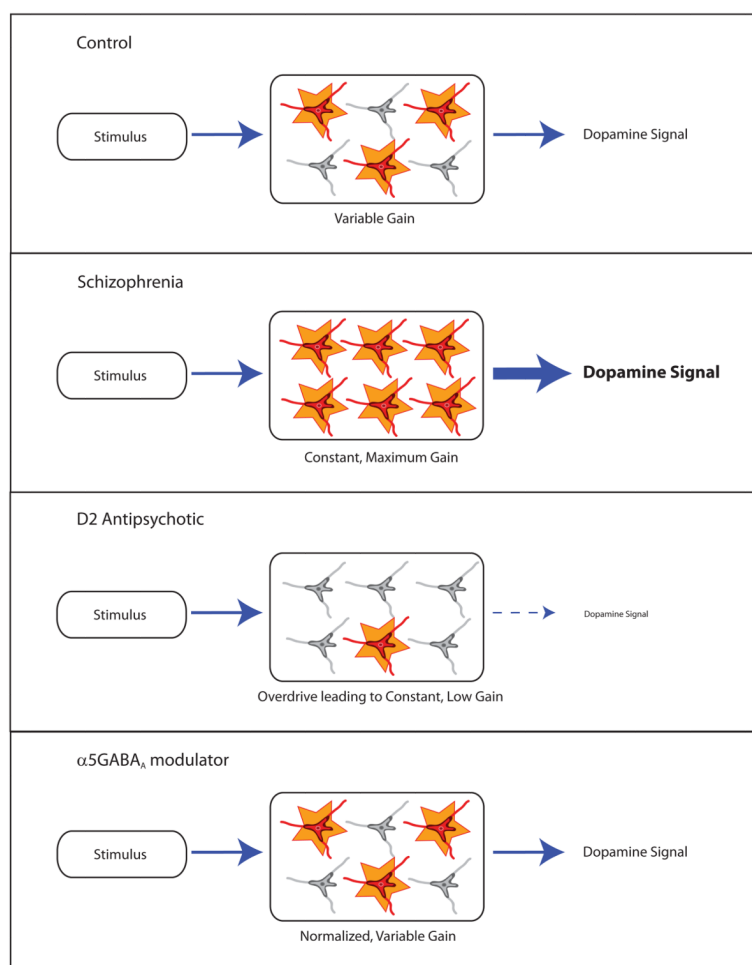
Figure 2.
Under normal (non-pathological) conditions, the number of dopamine neurons spontaneously active can be modulated to permit an appropriate behavioral response based on the environmental setting. In schizophrenia, the dopamine neuron population activity is pathologically in a constant high-activity state and, as such, all stimuli the organism encounters will lead to maximal dopamine output, resulting in the attribution of strong behavioral importance to stimuli, even to stimuli that should be safely ignored. Conventional antipsychotics decrease dopamine neuron activity via depolarization block; this would decrease the salience of all encountered stimuli but fails to restore the flexibility of the system. Novel therapeutics aimed at normalizing hippocampal function, i.e. allosteric modulators of the $\alpha5GABA_A$ receptor, restores normal dopamine function by acting upstream at the proposed site of pathology.
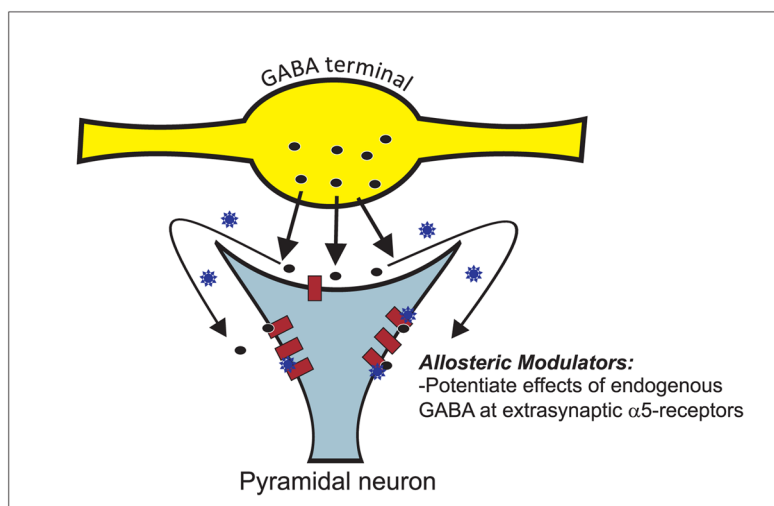
Figure 3.
The alpha 5 subunit is discretely distributed with high levels of expression limited to the hippocampus. These receptors are primarily extrasynaptic, localized to the base of the dendritic spines of pyramidal neurons. Thus, the α5-GABA$_A$ receptor is positioned to be activated by synaptic GABA (dark circles) as well as 'spillover' from adjacent synapses to provide an inhibitory input to glutamatergic hippocampal projection neurons. SH-053-2′F-R-CH$_3$ (blue stars) binds to an allosteric, benzodiazepine site of the α5-GABA$_A$ receptor, and augments the endogenous inhibition of the pyramidal neuron.