Low dose morphine adjuvant therapy for enhanced efficacy of antipsychotic drug action: Potential involvement of endogenous morphine in the pathophysiology of schizophrenia

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Summary

Major thematic threads linking extensive preclinical and clinical efforts have established a working mechanistic scheme whereby atypical antipsychotic drugs ameliorate negative DSM IV diagnostic criteria by effecting relatively potent blockade of serotonin (5-HT)(2A) receptors coupled with weaker antagonism of dopamine D(2) receptors in frontal cortical areas. These contentions are more or less supported by *in vitro* binding experiments employing cloned receptors on cultured cells, although significant functional involvement of 5-HT(2C) receptors has also been proposed. It is interesting that a key statistical analysis indicates a major shift in usage back to typical antipsychotic agents for management of schizophrenia from 1995–2008, whereas off-label usage of atypical antipsychotic agents was markedly increased or expanded for bipolar affective disorder. Importantly, meta-analyses generally did not support efficacy differences between the other atypical antipsychotics compared with the older typical agents. A critical examination of putative functional linkages of morphine and its type-selective mu opioid receptor to higher order cortical regulation of cognitive processes may provide novel insights into human behavioral processes that are severely impaired in schizophrenia spectrum disorders.

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MEDICAL HYPOTHESIS

Over the last 20 years, there has been a dramatic expansion in atypical antipsychotic drug development and usage for management of populations of psychiatric patients afflicted with schizophrenia spectrum disorders. Major thematic threads linking extensive preclinical and clinical efforts in this area have established a working mechanistic scheme whereby atypical antipsychotic drugs ameliorate negative DSM IV diagnostic criteria by effecting relatively potent blockade of serotonin (5-HT)(2A) receptors coupled with weaker antagonism of dopamine D(2) receptors in frontal cortical areas [1]. The combination of pharmacological effects is proposed to promote enhanced efflux of cortical and hippocampal dopamine (DA) with concurrent decreased DA efflux in the striatum. Furthermore, reciprocal functional activation of 5-HT(1A) receptors by 5-HT(2A) receptor blockade may also contribute to the apparent enhanced efficacy of new atypical antipsychotic drugs via potentiation of DA efflux in cortical regions [2,3]. These contentions are more or less supported by *in vitro* binding experiments employing cloned receptors on cultured cells, although significant functional involvement of 5-HT(2C) receptors has also been proposed [4].

It is interesting that a key statistical analysis indicates a major shift in usage back to typical antipsychotic agents for management of schizophrenia from 1995–2008, whereas off-label usage of atypical antipsychotic agents was markedly increased or expanded for bipolar affective disorder [5]. A recent Cochrane Database of Systematic Reviews affords a detailed comparative analysis of the widely used atypical antipsychotic agent olanzapine versus other atypical antipsychotics for schizophrenia [6]. Olanzapine was found to be slightly more efficacious than other widely used second generation antipsychotic drugs. Small incremental increases in efficacy were not paralleled by diminution of well documented side effects that include weight gain and associated metabolic disorders, most notably Type II diabetes. These conclusions are supported by a recent systematic review of meta-analyses of the efficacy of oral atypical antipsychotics for treatment of adult schizophrenics [7]. Importantly, the meta-analyses generally did not support efficacy differences between the other atypical antipsychotics compared with the older typical agents.

In light of the above, there remains a compelling need for novel pharmacotherapeutic strategies with markedly enhanced efficacies, limited side effects, and high potential for elevating quality of life parameters for outpatient populations of adult schizophrenics. Notably, cognitive disorders represent a hallmark core dysfunction in schizophrenics with the severity of cognitive symptoms serving as a better indicator of social and functional outcome, i.e., quality of life, than standard measures of antipsychotic drug efficacy via DSM IV criteria [8]. Cognitive processes that are specifically impaired in schizophrenia are verbal memory, working memory, motor function, attention, executive functions, and verbal fluency. Functional imaging studies indicate that schizophrenic patients fail to activate their frontal cortex following selective cognitive tasks [9,10]. Thus, deficiencies in cognitive measures should be recognized as a major element in social and professional integration of schizophrenia patients, and should become a standardized assessment

approach in clinical trials [11]. A recent study indicates that sensorimotor gating, assayed via prepulse inhibition (PPI) of the acoustic startle response (ASR), and attentional set-shifting are improved by a low 10 mg marginally analgesic oral dose of morphine in healthy human volunteers. Utilizing a double-blind, randomized, and counterbalanced design, morphine administered over period of a week significantly increased PPI without affecting startle reactivity or habituation. It was also observed that morphine selectively improved the error rate in an attentional set-shifting task but did not influence vigilance, memory, or executive functions. The results raise the question whether compromised mu opioid systems also play a crucial role in impaired sensorimotor gating, attentional set-shifting, and other critical cognitive processes in schizophrenia [12]. Human PPI is modulated by both attentional and emotional responses to prepulse stimulation, indicating that this cognitive response is "top-down" modulated by higher-order cortical organization [13]. Interestingly, a combined biological imaging and behavioral study reported significant positive correlations between diminished PPI and reductions in regional grey matter volumes in the dorsolateral prefrontal, middle frontal and the orbital/medial prefrontal cortices of schizophrenic patients [14].

A critical examination of putative functional linkages of morphine and its type-selective mu opioid receptor to higher order cortical regulation of cognitive processes may provide novel insights into human behavioral processes that are severely impaired in schizophrenia spectrum disorders. A 2006 pilot study utilized functional magnetic resonance imaging (fMRI) to monitor the effects of an intravenous low dose of morphine (4 mg/70 kg) or saline to healthy volunteers [15]. Overall, the study authors observed a segregation of fMRI responses in cortical versus subcortical regions suggesting a dissociation of reward from sensory-motor and cognitive functions. Despite the appearance of predictable activation patterns in established reward and nociceptive regions, morphine-mediated activation of areas within the orbitofrontal cortex and hippocampus was suggestive of its potential role as a cognitive enhancer. Selected clinical literature has also reported that cohorts of patients receiving daily dosages of morphine for postherpetic neuralgia pain were effectively managed without impaired cognition [16] and that morphine was a highly efficacious postoperative analgesic in cohorts of elderly patients without producing postoperative delirium or cognitive decline [17]. A recent study assessed potential neurocognitive effects of a single 10 mg dose of the morphine congener oxycodone administered to healthy, older and middle-aged adults not suffering from chronic or episodic daily pain. For almost all cognitive measures, there were no observed medication by age-interaction effects [18].

A high resolution window into potential therapeutic applications of morphine/mu opioid receptor driven cortical processes is provided by collected studies designed to probe the neurobiology of placebo analgesia [19,20]. As an example, a key 2007 study examined potential CNS *loci* mediating placebo analgesia *in vivo* via positron-emission tomography (PET) labeling with the highly selective mu opioid receptor agonist [11C]carfentanil [21]. Placebo treatments differentially affected [11C]carfentanil labeling of cortical and subcortical areas involved in nociceptive, antinociceptive, and

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affective modulation of human pain and included periaqueductal gray and nearby dorsal raphe and nucleus cuneiformis, amygdala, orbitofrontal cortex, insula, rostral anterior cingulate, and lateral prefrontal cortex. The authors correlated differential binding of [11C]carfentanil within discrete brain regions to behaviorally evoked activation of endogenous opioid systems and concluded that placebo conditioning effected increased connectivity within several limbic and prefrontal regions as an integral part of the mechanism whereby expectancies regulate affective and nociceptive circuits. The case for essential functional recruitment of cortical mu opioid receptor systems in the mediation of placebo analgesia also extends to reciprocal interactions with D(2) receptors in the mediation of integrative cognitive processes [20]. Interestingly, analgesic effects of sham acupuncture have also been functionally associated with differential binding of [11C]carfentanil within the dorsolateral prefrontal cortex [22]. Finally, a recent elegantly performed fMRI study sought to identify CNS pathways by which informational cues influence pain perception [23]. Anticipated activation effects within traditional nociceptive pathways were observed to be functionally linked to cue-evoked anticipatory activity in the medial orbitofrontal cortex and ventral striatum, areas not previously directly implicated in nociceptive/antinociceptive processes. The functional role of orbitofrontal cortical mu opioid receptors in mediating high order cortical processes relating to nociception, placebo antinociception, and other behaviors, and their dysregulation in psychiatric syndromes remains to be elucidated.

We have proposed a case for low dose morphine as a cognitive enhancer in schizophrenia patients based on functional and behavioral studies of cortical distributions of its type selective mu opioid receptor in discrete prefrontal and orbitofrontal regions. Our contentions are strengthened by complementary human studies of interactive 5-HT(2A) receptor systems in these same cortical areas. A 2011 controlled cross-over human PET study observed significantly enhanced 5-HT(2A) receptor PET ligand binding in the orbitofrontal cortex with the performance of executive functions of working memory and concluded that 5-HT(2A) receptor systems mediate and optimize basic cognitive functions [24]. A recent imaging study observed that schizophrenic patients had significantly lower 5-HT(2A) binding in the frontal cortex than did control subjects [25]. A significant negative correlation was observed between frontal cortical 5-HT(2A) binding and positive psychotic symptoms in male patients. The putative role of cortical 5-HT(2A) receptors in the regulation of cortical cognitive processes and in the pathophysiology of schizophrenia is further demonstrated by 2011 high resolution human PET study [26]. Here differences in PET ligand binding to cortical 5-HT(2A) receptor densities were functionally calibrated to measure 5-HT release. Furthermore, cortical 5-HT/5-HT(2A) receptor activation was established as a functional indicator of CNS dopaminergic transmission via effects on circulating plasma cortisol and prolactin concentrations. Interestingly, complementary biochemical studies have demonstrated reciprocal functional interactions of the 5-HT(2A) receptor and the mu opioid peptide receptor following activation by morphine [27] These data suggest that selective activation of the 5-HT(2A) receptor in concert with low dose morphine treatment may mediate positive effects on cognitive processes within the OFC.

In a related area of schizophrenia research, a recent study investigated the impact of two common nicotinic acetylcholine receptor CHRNA3 polymorphisms (rs1051730/rs1317286) on cortical cognitive tasks in two independent samples of 107 healthy British volunteers and 73 schizophrenia patients hailing from Germany. In both samples, PPI was influenced by both CHRNA3 polymorphisms which were strongly linked and associated with negative symptoms in the schizophrenia patients. These results suggest that sensorimotor gating is influenced by variations of the CHRNA3 gene, which might also have an impact on the course and severity of schizophrenia [28]. The case for compensatory low dose morphine as a restorative agent for impaired nicotinic systems in schizophrenics is strengthened by a 2007 preclinical study investigating mu-opioid transmission in acute slices of rat neocortex [29]. Morphine was found to inhibit interneurons that are selectively excited by nicotinic agonists. Study results suggest that neocortical mu-opioid transmission acts as an inhibitory feedback onto nicotinic-responsive interneurons, which may change network excitability and inhibition patterns during cholinergic excitation via GABAergic output onto pyramidal cells.

CONCLUSIONS

For over 30 years empirical studies have repeatedly demonstrated that endogenous morphine is expressed by diverse animal and human tissues. Because the prototype catecholamine DA and its major precursor L-3,4-dihydroxyphenylalanine (L-DOPA) were also found to be utilized as morphine precursors, a novel reciprocally interactive mechanism is compellingly apparent that links DA and "morphinergic" pathways in the activation and inhibition of behavioral/cognitive responses within discrete cortical regions [30,31]. In support of these contentions, immunohistochemical studies have revealed the presence of morphine-like immunoreactive material in the perikarya, fibers, and terminals of neurons in cortical areas of rat and human brain [32]. Furthermore, a 2011 anatomical study has observed colocalization of endogenous morphine-like to GABAergic cells in rodent cerebral cortex [33]. We therefore hypothesize that endogenous morphine systems are reciprocally dysregulated in schizophrenia and are intimately linked to major alterations in DA-ergic transmission and DA receptor expression. Accordingly, restorative non-analgesic dosages of morphine, morphine congener or morphine precursor is proposed to significantly enhance clinical outcomes of schizophrenic outpatients treated with standard dosages of atypical or typical antipsychotic agents.

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