enhancement of phasically released ENKs. In animal models, exogenous delta agonists such as SNC80 ((+)-4-(aR)-a-((2S,5R)-2,5-dimethyl-4-(2-propenyl)-1-piperazinyl)-(3-methoxyphenyl)methyl)-*N,N*-diethylbenzamide induce highly significant antidepressant effects whereas mu agonists do not. This is associated with an increase in brain-derived neurotrophic factor mRNA (Jutkiewicz, 2006), which has been suggested to have a role in antidepressant effects, as well as an indirect increase in DA efflux into the striatum (Bosse *et al*, 2008). As frequently observed with some delta agonists, SNC80 causes seizures. This is not observed with RB101, which is effective in almost all animal models of depression, eg, decreases conditioned suppression of mobility in mice, immobility in the forced swim test in rats (Jutkiewicz, 2006) and in mice (Nieto *et al*, 2005) and escape failures in the learned helplessness test (Noble and Roques, 2007). The effects of RB101 are observed after a single administration and no tolerance is observed during chronic use (Cordonnier *et al*, 2005). Moreover, stimulation of opioid receptors by RB101 protected ENKs does not induce the undesirable side effects of morphine (Noble and Roques, 2007). The selective DOR antagonist naltrindole or DA antagonists reverse antidepressant effects of RB101 and SNC80, demonstrating that the effects are mediated by DORs, and involve the DA-dependent mesolimbic pathway. Consistently, DOR KO mice present depressive-like behaviors, which are reversed by antidepressant drugs, whereas MOR KO mice are unaffected (Filliol *et al*, 2000; Nieto *et al*, 2005). The key role of interconnected endogenous opioid and DAergic systems in mood control is demonstrated by the facilitation of antidepressant-like effects of RB101 after deafferentation of the DAergic mesolimbic pathway (Cordonnier *et al*, 2005), which increases the concentrations of PENK and ENKs. Taken together, these results suggest a phasic control of the DAergic mesolimbic pathway by ENKs, which may be impaired in depressive-like syndromes, and clinical studies are starting to investigate this endogenous opioid-DA interaction in human depression (Kennedy *et al*, 2006; Scott *et al*, 2008). The development of (i) dual orally active ENK inhibitors with strong analgesic properties and immediate antidepressant effects (Noble and Roques, 2007) and (ii) delta agonists devoid of side effects may lead to significant improvements in the treatment of depression and mood disorders.

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DISCLOSURE

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Oxytocin as a Potential Therapeutic Target for Schizophrenia and Other Neuropsychiatric Conditions

Compelling preclinical evidence indicates that the nonapeptide hormone oxytocin has a critical role in the regulation of brain-mediated processes that are strongly relevant to many neuropsychiatric disorders. The fact that oxytocin has long been approved for non-CNS uses in humans has provided an unusually auspicious opportunity to conduct investigations of its CNS effects in human subjects without requiring the lengthy and expensive preclinical and clinical toxicology studies that typically hinder translational human research of promising novel compounds. Taking advantage of this favorable situation, investigators have generated a plethora of small studies demonstrating that even a single dose of intranasally delivered oxytocin can have striking effects on human cognition and behavior. Though an oversimplification, these effects can broadly be characterized as pro-social in nature (review Macdonald and Macdonald, 2010). Understandably, those findings have generated much discussion about the possibility of translating oxytocin's effects into therapeutic applications, with autism spectrum disorders and social phobia garnering the most attention. However, it is schizophrenia, in which the application of oxytocin as putative therapeutic has advanced the furthest to date. Several positive findings with oxytocin in animal models with predictive validity for antipsychotics (eg Feifel and Reza, 1999; Lee *et al*, 2005) inspired our group to conduct a proof-of-concept human trial: a double-

blinded, placebo-controlled crossover design enrolling schizophrenia patients who were highly symptomatic despite receiving therapeutic doses of an atypical antipsychotic. The results revealed that intranasal oxytocin (40 international units twice a day), administered as an adjunct to subjects' antipsychotic drugs for 3 weeks improved positive and negative symptoms significantly more than placebo (Feifel *et al*, 2010). In addition, oxytocin improved the performance on a verbal memory task (CVLT-II) (manuscript in preparation). Recently an independent group of investigators at University of North Carolina conducting an independent trial of adjunctive intranasal oxytocin in schizophrenia also reported positive therapeutic effects (Pedersen *et al*, 2010). These positive therapeutic findings are indirectly bolstered by growing evidence of endogenous oxytocin's role in the manifestation of schizophrenia symptoms. For example, a recent study found higher plasma oxytocin levels were associated with more pro-social behavior in schizophrenia patients and with less severe psychopathology in female patients (Rubin *et al*, 2010). The mechanisms underlying oxytocin's beneficial effects on schizophrenia symptoms are not known, but candidate processes are its known ability to regulate mesolimbic dopamine pathways and modify activation of the amygdala. Based upon the promising initial findings our group and others are now conducting larger clinical trials of intranasal oxytocin in schizophrenia and proof-of-concept studies in other disorders are also underway. However, many questions need to be addressed in order to develop optimized oxytocin-based treatments. For example, what is the optimal intranasal dose and dosing schedule for long-term therapeutic CNS effects? Also, is the intranasal route the optimum route of delivering oxytocin? Furthermore, development of proprietary oxytocin mimetics, preferably small molecule agonists, is needed to facilitate industry interest in this therapeutic target and accelerate translation of oxytocin's promise into widely available treatments. If these challenges can be met and the positive early results hold up in larger trials, it may signal the beginning of an exciting new era in the treatment of schizophrenia and perhaps other neuropsychiatric disorders, something desperately needed given the disappointing lack of progress in developing efficacious novel mechanism treatments in this field.

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Dysregulation of mTOR Signaling in Neuropsychiatric Disorders: Therapeutic Implications

Autism is a widespread disorder characterized by deficits in social interactions, impairments in communication, and repetitive and stereotypic behaviors. Identification of genetic markers has proved difficult, owing to the highly complex and variable nature of the disease. Although autism spectrum disorders (ASDs) arise as a consequence of mutations in genes with multiple molecular functions, they appear to converge on common biological pathways to give rise to autism-relevant behaviors (Abrahams and Geschwind, 2008). One such pathway is the PI3K-mammalian target of rapamycin (mTOR) signaling cascade. The mTOR pathway is a central regulator of cell growth, proliferation, survival, and cap-dependent protein translation. In brain, components of the mTOR pathway are present at synapses, where they regulate dendritic spine morphology, and are essential to synaptogenesis. Growing evidence indicates that dysregulation of mTOR is involved in human diseases, including cancer, diabetes, and autism. Mutations in tuberous sclerosis complex (*TSC*)1, *TSC2*, neurofibromatosis 1 (*NF1*), and *PTEN* lead to overactivated PI3K-mTOR pathway, autism-relevant behaviors, and tuberous sclerosis, neurofibromatosis, or macrocephaly.

Fragile X syndrome (FXS) is the most common heritable form of intellectual disabilities, and a leading genetic cause of autism. Recent findings that PI3K-mTOR signaling is overactivated at synapses of Fragile X mice (Sharma *et al*, 2010) and in humans with FXS provide the first evidence that genetic mutation not only of components within the mTOR signaling cascade, but also distant regulatory proteins, can lead to autism-related phenotypes. Overactivated mTOR signaling is linked to elevated cap-dependent translation and impaired synaptic plasticity in Fragile X mice (Sharma *et al*, 2010). mGluR1/5 links via Homer to PIKE (PI3 kinase enhancer) at synapses, where it engages PI3K–mTOR signaling in response to synaptic stimulation. PIKE, an upstream activator of mTOR and identified target of