neurotherapeutic potential of CRF_1 antagonists. Our hypothesis is that CRF antagonists may be valuable in specific psychiatric disorders in which stress is a dynamic rather than chronic condition. More explicitly, we suggest that CRF_1 antagonists in psychiatry may particularly be useful in post-traumatic stress disorder (PTSD), panic disorder, and addiction.

Non-peptide CRF_1 antagonists consistently produce anxiolytic-like effects in certain animal models, such as conditioned freezing, defensive burying, acoustic startle responding, the open field, the elevated plus maze, the light–dark box, the defensive withdrawal test, and the social interaction test. A CRF_1 antagonist (R317573/JNJ19567470/CRA5626) also recently showed activity in rodent (Shekhar *et al*, 2011) and human (Bailey *et al*, 2011) panic models. These models reflect a dynamic, active response to an acute stressor and, from a face validity perspective, may reflect more the symptoms of specific subtypes of anxiety disorders rather than of generalized anxiety disorder. Indeed, CRF_1 antagonists exhibited weak activity in punished drinking and punished crossing conflict models, unlike γ-aminobutyric acid anxiolytics. Despite initial positive results, small-molecule CRF_1 antagonists have not consistently shown efficacy in animal models of antidepressant activity (Zorrilla and Koob, 2010).

CRF_1 antagonists also reduce the activation of brain stress systems in models of addiction, supporting the therapeutic potential of CRF_1 antagonists for drug dependence. Hypothalamic-pituitary adrenl-axis and extrahypothalamic CRF systems are activated during acute withdrawal from all major substances of abuse in animals. CRF antagonists blocked anxiogenic-like responses to withdrawal from cocaine, alcohol, nicotine, cannabinoids, and palatable food and blocked the development of or reduced already escalated drug self-administration in addiction models (for details and references, see Koob and Zorrilla, 2010; Boyson *et al*, 2011). CRF_1 antagonists also blocked stress-induced reinstatement of heroin-, cocaine-, nicotine-, alcohol-, and palatable food-seeking behavior and stress-induced reactivation of conditioned place preference for opioids and cocaine (Koob and Zorrilla, 2010).

No CRF_1 antagonist has successfully completed a Phase III trial. R121919 and PF-00572778 were abandoned due to liver enzyme elevations (NCT00580190). The development of ONO-2333 Ms (NCT00514865) and CP-316,311 were halted because of negative efficacy in double-blind, placebo-controlled trials for major depression (Zorrilla and Koob, 2010). Verucerfont (GSK561679) also lacked efficacy in a major depression trial (Protocol # CRS106139). Pexacerfont (BMS-562086) was ineffective against generalized anxiety disorder (Coric *et al*, 2010). Trials of verucerfont and emicerfont for social anxiety disorder have been completed with undisclosed results (NCT00555139). Relevant to the hypothesis proposed herein, Glaxo SmithKline and NIH are currently evaluating verucerfont against startle in healthy women (NCT01059227), in women with PTSD (NCT01018992), and against stress-induced alcohol craving in anxious women (NCT 01187511). A trial for pexacerfont has likewise been initiated in anxious alcoholics by Bristol Myers Squibb and NIAAA (NCT01227980). Several other candidates are earlier in the pipeline, or their status has not been publicly updated by the pharmaceutical industry (eg, GSK586529 [NCT01059227], SSR125543 [NCT01034995], antalarmin). Should results from these trials concur that CRF_1 antagonists are ineffective for chronic anxiety and depression, a re-evaluation should be considered with emphasis on certain anxiety disorders, such as PTSD and possibly panic disorder, and on addiction disorders.

ACKNOWLEDGEMENTS

This study was supported by the Pearson Center for Alcoholism and Addiction Research and National Institutes of Health grants DK26741 from the National Institute of Diabetes, Digestive and Kidney Diseases and AA06420 from the National Institute on Alcohol Abuse and Alcoholism.

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DISCLOSURE

GFK consults for Addex Pharmaceuticals, Alkermes, Arkeo Pharmaceuticals, Embera Neurotherapeutics, GlaxoSmithKline, Lilly, and Psychogenics. GFK and EPZ are co-inventors on US patent no. 60/972,409, "MPZP: A Small Molecule Corticotropin-Releasing Factor Type 1 Receptor (CRF_1) Antagonist."

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Neuropsychopharmacology Reviews (2012) **37**, 308–309; doi:10.1038/npp.2011.213

Update on Omega-3 Polyunsaturated Fatty Acids in Early-Stage Psychotic Disorders

Polyunsaturated fatty acids (PUFAs) are the major constituents of cell membrane phospholipids. As such, they have

multiple important biological roles, including in receptor binding, neurotransmission, signal transduction, and eicosanoid synthesis. A growing body of studies suggests significant reductions in PUFA levels in people with schizophrenia (Berger *et al*, 2006). Concordant with these findings, fatty acids, particularly the omega-3 PUFA, may have a beneficial role in the treatment of first-episode schizophrenia, and in the prevention of schizophrenia, while results in chronic schizophrenia have been mixed (Peet, 2008). We have recently tested whether supplementation with omega-3 PUFA could reduce the rate of transition to first-episode psychosis in an ultra-high risk (UHR) cohort. In our study, we randomized 81 individuals aged 13–25 years to 12 weeks of either 1.2 g/day of omega-3 PUFA or placebo, followed by a 40-week monitoring period. In all, 2 of 41 (4.9%) of those receiving the active agent transitioned to psychosis, compared with 11 of 40 (27.5%) in the placebo group, a statistically significant difference (Amminger *et al*, 2010). While PUFAs have been investigated in schizophrenia, their role in the onset of psychotic symptoms is unclear. Therefore, we examined the relationship between omega-3 PUFA (ie, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA)) levels in erythrocyte membrane phosphatidylethanolamine and measures of psychopathology in our UHR cohort at baseline. Erythrocyte membrane phospholipid composition closely reflects that of neuronal membranes, and provides an easily accessible indicator of brain phospholipids. While ALA, EPA, and DHA did not correlate significantly with any symptom measure, low levels of DPA and the summary score of all assessed omega-3 fatty acids (ie, ALA, EPA, DPA, and DHA) correlated with more severe negative symptoms. These correlations remained significant after adjustment for potential confounders (ie, age, sex, and nicotine use). Reduced DPA has been previously reported in neuroleptic-naïve first-episode schizophrenia patients (Reddy *et al*, 2004). Given our intervention study provided support for the 'dose–response' criterion (McNamara, 2011), as an increase in erythrocyte omega-3 PUFA levels reduced the rate of transition to psychosis and correlated with functional improvement, we tested if the subjects with the lowest erythrocyte omega-3 levels at baseline were at higher risk for transitioning to psychosis. To eliminate treatment effects, we only investigated those participants who had received placebo. Cox regression analyses with adjustment for age, sex, and nicotine use indicated that no single omega-3 PUFA or their summary score predicted conversion to psychosis. Following studies reporting lower levels of arachidonic acid (AA) and nervonic acid (NA), as well as DHA, in people with schizophrenia (Assies *et al*, 2001), we also examined if these fatty acids predicted transition to psychosis. While AA was not found to be predictive, low NA levels at baseline significantly predicted transition to psychosis (Amminger *et al*, submitted). As NA is a major constituent of the myelin sheath, low levels of NA could reflect suboptimal myelination in those UHR individuals who develop a psychotic disorder. The finding is consistent with the well-established finding of white matter abnormalities in schizophrenia (Ellison-Wright and Bullmore, 2009). Notably, the observation that supplementation with omega-3 PUFAs may prevent transition to psychosis suggests that omega-3 fatty acids may offset the risk conferred by decreased levels of NA. A randomized controlled multicenter phase III clinical trial of omega-3 PUFA is now underway to replicate the findings (Australian New Zealand Clinical Trials Registry - ACTRN12608000475347).

ACKNOWLEDGEMENTS

Supported by grants from the Stanley Medical Research Institute (03T- 315, 07TGF-1102).

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DISCLOSURE

The authors declare no conflict of interest.

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Neuropsychopharmacology Reviews (2012) **37**, 309–310; doi:10.1038/npp.2011.187

Beyond Antipsychotics: Pharmacologically-Augmented Cognitive Therapies (PACTs) for Schizophrenia

The neuropathology of schizophrenia is substantial in scope and complexity. In patients, structural abnormalities in about 20 brain regions span wide swaths of cortical and subcortical tissue, reflecting processes presumably well advanced at birth. Roughly half as many regions are abnormal in unaffected relatives (cf. Swerdlow, 2011). Within any region, laminar synaptic and cellular arrangements