which continues to the end of the second decade, can, potentially, cause enduring, functionally significant changes in neuronal circuitry. The duration and timing of drug treatment are critical in determining long-term effects (Popa *et al*, 2008), owing to developmental changes in the neural substrates on which the drugs act.

Stress, which is associated with affective disorders, adversely impacts neural development during fetal life and postnatally, and is ameliorated by therapies that improve affect. Thus, potential, adverse, long-term effects of exposing the developing brain to medication must be weighed against the deleterious impact of stress elevation as a result of interrupted pharmacotherapy of pregnant women, or not treating children or adolescents.

Human studies have revealed few effects of fetal antidepressant drug (ADD) exposure that endure beyond infancy. By contrast, adult rodents exposed to ADDs only during stages corresponding to fetal life, childhood, or adolescence in humans exhibit a spectrum of abnormalities, many of which are, surprisingly, components of depression. Similar, long-term, 'mirror image' effects (that is, drug-induced increases in disease components that are reduced by pharmacological treatment of adults) occur after early-life anxiolytic treatment (Depino *et al*, 2008). Early exposure to atypical antipsychotic drugs, used to treat bipolar disorder in children and adolescents, induces significant, long-lasting cognitive deficits (Zuo *et al*, 2008) and morphological abnormalities (Frost *et al*, 2009).

Why do rodent and human data seem discrepant? In rodents, the behavioral syndromes induced by early ADD (Ansorge *et al*, 2008) or anxiolytic (Depino *et al*, 2008) treatment are progressive and emerge fully only in early adulthood. This is because early-life brain insults induce a cascade of effects over the course of development. Human studies of the effects on progeny of maternal ADD treatment during pregnancy so far reach only up to 7–10 years of age—too early to characterize long-term outcomes.

Early-life experience and environmental factors are emerging as additional, important modulators of the effects of psychotropic medications. We recently showed that, in rats, some of the enduring behavioral consequences of fetal exposure to fluoxetine do not occur if exposed infants are subjected to behavioral testing, which, by its nature, provides supplemental sensory stimulation and exercise (R Gibb, DO Frost and B Kolb, unpublished data). A provocative, parallel finding has recently been reported in humans: In infants who are not breast fed, maternal SSRI use during pregnancy is associated with altered hypothalamo–pituitary–adrenal (HPA) stress responses, whereas breast feeding abolishes this effect of fetal SSRI exposure by 3 months of age (Oberlander *et al*, 2008). The mode of feeding seems to act epigenetically: breast-fed infants have lower methylation (and probably higher expression) of the glucocorticoid receptor gene NR3C1 than nonbreast-fed infants (Oberlander *et al*, 2008).

Animal and human studies are consistent in demonstrating that environment and experience during fetal and postnatal brain maturation interact with early-life psychotropic drug exposure to shape the ontogeny of behavior and neural circuitry. Epigenetic modulation of gene expression appears to be one important mediator of these effects. These findings suggest possibilities for designing new therapeutic strategies that mitigate the effects of early-life ADD exposure.

ACKNOWLEDGEMENTS

This work was funded by 5R01 MH074083 from the National Institutes of Health, a Research Enhancement Award Program from the Research Service of the US Department of Veterans Affairs to DOF and the Canadian Institutes of Health Research (BK). We declare that, except for income received from their primary employers, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

Douglas O Frost[1], Robbin Gibb[2] and Bryan Kolb[2]

[1]Department of Pharmacology and Experimental Therapetics, Program in Neuroscience, University of Maryland School of Medicine, Baltimore, MD, USA; [2]Canadian Center for Behavioral Neuroscience, University of Lethbridge, Lethbridge, AB, Canada
E-mail: dfrost@umaryland.edu

Ansorge MS, Morelli E, Gingrich JA (2008). Inhibition of serotonin but not norepinephrine transport during development produces delayed, persistent perturbations of emotional behaviors in mice. *J Neurosci* **28**: 199–207.

Depino AM, Tsetsenis T, Gross C (2008). GABA homeostasis contributes to the developmental programming of anxiety-related behavior. *Brain Res* **1210**: 189–199.

Frost DO, Cercio Page S, Carroll C, Kolb B (2009). Early exposure to haloperidol or olanzapine induces long term alterations of dendritic form. *Synapse* (in press).

Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics* **3**: 97–106.

Popa D, Lena C, Alexandre C, Adrien J (2008). Lasting syndrome of depression produced by reduction in serotonin uptake during postnatal development: evidence from sleep, stress, and behavior. *J Neurosci* **28**: 3546–3554.

Zuo J, Liu Z, Ouyang X, Liu H, Hao Y, Xu L *et al* (2008). Distinct neurobehavioral consequences of prenatal exposure to sulpiride (SUL) and risperidone (RIS) in rats. *Prog Neuropsychopharmacol Biol Psychiatry* **32**: 387–397.

Neuropsychopharmacology Reviews (2010) **35,** 344–345; doi:10.1038/npp.2009.133

Ligand functional selectivity advances our understanding of drug mechanisms and drug discovery

'Intrinsic efficacy' (the concept that a drug acting at a single receptor is

always an agonist, partial agonist, or antagonist/inverse agonist) had been accepted for a half-century. Two decades ago, it became clear that a single G protein-coupled receptor (GPCR) could have promiscuous G protein interactions. This suggested that some drugs might cause differential effects on signaling via a single receptor, and within a few years, there were data showing such 'anomalous' functional responses—in the extreme, a ligand acting at a single receptor being a full agonist at one function and an antagonist at another (Kilts *et al*, 2002).

Strikingly, most laboratories engaged with this phenomenon recognized its implications, each proffering a unique name (eg, agonist-directed trafficking of signaling, biased agonism, etc), with *functional selectivity* emerging as the apparent consensus. The naming quandary, the involved mechanisms, the impact on understanding drug action, the relevance to drug discovery, and even the implications for teaching have been reviewed recently (Urban *et al*, 2007), now including the first book on the subject (Neve, 2009). It appears that this is a universal phenomenon for all GPCRs and other drug targets, and that many drugs may cause such differential signaling.

The question is whether functional selectivity is an interesting artifact for the specialist, or a mechanism that affects psychoactive drug action and drug discovery. The data suggest that both are true (Kilts *et al*, 2002; Smith *et al*, 1997). As an example, a recent publication examined the impact of functional selectivity on valvulopathy, which was thought to be due to 5-HT_{2B} agonist-induced mitogenic action in the heart. Clinical drugs were selected for their 5-HT_{2B} agonist profile in traditional assays, and then functionally profiled. Of this group, ropinirole was differentiated from the other compounds by its signaling profile, possibly explaining why it has a decreased risk of valvulopathy (Huang *et al*, 2009). To our knowledge, this is the first example for the differentiated side-effect profiles of functional selectivity.

Of direct neuropsychopharmacological relevance is the dopamine mechanism of action of aripiprazole. The most commonly disseminated hypothesis is that aripiprazole causes 'dopamine stabilization' through D_2 partial agonism. Conversely, other data have shown that aripiprazole, although sometimes a partial agonist, can also be a D_2 pure antagonist or full agonist depending on the assay system. As we have reviewed recently (Mailman, 2007), the original *in vivo*/*ex vivo* data from the drug's discoverers are consistent with D_2 functional selectivity, but not with simple partial agonism. Functional selectivity would thus predict that D_2 ligands selected as partial agonists in a single common functional assay may not be similar clinically. From this perspective, the failure of preclamol or bifeprunox to have adequate antipsychotic efficacy may not be surprising.

The level of complexity added by functional selectivity also provides opportunity. In the short term, it permits a greater understanding of the differential neuropsychopharmacology of drugs once thought to be functionally similar, and may permit discrimination of potential drug candidates. In the long term, scientific advances showing how individual signaling pathways affect cellular function (and subsequent physiological responses) will provide a mechanistic foundation for the discovery of rationally chosen functionally selective drugs.

Richard B Mailman[1] and Vishakantha Murthy[1]

[1]Departments of Pharmacology and Neurology and The Neuroscience Institute, Pennsylvania State University College of Medicine and Milton S. Hershey Medical Center, Hershey, PA, USA
E-mail: rmailman@psu.edu

DISCLOSURE

In addition to income from his primary employer, Dr Richard Mailman has an equity interest in Biovalve Technologies and Effipharma, which creates a potential conflict of interest that has been monitored by committees at his current and previous employer. In the past three years, Dr Mailman has also been compensated for providing scientific opinions relevant to legal or public policy matters that are not related to the topic of this commentary. Except for his primary employment, Dr Vishakantha Murthy declares that no compensation or support has been received from any entity over the past three years for research or professional service. This work was supported by grants MH040537 and MH082441.

Huang XP, Setola V, Yadav PN, Allen JA, Rogan SC, Hanson BJ *et al* (2009). Parallel functional activity profiling reveals valvulopathogens are potent 5-HT2B receptor agonists: implications for drug safety assessment. *Mol Pharmacol* Online July 1, 2009; doi:10.1124/mol.109.058057.

Kilts JD, Connery HS, Arrington EG, Lewis MM, Lawler CP, Oxford GS *et al* (2002). Functional selectivity of dopamine receptor agonists. II. Actions of dihydrexidine in D2L receptor-transfected MN9D cells and pituitary lactotrophs. *J Pharmacol Exp Ther* **301**: 1179–1189.

Mailman RB (2007). GPCR functional selectivity has therapeutic impact. *Trends Pharmacol Sci* **28**: 390–396.

Neve KA (2009). *Functional Selectivity of G Protein-Coupled Receptor Ligands*. Humana: New York.

Smith HP, Nichols DE, Mailman RB, Lawler CP (1997). Locomotor inhibition, yawning and vacuous chewing induced by a novel dopamine D2 post-synaptic receptor agonist. *Eur J Pharmacol* **323**: 27–36.

Urban JD, Clarke WP, von Zastrow M, Nichols DE, Kobilka B, Weinstein H *et al* (2007). Functional selectivity and classical concepts of quantitative pharmacology. *J Pharmacol Exp Ther* **320**: 1–13.

Neuropsychopharmacology Reviews (2010) **35**, 345–346; doi:10.1038/npp.2009.117

Induced pluripotent stem (iPS) cells and their future in psychiatry

One of the most significant challenges in neuroscience for the twenty-first century is to understand the molecular and cellular basis of neuropsychiatric disorders. Despite extensive research, the last several decades failed to yield clearly validated new drug targets or therapeutic mechanisms for major psychiatric disorders (Hyman, 2008). One important limitation is the lack of pathogenically and physiologically reliable animal and cellular model systems of psychiatric disorders. This challenging situation is now changing through the advances that followed Shinya Yamanaka and his colleagues' successful generation of pluripotent stem cells in 2006, so called 'induced' pluripotent stem (iPS) cells, from