RESEARCH SUMMARIES

Early-Life Stress and the Biochemistry of Addiction (two papers – 2016 & 2012)

Alcoholism and drug dependence are serious problems in most countries, affecting millions of people. The reasons why some people are more vulnerable to developing addictions than others have been discussed for decades, sometimes controversially. Studies in non-human mammals have now implicated stress during early life as a likely cause of vulnerability to addiction and we have begun to understand the biochemical pathways in the brain that are involved in this link.

The two papers summarised below, published four years apart, describe some recent work in this area. The earlier paper, by the Canadian physician, author and columnist Gabor Maté, reviews a number of such animal studies and compares them to studies in human children, concluding that emotional trauma in childhood can create a 'template' for addiction. The later paper reports a study in juvenile rats that suggests a pathway through which stress leads to the disruption of signalling pathways in the brain and thence to alcohol-seeking behaviour.

Addiction: Childhood Trauma, Stress and the Biology of Addiction
Maté, G.
Journal of Restorative Medicine (2012) 1, 56-63

Gabor Maté, a Jewish Holocaust survivor, physician and author based at Simon Fraser University, British Columbia, Canada, began his wide-ranging review by summarising the extent of alcoholism and substance dependence in North America. He then briefly stated his main hypothesis: that stressful experiences in early childhood can alter brain development in such a way that the risk of developing addictive behaviour is increased.

Infants who develop consistent, loving relationships with their carers – and in particular with their parents – release a set of natural brain chemicals known as opioids that promote feelings of pleasure and stimulate the development of brain circuits that respond to these chemicals and to the so-called 'reward chemical', dopamine. In contrast, numbers of dopamine and opioid receptors are depleted in infants who frequently experience severe stress.

Studies in non-human mammals have shown that stress arising from separation from the mother leads directly to similar changes in brain chemistry. The brains of four-month-old monkeys, for example, show a significant loss of dopamine only six days after separation. Long-term isolation can cause disruption of the dopamine system in adult rats, and the effect of this isolation is stronger in infancy. Separating rat pups from their mother for only an hour a day in the first week of life leads not only to changes in the brain but also to an increased tendency to take cocaine in adulthood.

It seems that the 'normal' development of signalling systems in the brain that offer some protection against the development of addictive behaviour requires parental relationships that are not only consistent but of high quality. All female mammals, and many males, stimulate their young, and this stimulation – licking in rats, and holding and cuddling in humans – has long-term positive effects on babies' and young animals' brains. Adult rats whose mothers licked and nurtured them more consistently and intensively have brain chemistry that

responds more strongly to natural tranquillizing chemicals and is generally more efficient in reducing anxiety. Infant rats who are transferred to nurturing mothers from less affectionate ones develop this efficient anxiety-reduction circuitry, suggesting that it is an environmental rather than a genetic effect.

The quality of nurturing by parents, and particularly by the mother, also affects levels of serotonin: the 'positive mood' chemical that is enhanced by anti-depressants. Monkeys separated from their mothers during infancy have lower serotonin levels in their brains than those raised by their mothers, and as adults they are more aggressive and more likely to consume excess quantities of alcohol. Levels of some other brain chemicals that regulate mood and behaviour, including norepinephrine and oxytocin, are also affected by the presence or absence of maternal nurturing behaviours. Oxytocin, which is sometimes known as the 'cuddle hormone', is associated with affection and social bonding.

In humans and other mammals, early-life stress can lead to depletion of these 'good' brain chemicals but also to a dangerous excess of others. One of the most important of these is the stress hormone, cortisol: enhanced levels of cortisol in the infant and juvenile brain can disrupt brain development, with lifelong consequences particularly for the development of memory and emotional control.

Maté stressed that although the relationship with the mother seems of primary importance, the most important relationship of an infant is with his or her 'primary caregiver or caregivers', who may be of either gender. Children whose relationship with those who care for them is disrupted will develop brain circuitry that makes it harder for them to respond to changes in their environment in healthy ways. Inborn temperament can modify this, and consistent nurturing is most important in the early years when the brain is most sensitive to external influence.

The 'typical' trajectory of an emotionally deprived child towards addictive behaviour as an adolescent and young adult has been widely reported in the media. The studies described in this review suggest that there is biochemical reasoning behind this frequently discussed stereotype and that it should have implications for public policy. Studies of drug addicts' life histories have frequently shown an 'extraordinarily high' incidence of childhood trauma. One example is the reputable Adverse Childhood Experiences (ACE) study, which catalogued painful childhood experiences in thousands of adults and found that each such experience at least doubled the risk of that individual developing an addictive behaviour. The authors of this study concluded that, although not every abused child becomes an addict and not every addict has suffered from abuse, severe childhood trauma can increase the risk of substance abuse up to ten times. Childhood trauma is linked to an increased risk of alcoholism in a similar pattern.

Studies of the brains of mistreated children, both in childhood and as adults, have shed light on the brain areas that are most severely affected. Victims of childhood sexual abuse show abnormal patterns of blood flow through part of the cerebellum, and areas of the brain that are involved in processing emotion and memory are poorly developed in adults who were abused in childhood and who suffer from addiction. These include the corpus callosum, which integrates the functions of the left and right brain hemispheres. This seems to fit in with an idea that suggests that people with addictive personalities – not just substance addicts – have difficulty in reconciling conflicting information, particularly in relationships.

Another aspect of the relationship between childhood trauma and addiction concerns the physiology of the stress response. Any stress causes a release of hormones, particularly

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cortisol and adrenaline, and this affects almost all body systems to some extent. Early exposure to chronic stress lowers an individual's 'set point' for this response, so he or she responds more rapidly and more intensely to stress: or, put more simply, is more anxious and neurotic. Even a mild level of chronic stress in early childhood can have a small effect on an adult's stress 'set point'. Individuals with this enhanced base level of arousal are likely to experience greater pleasure from a stimulant such as alcohol, and be more likely to seek it out; conversely, they are less able to derive pleasure from intimate relationships. Addiction, then, is a natural and ingrained response to stress in those who have an enhanced response to it, and exposure to a new stress is a frequent trigger of relapse in recovering addicts and alcoholics.

Maté concluded his review by stating that childhood trauma and loss can provide a 'template' for addictive behaviours in later life. His last main point, however, highlighted an issue that is discussed in much greater length in the second paper summarised here: that social isolation in non-human mammals and emotional isolation in humans is frequently a cause of chronic stress and thus, via the biochemical triggers discussed, to addictive behaviour.

Early-Life Social Isolation Stress Increases Kappa Opioid Receptor Responsiveness and Downregulates the Dopamine System
Karkhanis, A.N., Rose, J.H., Weiner, J.L. and Jones, S.R.
Neuropsychopharmacology **(2016)** 41, 2263–2274

Sara Jones and her co-workers at the Wake Forest School of Medicine, Winston-Salem, North Carolina, USA have recently published a detailed study in rats that confirmed a relationship between early-life isolation, stress and addictive behaviours and shed further light on its basis in the biochemistry of the brain. This focused in particular on the roles of dopamine, one of the brain chemicals discussed extensively in Malé's review, and one particular type of receptor that responds to the opioids, known as the kappa opioid receptor or KOR. Dopamine release stimulates the 'reward and pleasure centres' in the brain. Stimulation of kappa opioid receptors on dopamine-releasing nerves in a brain region known as the nucleus accumbens (NAc) suppresses dopamine release, and KOR activity is increased by exposure to chronic stress. This, in turn, is thought to arise through an increase in the synthesis of a chemical, dynorphin, that binds to the receptor. KOR activation by dynorphin increases drug-seeking behaviour in animals, and its deactivation can suppress this behaviour once addiction has developed. Jones and her co-workers defined a study to test the hypothesis that stress associated with social isolation would increase dynorphin-KOR signalling and so reduce dopamine activity. These biochemical changes could be expected to lead to an increase in alcohol consumption.

The rodent model of social isolation chosen by Jones and her co-workers to study these responses was a well-established one in which 28-day-old male rats were housed for the following eight weeks either completely alone (socially isolated, SI) or in 'standard' groups of four (group housed, GH). A 28-day-old rat has reached a life stage that is approximately equivalent to human adolescence. After eight weeks, some were killed and the electrical activity in their brains tested using a technique called voltammetry; others were implanted with cannulas to monitor their dopamine levels; and others were tested for their preference for alcohol over water. These rats were given access to a choice of water with 20% ethanol (the

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addictive alcohol in beer, wine and spirits) three days a week for 7 weeks, but only water on the other days; by that point, the ethanol intake of all rats had stopped changing with time.

The voltammetry experiments tested dopamine transmission and kappa opioid receptor sensitivity in the nucleus accumbens of the rat brains under a variety of stimuli. The brains of socially isolated rats had lower base levels of dopamine but released more dopamine after electrical stimulation than those of the group-housed rats. A compound that stimulates the kappa receptors decreased the dopamine response more strongly in the SI rats than in the GH ones. Pre-treatment with nor-binaltorphimine (nor-BNI), a compound that blocks KOR activity, increased the baseline levels of dopamine more in SI than in GH rats. Pre-treatment with nor-BNI also increased the amount by which ethanol induced dopamine release in the SI rats only.

Not surprisingly, the researchers found that the SI rats chose a significantly larger intake of ethanol than the GH rats when all rats were given a free choice. Furthermore, pre-treatment with nor-BNI to block KOR activity reduced the alcohol intake of the SI rats to levels close to those of the GH ones; the GH rats' alcohol intake was not further reduced with nor-BNI. The SI rats had lower base levels of dopamine but released more in response to stimuli. Taken together, these results suggest that social isolation enhances KOR signalling in the rat brains, leading to dopamine depletion and thus to an enhanced preference for the addictive substance, ethanol.

These results further suggest that social isolation in these adolescent rats therefore leads to a pattern in which the base concentration of dopamine is lower than normal but an unusually high concentration is released following electrical stimulation. This pattern was confirmed in the rats in which cannulas were used to monitor dopamine concentration over time. Specifically, dopamine uptake increased in the striatum of the SI animals, leading to decreased levels of circulating dopamine. Increased dopamine uptake has also been seen following chronic alcohol exposure and other types of chronic stress.

These results all support the basic hypothesis that exposure to chronic stress in early life – social isolation in this adolescent rat model – leads to a reduction in base levels of dopamine combined with an increased response of the dopamine system to stimuli arising through kappa opioid receptor activation. Thus, the KOR system appears to be hyper-reactive in the stressed animals. Blocking KOR activation with nor-BNI increased base dopamine and decreased alcohol intake in the isolated rats. The fact that these rats also behaved in an 'anxious' manner suggested that elevated anxiety levels might be driving the increase in alcohol intake.

Some researchers have suggested that compounds that block KOR signalling, such as nor-BNI, might alleviate the stress-induced need for alcohol and thus have a therapeutic role in treating alcoholism. These results tend to back up this hypothesis. Reducing early life stress, however, might also reduce the levels of alcohol and drug dependence and thus the need for therapeutic intervention at all.

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