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Editorial

Microdialysis in vivo, in a form that would be recognised today, was first developed at the Karolinska Institute (Zetterstrom et al., 1982). This group started by harvesting adenosine (and other purine nucleosides) in a loop of dialysis tubing implanted in the rat dorsal striatum. In their paper, the authors concentrate on the possibility that adenosine (and its manipulation by drugs) could have an important influence on brain function. In a triumph of understatement, their final sentence concedes that "Our results show that implantable dialysis tube may be used to advantage in such studies".

Over the next four years, landmark studies followed in quick succession. Hamberger's group monitored changes in extracellular amino acids in the rabbit hippocampus following a neurotoxic insult (Lehmann et al., 1983) and there was widespread interest in efflux of amino acids after a bout of cerebral ischaemia (e.g., Benveniste et al., 1984). The construction of side-by-side (Blakely et al., 1984) and concentric cannulae (Hernandez et al., 1986) reduced the damage caused by implantation of the probes, which by then were being used to monitor small peptides, such as substance P (Lindefors et al., 1986). A handful of studies used microdialysis to monitor extracellular monoamines, but this was not its major application. Indeed, the first microdialysis investigation of 6-OHDA-lesioned rats was more interested in the effects of the lesion on GABA (Segovia et al., 1986). Within the next couple of years, microdialysis was even being used to study peptides and amino acid efflux in rabbit and rat spinal cord (Pilowsky et al., 1987; Skilling et al., 1988).

These early studies are all the more remarkable because, with the benefit of hindsight, they tackled what are now regarded as the most difficult targets for microdialysis. The spinal cord is still not an option for the faint-hearted and authors of several papers in this Special Issue urge caution when interpreting changes in extracellular peptides and amino acids. In the opening paper, Carsten Wojtak and colleagues deal with precisely this point and highlight key factors and variables to bear in mind when using microdialysis to study peptides. In so doing, they review microdialysis of the hypothalamo-neurohypophyseal system and the influence of oxytocin and vasopressin on behaviour.

The next paper moves on to microdialysis of amino acids (glutamate and GABA) and discusses two interrelated gremlins. One is the apparent mismatch in the duration of transmitter release (msec) and sample collection (about four log-units longer than that). The other is the source of the amino acids harvested by the probe. As van der Zeyden and colleagues explain, the sampling time-frame (which is constrained by the sensitivity of the system for detecting solutes in the dialysate) is far too long to give any useful information about phasic changes in impulse-evoked (synaptic) release of amino acids. Indeed, this limitation has driven the development of microsensors that can follow rapid changes in extracellular amino acids: this paper describes the current status of this technology. However, it should be borne in mind that it is long-lasting changes in extracellular amino acids that are likely to be of greatest relevance to long-lasting changes in behavior. Since it is the extrasynaptic pool of glutamate, rather than synaptic release, that shows such sustained changes, microdialysis is probably sampling the correct (non-neuronal) pool of transmitter. As a consequence, this technique has an important role to play in characterizing the role of glial cells in regulation of mood and behavior. Ironically, the authors tentatively conclude that microsensors may well be sampling neuronally-derived glutamate and so would be used alongside microdialysis, rather than replacing it. Continuing this emphasis on the evolution of technology, Borjigon and Liu's paper explains how microdialysis can be used for prolonged sampling periods (weeks), rather than the usual hours/days. The authors illustrate the advantages to be gleaned from this approach in their studies of melatonin and entrainment of circadian rhythms.

In the next paper, the theme changes to using microdialysis to investigate neuronal networks. By way of example, Fadel and Frederick-Duus review evidence that orexin A regulates acetylcholine and glutamate release in the cortex and basal forebrain, respectively. The authors describe these orexin-releasing neurons as "physiological integrators" and discuss their role in linking the hypothalamus with forebrain systems that govern arousal, cognition and other behaviors essential for homeostasis. Reciprocal influences between the hypothalamus and another forebrain region, the hippocampus, are described by Linthorst and Reul. These authors have used microdialysis to study changes in serotonin and GABA efflux in this region and, by combining this and other techniques (e.g., telemetry and measures of plasma corticosterone), have gathered evidence that the neurochemical response to stress is stimulus-specific. Moreover, they argue that disruption of coupling between the hypothalamic/pituitary/adrenal axis and the hippocampus could underlie stress-related psychiatric disorders. Some of this work was carried out on mutant mice, an approach that was first reported in the late 1980s (Rollema et al., 1989). Obviously, spatial resolution is a limiting factor in this species and only studies of larger brain regions are feasible. Nevertheless, the use of microdialysis to profile the phenotype of mice with targeted gene mutation(s) is becoming more widespread, with over 600 publications in this field since 2007. It is telling that only 23 of these derive from the UK.

Staying with the hippocampus, Alain Gardier and his team describe their research of Brain-Derived Neuroptrophic Factor (BDNF) and its putative role in antidepression. Again, microdialysis of mutant mice (in this case tropomysin kinase B heterozygotes), has made a major contribution to this story. This paper also describes the 'no-net flux' method, for estimating the concentration of extracellular transmitter, and the functional significance of the 'extraction fraction', both of which help to interpret changes in the amount of transmitter that reaches the microdialysis probe. In the next paper, Heal and colleagues review another example of using microdialysis to profile phenotype: the Spontaneously Hypertensive rat. They offer a detailed description of the behavioural and neurochemical status of this inbred strain and appraise its validity as a rodent model of ADHD.

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The next three papers deal with using microdialysis to study the actions of psychotropic agents. The first reviews the pharmacology of methylenedioxymethamphetamine (MDMA). Here, Gudelsky and Yamamoto discuss the effects of this psychostimulant on monoamine and acetylcholine efflux in key brain areas (dorsal and ventral striatum, prefrontal cortex and hippocampus) and explain how its interaction with stress could affect its toxicity. These authors also note that MDMA alters brain metabolism, a topic which is covered in depth in a later paper. Baumann and colleagues extend this topic by describing their research of the neurotransmitter(s) and brain region(s) that could be responsible for the changes in behavior and mood induced by MDMA. The third covers the use of microdialysis in studies of dopaminergic transmission and its regulation of behavior. McQuade and colleagues review the pharmacology of Li^+, including their own microdialysis investigation of Li^+-induced changes in extracellular dopaminergic transmission as a substrate for its mood-stabilizing effects.

Continuing this dopamine trail, is a cluster of reviews that deal with different aspects of corticostriatal circuits in the brain. First, del Arco and Mora describe the complex interactions between dopaminergic and glutamatergic neurones and their combined influence on cholinergic transmission in the nucleus accumbens. This paper includes a topical warning that animals' (enriched) environment can affect their brain neurochemistry as well as their behavior. Then, Phillips and colleagues focus on the role of dopamine in reward and satiety and review interactions with the amygdala and medial prefrontal cortex that could govern these processes. These authors conclude that dopaminergic transmission encodes the motivational value of external signals and triggers behaviors that ensure a reward will be secured. Dalley and colleagues are interested in the neurochemical basis of impulsivity. Here, they explain how to combine microdialysis with a complex behavioural task (5-Choice Serial Reaction Time task) in order to study the role of acetylcholine, noradrenaline and dopamine in sustained attention and impulsivity. Next, Torregrossa and Kalivas review the role of corticostrial dopaminergic transmission in reward and impulsivity, in the context of drug addiction and relapse, and broaden the evidence to include peptides and amino acids, as well as acetylcholine and dopamine.

The last two papers are shining examples of ‘what goes around comes around’. First, we return to microdialysis of glutamate but, this time, there is a metabolomic angle. Uehara and colleagues review the link between extracellular glutamate and lactate and the evidence that glial cells extrude lactate as a metabolic substrate for neurones. Finally, McAdoo and Wu return to the spinal cord and review recent research of the CNS response to traumatic insult. They end their paper on the optimistic note that microdialysis will have a vital role to play in research of trophic/growth factors and the viability of stem of cells and neuronal grafts, all of which are being explored as future treatments for spinal cord injury and neurodegenerative disorders.

All that remains is for me to thank all the authors for their contributions to this Special Issue. Microdialysers are evidently conscientious and reliable folk because everyone who volunteered a paper produced a manuscript within my deadline. Some contributors acted as referees as well as authors and so deserve a special tribute (you know who you are!) — as do referees who are not microdialysers but were willing to comment on the other aspects of these papers, nonetheless. I also thank Dai Stephens for suggesting this topic and for giving me the chance to wave the microdialysis flag. Finally, a special thank you goes to Eve Naughton, at Elsevier, who kept a watchful eye on me and all the manuscripts and ensured that none was left to flounder. It has been a privilege to work with such a professional and committed team.

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