Restoring cerebral circulation and function postmortem: A multidimensional analysis

While many types of mammalian cells have been shown to remain viable after the cessation of blood flow and/or deprivation of oxygen, neurons have not been known to recover well after substantial insult, thus making the brain susceptible to irreversible damage. However, recent studies have demonstrated that neuronal apoptosis and necrosis may be delayed for several hours if the brain is kept under certain conditions postmortem. Vrselja *et al*.[1] isolated the brain of a pig (*Sus scrofa domesticus*) 4-h postmortem and showed that with specific intervention, cerebral blood vessel perfusion and glial function could be restored and sustained, and neuroanatomical structure and neuronal vitality maintained. Employing a system of their own design called Brain*Ex* (B*Ex*), the carotid arteries were connected and perfused following isolation of the brain just superior (i.e., rostral) to the medulla oblongata. The perfusate was primarily composed of *Hemopure*, a bovine hemoglobin-based solution previously employed as a medium for tissue delivery of oxygen.[2] At 4-h postmortem, porcine brains were perfused for 6-h *ex vivo* using the B*Ex* device (i.e., for a total postmortem interval [PMI] of 10 h). The effects of B*Ex* perfusion on neural integrity and function were evaluated against three control brain groups: (1) a 1-h PMI, (2) a 10-h PMI, which had been left in crania at room temperature, and (3) B*Ex* perfusion using a control liquid.

To be sure, many of the reported results were indubitably important, if not "landmark." First, it was found that the B*Ex* system enabled successful circulation of the perfusate throughout the brain. Second, administration of nimodipine increased perfusion, thereby demonstrating that the B*Ex* system sustained cerebrovascular responsivity postmortem. Third, it was found that *Hemopure* perfusion using the B*Ex* system significantly reduced postmortem deterioration of both gray matter and white matter, with neuroanatomical (i.e., morphologic and histologic) integrity preserved in the hippocampus, neocortex, and cerebellum.

When compared to the 1-h PMI (and the other two control groups), hippocampi perfused with the B*Ex* system showed considerably less swelling and significantly preserved neural circuitry. As well, it was found that B*Ex* perfusion resulted in increased levels of cerebral interleukin (viz., a glial-derived immunomodulatory peptide in the brain), thereby suggesting that glia remained viable 4-h postmortem. Finally, perhaps of most significant media interest, perfusion using the B*Ex* system enabled spontaneous excitatory postsynaptic currents in hippocampal pyramidal neurons, thus possibly demonstrating postmortem neuronal viability.

These findings could and should foster further research on the viability of this system, and other technologies and techniques of cerebral perfusion that could be instrumental to developing improved interventions for neurological trauma and disorders. For example, such approaches could be developed and employed for retaining and/or restoring certain brain functions after traumatic brain injuries, stroke, and/or loss of network activity as a consequence of progressive insult of neurodegenerative diseases.

Of particular note is that the use of the B*Ex* system can reestablish, if not completely restore, cerebral blood flow and thereby mitigate loss of cerebral perfusion and the effects of anoxia even after a substantial PMI. This is of interest in light of our ongoing work examining the effects of acute and chronic metabolic stress on neural biochemistry, function, and integrity.[3] In almost every instance, the integrity or disruption of oxygen-dependent neuronal and/or glial metabolic pathways involves hormetic mechanisms and responses.[4,5]

Hormesis is a highly conserved and generally adaptive process that is manifested as a biphasic dose response, with specific quantitative features (i.e., 30%–60% stimulatory amplitude, typically 5–20-fold stimulatory range).[6,7] It occurs as a consequence of either direct stimulation or within pre- or postconditioning contexts in a variety of species and in several organ systems, including the brain (i.e., in both neuronal and glial cell types).[8] Hormetic agents upregulate a number of adaptive mechanisms that can be activated within hours to days following hormetic induction to protect neural cells against numerous types of insult, including anoxia and oxidative stress (which can subsequently induce apoptosis and/or necrosis).[9] We believe that further understanding these mechanisms – and their dosimetric properties – may be important to developing improved methods of postinsult (and/or postmortem) cerebral protection, perfusion, and possible sustenance or recovery of function.[10]

However, keeping in mind the maxim that "small doses can exert a profound effect," it is equally important to address the media – and some academic – handling of, and reactions to Vrselja *et al*.'s work. On one hand, the media response(s) can be seen as viable promotion, if not advocacy for "brave new advances" in the brain sciences.[11] Yet, the nature of the findings led to ampliative claims and debates about the ethical improbity of "reviving brain cells"[12] and bringing "a dead pig brain back to life outside its corpse."[13] Importantly, Vrselja *et al*. explicitly stated that their results do not demonstrate or prove the recovery of brain functions after 4-h PMI. Hence, reactive assertions of both fantastical scientific interventions and abrogation of ethical probity were exaggerated at least, and wholly misrepresentational, at worst.

Both science fiction tales and nonfictional speculations about the (outer) limits of restorative biomedicine often center upon goals and/or unrealistic hopes and claims of extending the life – or "consciousness – span;" sometimes with view *saecula saeculorum* (viz., for ever and ever).[14] However, any ethical analyses of emergent capabilities in science and technology must be based on, proceed from, and adhere to the fact(s). While it may be tempting – and not without some merit – to extrapolate future possibilities and potentialities, and/or allude to science fictional accounts, both should be explicitly stated as such. The former, as based on realistic models that forecast trajectories of scientific and technological developments, and their uses in practices in varied socioeconomic, cultural, and political environments.[15] The latter as means to communicate what might be possible or potentially viable, in explicitly defined scenarios of near – or far – term futures, given certain directions and valences of what is currently probable (or at least imaginable).[16] Nevertheless, we have argued that here too, perhaps even more than ever, there is an ethical importance (if not responsibility) to adhere to fact, while entertaining creative license, so as to create depictions of "what might be" given distinct manifestations of science, and effects and manifestations of its use (or misuse) given certain pushing and pulling forces in the social milieu.[16]

It is likely that the efforts of Vrselja *et al*. will prompt future research using B*Ex* and related and/or derived technologies. Although there are existing regulations that govern research and its clinical applications, there is an increasing concern that not every nation state or culture is willing to comply with those ethical guidelines.[17] Thus, what may need to be "resuscitated" and "kept alive" are genuine efforts to sustain more accurate media (and academic) representation of science and technology and methods and opportunities for cosmopolitan ethical discourse and address of the real issues, problems, and solutions that such science fosters on the global stage.

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