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COMMENTARY

Neonates have a spinal alpha receptor too, as do adults

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Reading the paper by Walker and Fitzgerald (2007) started a train of thoughts in my mind.

When examined, neonates show most, if not all, of the complexities found in the adult pain phenotype resulting from tissue injury and inflammation. As indicated in a long series of papers by Fitzgerald's group, tissue injury and inflammation lead in the neonate, as they do in the adult, to hyperalgesia and allodynia. This emphasizes that the functional properties of pain processing occur in the newborn rat (and, by extension, in the human neonate). While the neonate limbic forebrain may not express the full panoply of higher order function, the organized autonomic (blood pressure) and somatic behaviour (crying, generalized motor reactions) indicate that reactions to tissue injury are already well developed. In the current environment, the above comments seem strangely naïve until one considers that there was a time in the 1960s when people argued that the newborn, given their neural development, were not able to respond to painful stimuli. The perception that drugs were not necessary to block pain, extended even to the point that major surgery to correct cardiac defects was undertaken with nitrous oxide and muscle relaxants (the 'Liverpool technique'). Landmark work by Anand *et al.* (1987) demonstrated that survival of such babies was remarkably increased by the use of appropriate analgesics. Such observations clearly define neonates as being eminently capable of processing nociceptive stimulation, as though they were adult.

Although it seems self-evident, the organized pain behaviour in an adult evoked by a peripheral stimulus depends upon the content of the spinofugal message. For example, these behavioural events are driven by information contained in the output of the spinal dorsal horn. Accordingly, factors increasing the transmitted spinofugal content will lead to enhanced pain behaviour in the neonate. Thus facilitated spinal states induced by peripheral injury and inflammation lead to an exaggerated discharge in dorsal horn neurons involved with nociceptive transmission and we see corresponding increases in allied pain behaviour otherwise evoked by a given stimulus, as it happens in adults.

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Previous studies in neonatal rats have shown that epidural opiates (Marsh *et al.*, 1999a, b) and the present studies (Walker and Fitzgerald, 2007) show that epidural α_2-agonists, such as dexmedetomidine, can alter spinal outflow and attenuate supraspinally organized nociceptive processing, as in the adult. An interesting aspect of the present longitudinal study is the demonstration that the P3 (3-day-old) animals showed a 10-fold leftward shift in the dose–response curve for dexmedetomidine, compared to P10 and P21 rats. This enhanced responsiveness appears not be unique to α_2-agonists as similar results have been reported for epidural morphine (Marsh *et al.*, 1999a, b). It is, however, not a general property of the system. Thus, the concentrations of volatile anaesthetic necessary to block spontaneous movement are highest in P2 animals and lowest in P30 animals (Orliaguet *et al.*, 2001). The mechanisms underlying the differential potency across agents are not certain, but results such as these alert us that age is a major component of the final drug response and that the variation may be greatest during the very early postnatal days of development.

The present studies also raise the obvious question of the clinical applicability of spinally delivered α_2-agonists. Drugs such as opiates and α_2-agonists have good systemic bioavailability, so what is the theoretical merit in the spinal approach? Spinal delivery of analgesic drugs is predicated (i) on an analgesic effect of the spinal drug target and (ii) an absence of deleterious physiological consequences of the spinal drug target. The hope is that such a delivery will enhance the therapeutic (safety) ratio. Intrathecal α_2-agonists produce hypotension and bradycardia and this effect is likely to be mediated by an action upon thoraco-lumbar preganglionic neurons (Eisenach and Tong, 1991), although these studies suggest the heart rate change may not be mediated spinally. This profile looks good. However, in human neonates, clonidine by the spinal route, typically in combination with local anaesthetics produces prolonged anaesthesia with minimal effects upon blood pressure (Rochette *et al.,* 2004). However, it should be noted that α_2-agonists are known to produce sedation and there are several case reports of apnoea in neonates who received spinal clonidine (Breschan *et al.*, 1999; Bouchut *et al.,* 2001; Fellmann *et al.*, 2002). In the present study, the newborn rats were artificially ventilated, obscuring possible respiratory effects.

A final consideration relates to the translation into human patients of preclinical results. There is little doubt that the present studies show a potent spinal effect of dexmedetomidine in the newborn rat, a finding that parallels the reports on clonidine in human neonates. Nevertheless, great caution is needed in applying these results to the treatment of human babies. The spinal (epidural or intrathecal) delivery of novel agents must, in general, be approached with great trepidation (Eisenach *et al.*, 1998; Eisenach and Yaksh, 2002). Although we have a great deal of experience using clonidine and dexmedetomidine systemically, the administration of these agents into the spinal canal is done with only limited information as to potential toxicity in adults and almost none in neonates and others. Importantly, there is potential toxicity associated with spinal drugs about which we know a great deal, such as local anesthetics (Hampl *et al.*, 1999). With agents not previously given into the spinal space, is there any report that we can point to arguing cogently that toxicity is not an issue? We have reasonably good preclinical models for assessing safety in adults (Yaksh *et al.*, 1999) and experience in how such development should be done (Yaksh and Allen, 2004); however, there has been little effort to develop models for assessing toxicity in neonates, which is undoubtedly needed before the procedure is adopted for clinical use.

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