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ORIGINAL ARTICLE

The mediating role of cutaneous sensitivity within neonatal psychoneuroimmunology

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Abstract

Preliminary results of this study have been presented at the ICIS Conferences held in Atlanta, 1998; a Summary of results has been quoted in Adamson-Macedo (1997; 1998).

OBJECTIVES: Despite knowledge that preterm infants in intensive care are in distress and need to be provided with appropriate intervention, studies with ventilated babies are still rare particularly during their first weeks of life. This study tested the hypothesis that cutaneous stimulation in the form of TAC-TIC therapy, involving only light stroking and NOT massage or kinesthetic massage, has a mediating role in eliciting beneficial psychoneuroimmunological coactions in the ventilated preterm during the first week of post-natal life. METHODS: A repeated measure, counterbalanced design, was used to collect data twice daily for three consecutive days. This intervention was compared with a control condition consisting of a period of spontaneous activity during which the same infants lay alone with no intervention taking place. For the first time, monitoring facilities were made available for immunological, physiological and behavioral responses to be assessed simultaneously before and after intervention and before and after spontaneous activities. RESULTS: A one tailed t-test indicated that the cutaneous intervention resulted in significantly more episodes of beneficial coactions than matched sessions of spontaneous activity. CONCLUSION: It is suggested that the sensory nerves endings in the skin receive the stimulation from the stroking actions; consequently impulses are being sent via afferent nerve fibers to the limbic system where the sensation is interpreted, by 68% of the neonates, as being comforting or not distressing.

Introduction

Relationships between the behavioral, neuroendocrine and immune functions, the field which Solomon and Moos [1] have called psychoneuroimmunology, have attracted increasing interest during the last two decades. Ader [2] noted that, despite the self-regulatory capability of the immune system, data appeared to demonstrate the additional role of the neuroendocrine system in the regulation of immune function. In the light of such findings current research tends toward examination of the nervous and endocrine pathways linking the central nervous and immune systems. Ader [2] further suggested that those behavioral interventions which are designed to assist with coping strategies for stress may influence immune function, and thus the disease process.

Black [3] reviewed studies of psychoneuroimmunology which indicated that mutual interactions existed between the immune system and the central nervous system (CNS). Moreover stressful situations appeared likely to reduce activity of the immune system, thereby increasing susceptibility to disease with much neural influence exerted through Hypothalamic-Pituitary-Adrenal (HPA) relationships. The evidence that emotional factors are related to immune function has been accumulating for some years; nevertheless studies investigating the psychoneuroimmunological (PNI) relationships in children is almost non-existent [4], particularly with distressed babies born preterm and receiving oxygen therapy.

Distressed ventilated babies are prone to infections, and those born at less than 32 weeks of gestation age tend to have immunoglobulin deficiency [5]. Secretory Immunoglobulin A (sIgA) is the most abundantly produced immunoglobulin and can be detected in tears, saliva, respiratory and gastrointestinal tract mucosal secretions; it protects epithelial surfaces which are exposed to external environmental influences, in particular those of the upper respiratory tract [6] and is often used as an indirect marker of mucosal immunity [7].

Although it is well acknowledged that preterm infants in intensive care are in distress, and consequently require appropriate intervention, studies with ventilated babies are still rare particularly during their first weeks of life. Some of the proposed interventions are non-pharmacological and involve sensory (tactile or tactile-kinesthetic) stimulation. A study carried out in 1993 [8], for example, recruited eleven preterms with a postnatal age ranging from 4 to 132 days and with only six infants receiving supplemental oxygen. These investigators reported that massaging preterm infants decreased concentration of cortisol but not of catecholamine. Another study [9] recruited preterms with an average hospital stay prior to the beginning of the study of 26 days; the authors did not state the postnatal range of these babies but did report that transcutaneous levels of oxygen tension ($TcPO_2$) during tactile-kinesthetic massage were lower but remained clinically safe. A more recent study [10] also did not focus solely on the first weeks of life; in this case, thirteen of sixteen preterms were mechanically ventilated, and the authors investigated their recovery time from blood sampling as a function of being touched, and found that compared with control (without touch) babies those who were touched had faster behavioral and physiological (heart rate) recovery.

Other studies [11] investigated the effects of early parental touch on preterms' heart rates and arterial oxygen saturation levels during the first two weeks of postnatal life, and found that heart rates were higher in 43% and lower on 17% of the visits; mean O_2 saturation levels were significantly lower during 45% and higher on 19% of the visits. Our own studies [12] have also shown a decrease in transcutaneous levels of oxygen tension ($TcPO_2$) during parental touch, while maintaining clinical safety. These results could be indicating that distress of babies has not been alleviated.

The first week of life of the ventilated preterm neonate can be very stressful and studies focusing only on this period are rare. With this in view, we [12, 13, 14] recruited ventilated preterms which were between 2 and 8 days of their postnatal life and measured transcutaneous levels of oxygen tension ($TcPO_2$). The studies reported that $TcPO_2$ did not significantly decrease or increase during and after cutaneous stimulation via stroking only (TAC-TIC therapy), a result which minimally indicates that the intervention did not increase distress. However, these studies correlated with the majority of published reports available to the authors, but investigated the mediating role of stimulation in only one system of the babies (*i.e.* the physiological system) as an indicator of distress; clearly such results require closer scrutiny and further investigation.

In order to investigate the psychoneuroimmunologic relationships (PNI) in ventilated preterms, firstly it was necessary to know if IgA could be detected very early after birth. Our recent studies [15, 16] showed that IgA could be detected during the first days after the birth of ventilated preterms which were receiving intravenous total parenteral nutrition. Neonatal Psychoneuroimmunology was defined [17] as the scientific study of the complex horizontal and vertical coactions of the phenomena of mental life, behavior, neural, endocrine and

immune processes of the preterm neonate and their consequential role in the facilitation and maintenance of health and treatment of disease. As a contribution to the development of this emergent discipline, we needed also to observe the behaviors of those babies during the cutaneous stimulation and record them simultaneously with both their heart rate and saliva secretion of Immunoglobulin (sIgA).

This paper is a full report of the first study which investigates the mediating role of systematic cutaneous stimulation in eliciting coactions [18, 19] between the physiological (heart rate), psychological (behaviors indicating distress or comfort) and the secretory immunological system (sIgA) of distressed ventilated low and extremely-low birthweight (L/ELBW) preterm neonates. This study tested the hypothesis that cutaneous stimulation, in the form of TAC-TIC therapy involving only light stroking and NOT massage or kinesthetic massage, has a mediating role in eliciting beneficial psychoneuroimmunological coactions in the ventilated preterm during the first week of post-natal life. Lack of significantly sharp fall or decrease in both heart rate and $TcP0_2$, and greater number of behaviors which indicate conditions of comfort rather than distress, further imply that the baby's various systems are in equilibrium [17, 20].

Method

Thirty-five high-risk premature neonates (17 male, 18 female) were recruited from four neonatal intensive-care units in UK general hospitals, in the West Midlands and Shropshire, with parental written consent and approvals from each relevant Institutional Board of Ethics Committee; details of sample are given below. Recruitment adhered to the following criteria:

1. Birthweight of less than 1.5 kgs.
2. Gestational age of less than 32 weeks.
3. Mechanical ventilation required for a minimum of three days which could include the study period.
4. Less than seven days post-natal age.
5. Absence of congenital malformation.

There were 21 spontaneous vaginal deliveries (SVD), 11 emergency (EMCS) and 3 elective (ELCS) cesarean sections. Thirty-three (94.4%) of the participants had received surfactant therapy after delivery to improve lung maturity, and 23 (65.7%) were receiving morphine as a sedative agent at the time of the study. Thirty-one (88.6%) of the infants were diagnosed as suffering from respiratory distress syndrome, and thirty-two (91.4%) had jaundice. Nutrition was primarily via intravenous total parenteral nutrition (TPN), and none of the babies were receiving oral nutrition. There were 8 confirmed cases of sepsis, 18 cases of presumed sepsis and 9 infants had no indication of infection; there were two incidences of necrotizing enterocolitis and three suspected cases.

Design

A repeated measure, counterbalanced, within-subject design was adopted, with the heterogeneous population of neonates acting as their own controls. Data collection before and after both a period of spontaneous activity (control condition) and a period of cutaneous stimulation (experimental condition) thus ensued, approximately at three-minute intervals; data were collected twice daily, at the same time morning and afternoon, on three successive days.

Intervention and control

The intervention used in this study was version-3 [15] of Touching and Caressing - Tender in Caring (TAC-TIC) therapy [21] and involves cutaneous stimulation in the form of *gentle/light* systematic and rhythmic cefalocaudal stroking.

Literature searches have failed to identify research which could indicate that the preterm neonate lying alone may be experiencing stress or pain; the literature has primarily focused on responses by infants to specific painful procedures, *e.g.*, heel pricks [22, 23]. In this study a control condition was introduced, referred to as spontaneous activity, and covers those periods of time when the neonate is lying alone without any intervention.

Procedures

In order to obtain the Immunological, Physiological, and Neurobehavioral (Psychological) data, different but simultaneously-taken measurements are required. A system for this which uses three orthogonal axes has been described [17, 24] and is known as 'the Equilibrium Model,' and was used here for recording and displaying the data:

1. Immunologic data (IM axis).

Secretory Immunoglobulin A (sIgA) is widely used as an index of stress in psychoneuroimmunological research, and was chosen as the IM indicator. Unstimulated saliva samples were obtained from just inside the buccal cavity of the participants before and after each control and experimental condition. Samples were obtained when the infant had been

lying alone for forty-five minutes to one hour thus minimizing, if not avoiding contamination which could arise from the consequences of any stressful procedures which might have preceded the sampling. Care was taken to avoid trauma to the delicate mucosa of the mouth, for reasons of both discomfort and avoiding contamination with blood.

The samples were obtained using sterile equipment consisting of a small flexible plastic filament attached to a 5 ml syringe; samples were stored at -20°C until analyzed. An enzyme-linked immunosorbant assay, ELISA method, was used to ascertain sIgA concentrations (Sigma Chemicals, Poole, Dorset, U.K.). All standards and samples were duplicated, and data were expressed in micro-g/ml units.

2. Physiological data (P axis).

Ohmeda cotside heart rate monitors were already in place and were used in the first part of the study in conjunction with a minute-by-minute score sheet; heart rate was recorded in the first three seconds of each minute both before and after either intervention or control condition. Independent-observer reliability for this method was 75%. Data from nine infants were also analyzed in greater depth using the VITAPORT II physiological data acquisition module and software run on a Macintosh powerbook; data were presented in units of beats per minute (bpm).

3. Behavioral data (NB axis).

Video recordings were made of each session, great care being taken in both labelling and storing; analysis was made using the Observer software (Noldus, Netherlands) on an Apricot PC. This program ran in three-minute time segments for analysis before, during and after episodes for both intervention and control conditions. Computer keys were coded for each of the behaviors identified as indicating either pain or comfort [15]. For the study described here, only the data from 'before' and 'after' time segments were analyzed; data were presented as frequency of particular observed behaviors.

Results

Of the 35 neonates originally recruited, data for 25 (71%) participants finally became available, and corresponded with the cases where P, IM, and NB readings had all been collected simultaneously; incomplete sets of all-three readings had to be abandoned as inadequate for analysis. Missing IM data were attributable to failure to obtain sIgA in cases where insufficient saliva was obtained to run the assay; video data for NB determination was not available from some infants, either because camera faults had occurred or there was too much hospital equipment around the incubator to permit the camera to be used safely.

Differences were calculated between measurements obtained before and after therapy for each infant, and before and after control condition or spontaneous activity. Values around zero indicated that there had been no change and are referred to as stability (=); values above or below zero indicated enhancement (+) or decrease (-) in the observed measure, respectively.

Statistical analysis of data

From the results and assessments of the data, as derived above and represented on a three axis display, a statistical analysis was made. Scores were assigned to each infant, as follows:

-2 = Simultaneous decreases in three axes, indicating 'desequilibrium'
-1 = Simultaneous decreases in two axes, as above
0 = Lack of integration
1 = Simultaneous stability in two axes, indicating 'equilibrium'
2 = Simultaneous enhancement of two axes, as immediately above
3 = Simultaneous enhancement of three axes, as immediately above

The frequency distribution of each score can be seen in Fig. 1. A one tailed related t-test indicated that experimental condition had scores which were significantly higher than matched sessions of spontaneous activity ($df = 24$, $t = -1.84$, $p < 0.04$), indicating more positive responses. Overall the results indicated that TAC-TIC resulted in stability (=) or enhancement (+) of the IM, P and NB axes for 68% of the neonates.

Discussion

This study investigated the mediating role of cutaneous stimulation in the form of TAC-TIC therapy in order to elicit beneficial psychoneuroimmunological coactions in the ventilated preterm, and consequently to promote equilibrium. In deriving experimental data, mean differences between 'before' and 'after' sessions of spontaneous activity and the intervention were calculated for each individual participant; the hypothesis was supported by results which showed significantly more positive and stable reponses for intervention compared to spontaneous activity. This outcome was made possible by initiating simultaneous collection of the corresponding sets

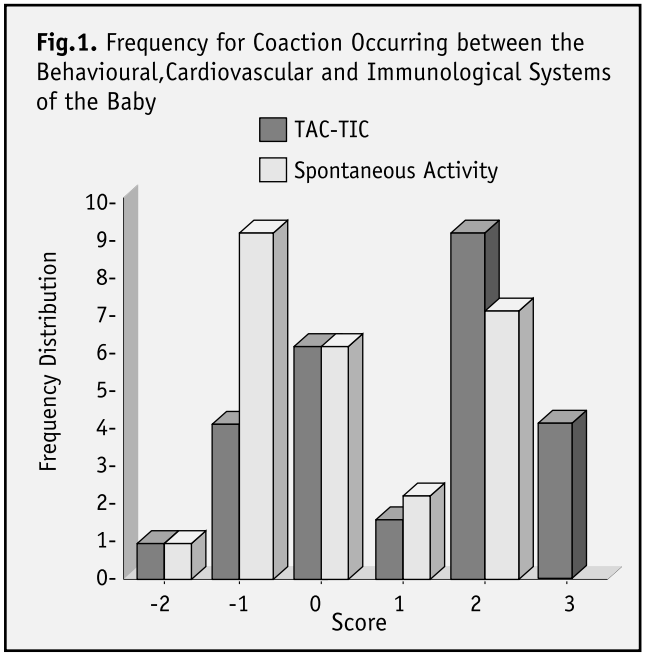


Fig. 1. Frequency Histogram for Equilibrium Model.

of data, as applied to very and extremely-low birthweight (V/ELBW) ventilated preterms within their first week of life after birth.

In order to move towards an explanation of the results of this study, a representation of the interrelated elements is given in Fig. 2. The key role of the hypothalamus in physiological homeostasis and in psychoneuroimmunological theory is acknowledged by the authors. The hypothalamus is the brain region most notably involved in the direct regulation of the internal environment; it plays a role in producing and controlling a number of hormones, is a major autonomic nervous system co-ordinating center, and plays a role in emotional and behavioral patterns through linkages to the limbic system. It is suggested here that the sensory nerve endings in the skin receive stimulation from the stroking actions in TAC-TIC therapy, impulses are consequently sent via afferent nerve fibers to the limbic system where the sensation is interpreted as being comforting or not distressing. This information is then relayed to the hypothalamus via the extensive neural network which exists between the two brain regions; the reactions which are produced by the interpretation received at the hypothalamus could not only account for some of the findings of the experiments recounted in this study, but also those reported in other studies [20, 24].

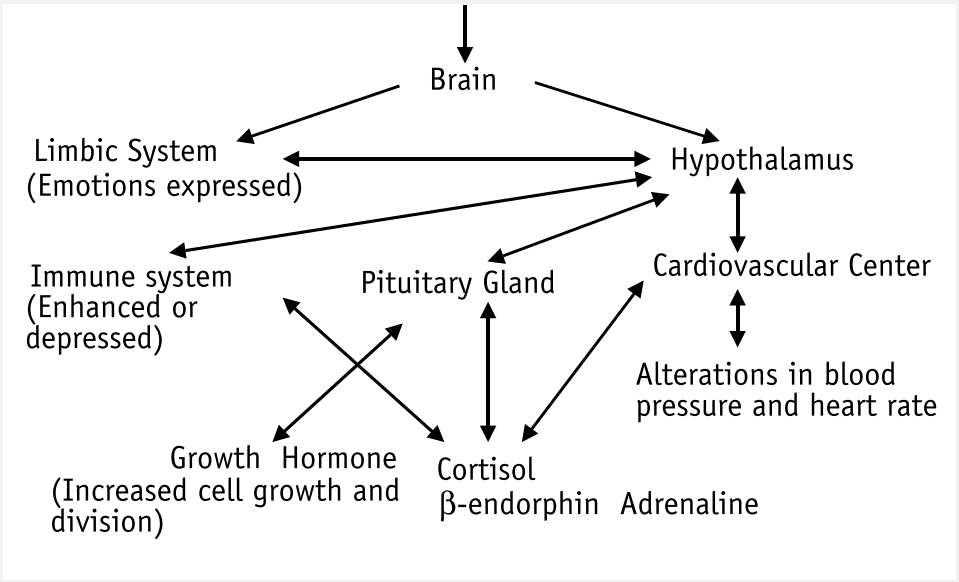
It thus appears that the experiences of cutaneous stimulation, in this case via TAC-TIC therapy, are interpreted by the hypothalamus. By acting on the pituitary gland the hypothalamus can control the reduction of the secretion of stress hormones such as cortisol. Comparison with other studies are notoriously difficult because of different methods and particularly different interventions, but it is nevertheless noteworthy that reduction of cortisol levels after massage has been reported [8]. Reduction of stress hormones which are known to suppress immunity may result in the overall enhancement reported in this study. The hypothalamus also controls the secretion of growth hormone via the pituitary gland, and growth hormone may be involved in the observation of weight gain reported elsewhere [20, 25]. The cardiovascular centre is also under the regulation of the hypothalamus. If new experiences are interpreted as not being suggestive of pain or distress then the hypothalamus may act as a self regulator of cardiovascular responses, thus resulting in the stabilization of heart rate reported in our recent studies [15].

The use of individualized touch with preterm neonates was reported [10]; thirteen of sixteen were mechanically ventilated. These investigators hypothesized that individualized touch would reduce the recovery time of those babies from blood sampling procedure. The measures of recovery which were adopted were behavior, oxygen saturation and heart rate; significant differences were found in favor of individualized touch as compared with control (without touch) for both behavior recovery time and heart rate recovery time. These results could be interpreted as beneficial horizontal and vertical coactions taking place, thereby providing the opportunity for babies to exercise self-regulatory efficacy. It is thus suggested that the hypothalamus is the central self regulating mechanism through which cutaneous stimulation can have a mediating effect through the occurrence of vertical and horizontal coactions.

An attempt has been made to represent the dynamical interconnections of the coactions described here, in order to emphasize that it is the neonate that is the central self-regulator as distinct from being an integrator of his/her body system (Fig. 2). However, it should be noted that this is a hypothetical model and the elements suggested in Fig. 2 have not all been tested experimentally and involve assumptions which require further investigation.

To summarize, the hypothalamic mechanism is advanced as an underlying explanation of the occurrence of horizontal and vertical coactions. The important finding is that even when a cutaneous stimulation program, which is initially a novel experience, is introduced these tiny preterm neonates are capable of interpreting afferent stimuli and regulating themselves by their responses which show more comforting rather than distressing behaviors,

Fig. 2. Theoretical model of Hypothalamic self regulatory mechanism of tactile stimulation. TAC-TIC



(Hayes, 1996)

Fig. 2. Theoretical Model of Hypothalamic Self-Regulatory Mechanism of Tactile Stimulation.

and in maintaining their heart rate stable while simultaneously enhancing their secretory immune system by increasing the secretion of sIgA.

The tactile sense is the first to develop; tactile sensibility is present from 7.5 weeks and nearly coincides with the time when the fetus begins to acquire biological individuality or a 'biological ego,' this latter being a result of the immune system attaining the capacity to discriminate between self and non-self [7]. Our results, showing that the majority of the babies were in equilibrium between their behavioral, cardiovascular and immunologic systems through the mediation of cutaneous stimulation, lend support to the claim that the tactile sense should be the first to be nurtured in the ventilated preterms, particularly during their first week of postnatal life but always through appropriate type of stimuli.

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