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Neural and pulmonary aspects of the porcine stress syndrome

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Neural and pulmonary aspects of the porcine stress syndrome

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INTRODUCTION

The Porcine Stress Syndrome (PSS) has been extensively researched and yet the etiology remains unknown. PSS susceptible pigs have been shown to have abnormalities in muscle function (Kerr et al., 1975), structure (Gallant et al., 1979), metabolism (Lucke et al., 1976; Cheah and Cheah, 1981), serum creatine phosphokinase levels (Allen et al., 1970b; Christian, 1974; Hallberg et al., 1979; Ahern et al., 1980) and central nervous system catecholamines (Altrogge et al., 1980; Hallberg et al., 1983).

After initial stress for a PSS susceptible pig, a definite syndrome develops. Muscle tremor and blotchy cyanosis become obvious and the stressed pigs show dyspnea and shallow, labored, open-mouthed respiration. After 20-60 minutes of the onset of clinical signs, the pigs will become reluctant to move and collapse into lateral recumbency with legs in extensor rigidity. Physiologic changes such as increased heart and respiratory rates, body temperature, blood pCO_2 and decreased blood pH have been shown (Forrest et al., 1968; Topel et al., 1968).

The role of the central nervous system (CNS) is not clearly understood in the PSS. Some researchers have shown that epidural anesthesia will prevent malignant hyperthermia and others have shown that sympathetic nervous system catecholamine response is secondary to the main syndrome (Weiss

et al., 1974; Lucke et al., 1976; Gronert et al., 1977). Our laboratory has shown a definite deficiency in dopamine in the urine and caudate nuclei, which may point to some neural involvement in the cause of the PSS (Altrogge et al., 1980).

The following research was designed to answer two major questions about the stress-susceptible (SS) pig. Because of the close structural and functional relationships between the substantia nigra (SN) and the caudate nucleus (CN) and the decreased concentrations of dopamine found in the CN, the first part of this study was undertaken to determine catecholamine concentrations in the CN and SN of both rested and stressed pigs representing both SS and normal genetic backgrounds.

Secondly, because of the clinical signs associated with the PSS, especially respiratory difficulty, it was postulated that SS pigs may have some abnormalities in pulmonary function. The purpose of the second study was to investigate and compare pulmonary and hematologic function in SS and control pigs and to establish some normal pulmonary and hematologic values in the pig.

EXPLANATION OF FORMAT

This dissertation is written as two papers covering: 1) Neural Catecholamine Deficiency and 2) Pulmonary and Hematologic Function of the Stress-Susceptible Pig. Each paper is complete in itself. The first paper has been published in the American Journal of Veterinary Research. The second paper is undergoing the review process. Each paper includes a summary, introduction, materials and methods, and results and discussion. All the references have been combined into one large reference list at the end of the dissertation. A general literature review precedes the two papers and a summary concludes the dissertation.

LITERATURE REVIEW

Porcine Stress Syndrome (PSS)

The Porcine Stress Syndrome (PSS) has been the subject of extensive research for at least fifteen years. Topel et al. (1968) described a shock-like condition in pigs subjected to the extreme stress of marketing and fighting. Nearly 36% of the hog producers in the United States in 1971 had encountered the syndrome (Cassens et al., 1975). Also in 1971, Nelson et al. (1972) estimated that 30% of the purebred swine in the United States demonstrated some degree of the PSS. This syndrome was evident in many countries including the United Kingdom (Winstanley, 1979), South Africa (Heffron and Mitchell, 1975a,b; Mitchell and Heffron, 1975a) and Germany (Harrison et al., 1968). Many breeds of swine experience the PSS. These include Landrace (Eikelenboom and Sybesma, 1969; Berman and Kench, 1973), Yorkshire (Christian, 1972), Pietrain (Allen et al., 1970a) and Poland China (Harrison et al., 1968; Woolf et al., 1970; Jones et al., 1972) to name a few.

A need for research to determine the cause of the PSS became obvious due to the great financial loss to the swine industry. In 1972, it was estimated that between $230 and $320 million dollars were lost in the United States alone (Williams et al., 1978). The losses included deaths but also include production and quality losses because of pale, soft

and exudative pork that was often produced by these PSS pigs. These quality changes were linked to rapid post-mortem glycolysis and denaturation of myofibrillar and sarcoplasmic proteins (Bendall and Wismer-Pedersen, 1962; Cheah and Cheah, 1976).

These SS pigs develop a distinct set of clinical signs prior to death and biochemical changes that characterize the PSS. After a severe physical stress such as fighting, sorting or marketing, muscle tremors and blotchy cyanosis develop. Subsequently pigs begin to show labored open-mouth respiration. As the stress continues, the pig will refuse to move and will collapse within 20-60 minutes after the first signs are observed. These SS pigs will lay on their sides with all four legs extended rigidly parallel to the ground (Topel et al., 1968). Once the PSS pig has collapsed, death follows quickly with a very rapid onset of rigor mortis (Nelson, 1973). These clinical signs are accompanied by a distinct set of physiologic changes which include increased heart rate, initial rapid increase followed by a rapid decrease in respiratory rate, marked increase in body temperature, increase in blood pCO_2, a decrease in blood pH, elevated serum inorganic phosphate, potassium, chloride, magnesium, catecholamines (Brucker et al., 1973; Lister et al., 1977; Forrest et al., 1968; Topel et al., 1968; Sybesma and Eikelenboom, 1969; Nelson et al., 1972), creatine phosphokinase (CPK) (Christian, 1972; Addis et al., 1974), glutamic oxaloacetic

transaminase (SGOT) and lactate dehydrogenase (LDH) (Allen et al., 1970b; Schmidt et al., 1974). Cassens et al. (1975) theorized that the increase in the blood constituents, especially the tissue enzymes, was due to a decrease in the selective permeability of skeletal muscle membranes.

Malignant Hyperthermia (MH)

The PSS pig shows a definite set of clinical signs as discussed in the previous section. A syndrome very similar to the PSS is seen in people and is called the Malignant Hyperthermia Syndrome. Malignant Hyperthermia (MH) is a frequently fatal syndrome recognized in man. MH is characterized by progressive body temperature increases, severe generalized muscle spasms and a metabolic acidosis after exposure to certain types of anesthesia (Wilson et al., 1967; Stephen, 1967; Britt and Kalow, 1970a). Hall et al. (1966) demonstrated that a syndrome similar to MH was seen in the pig when exposed to halothane and suxamethonium anesthesia. Harrison et al. (1968) showed that pigs given halothane alone suffered from hyperthermia. Symptoms identical to the PSS including gross muscle rigidity, rapid rise in body temperature, tachycardia, hyperthermia, and blotchy cyanosis were noted by Campion and Topel (1975) in pigs suffering from porcine MH.

It was found through experimentation that MH can be triggered by succinylcholine, halothane, suxamethonium (Hall et al., 1966; Harrison et al., 1969) and physiologic stress

(Allen et al., 1970a; Sybesma and Eikelenboom, 1969) in the pig. Similarly in humans, MH can be triggered by methoxyflurane, diethyl ether, halothane, and muscle relaxants such as decamethonium, gallamine, or succinylcholine (Britt, 1972).

This syndrome in pigs has provided an excellent model for human research. Examination of pigs dying of MH revealed the development of pale, soft, and exudative (PSE) pork as is seen in the PSS susceptible pigs (Allen et al., 1970a; Nelson, 1973; Nelson et al., 1974; Cheah and Cheah, 1976). These findings suggest that porcine MH is only an anesthetic manifestation of a generalized genetic susceptibility to stress and it has similar symptoms and biochemical changes as described in the PSS and PSE in swine (Briskey, et al., 1966; Forrest et al., 1968; Nelson et al., 1974; Sybesma and Eikelenboom, 1978). The use of the pig as a model in MH does have some limitations. The MH susceptible pig seldom shows histologic changes in muscle after the development of MH. Swine can also develop the syndrome without exposure to anesthesia. Further, serum calcium increases in pigs during the syndrome while it decreases in humans (Gronert, 1980).

Other species may also show an uncontrolled hyperthermia during anesthesia. These include the dog (Short and Paddleford, 1973; Bagshaw et al., 1978), cat (DeJong et al., 1974), horse (Klein, 1975; Waldron-Mease, 1978), fallow deer (Pertz and Sundberg, 1978), chick (Korczyn et al., 1980) and rabbit

(Lefever and Rosenberg, 1980).

The porcine stress syndrome and malignant hyperthermia syndrome are distinctly different from the exertional myopathies such as azoturia or monday morning disease. These diseases of horses are characterized by muscle stiffness during exercise, hyperthermia, sweating, myoglobinuria, acidosis, and increased serum CPK and lactate dehydrogenase activity (Axt et al., 1968; Hammel and Raker, 1972; Dietmuller and Wels, 1972). These exertional diseases seem to be precipitated by rapid glycolysis and the production of lactate in poorly perfused muscle, which on post-mortem exam is very pale. These animals, however, generally have no genetic predisposition to stress.

Genetics and Predictive Tests

The identification of pigs susceptible to the PSS is the key to elimination of the problem as well as allowing the selection of stress-susceptible (SS) pigs to be used by researchers. Studies of the genetics for the syndrome have lead to a multitude of theories on its exact inheritance. These theories include one major recessive gene with complete penetrance (Eikelenboom et al., 1978; Smith and Bampton, 1977), high penetrance (Andresen, 1979), incomplete penetrance (Ollivier et al., 1975), or variable penetrance (Cheah and Cheah, 1979). Other researchers have suggested a single autosomal dominant gene with complete penetrance or two

different dominant genes (Hall et al., 1966; Allen et al., 1970b; Christian, 1972; Jones et al., 1972; Britt et al., 1978).

Regardless of the exact genetic inheritance, a range of phenotypes does exist for several physiologic parameters. These include five phenotypes to the response to halothane (Britt et al., 1978), four on the rate of post-mortem glycolysis (Wismer-Pedersen and Briskey, 1961), three on the basis of hormonal studies (Judge et al., 1966), three on the basis of heat production and muscle pH (Williams et al., 1978), three on the basis of serum CPK activity after stress (Allen et al., 1970b; Jones et al., 1972; Patterson and Allen, 1972), three on the combined basis of serum CPK, muscle pH and halothane sensitivity (Mitchell and Heffron, 1980), and three on the basis of the concentration of glutathione peroxidase in erythrocytes (Schanus et al., 1979).

The precise genetic origin of the PSS is still open for debate. This leaves reliable detection of these SS pigs a matter of extreme importance. The four major methods utilized include serological changes in muscle enzymes, hematological tests, halothane exposure, and muscle biopsies.

Serum CPK is a cytoplasmic enzyme which forms high energy bonds by transforming creatine to creatine phosphate. The vast majority of the CPK in the body is found in cardiac and skeletal muscle (Baskin and Deamer, 1970). Muscle damage, trauma or disease are readily indicated by an elevation

of serum CPK levels. Both halothane exposure and physical stress elevate serum CPK levels significantly in SS pigs (Allen et al., 1970b; Woolf et al., 1970; Jones et al., 1972; Nelson et al., 1974; Eikelenboom and Minkema, 1974; Mitchell and Heffron, 1975b; Hallberg et al., 1979; Watson et al., 1980). There is considerable variability in the serum CPK response to stress so the use of serum CPK levels alone can be misleading.

Hematologic changes such as platelet function, blood typing, and red blood cell fragility have been examined and found to be good predictors of stress. Rasmussen and Christian (1976) correlated A, O, Ha, and Hc blood types as possible predictors of stress susceptibility in pigs. Blood types Ha/a, A or O negative and H-/-, A or O positive were highly correlated with stress susceptibility. Conversely Ha/a, A or O positive blood types are excellent indicators of stress resistance. In an intermediate group (Ha/-, A or O positive or negative), both SS and stress resistant (SR) pigs were found. SS pigs and MH susceptible humans both show a tendency towards increased erythrocyte fragility when compared to SR pigs (Britt and Kalow, 1968; Cheah and Cheah, 1976; Schanus et al., 1979).

Finally, the use of muscle biopsy and halothane exposure have also been used for prediction of stress susceptibility. Exposure of SS pigs to halothane at weaning age will result in the SS pigs showing muscle rigidity and signs of the PSS

within 20-60 seconds after exposure. SR pigs will accept halothane anesthesia for three minutes without any adverse effects (Christian, 1972).

The use of muscle biopsies exposed to halothane or other triggering agents has been attempted in both man and pig (Kalow et al., 1977; Nelson et al., 1977; Okumura et al., 1979). The results have not been a reliable indicator of stress. Microscopic examination of muscle from susceptible animals has produced a variety of results, none of which could be used as a predictive index (Swatland and Cassens, 1972; Muir, 1970; Hall et al., 1980b).

Possible Etiologies of the PSS-MH Syndromes

It has been generally accepted that one possible location of the genetic defect is skeletal muscle. The combined muscles of the body are the only tissues with sufficient mass and ability to produce very large amounts of CPK and lactate (Mitchell and Heffron, 1982). A defect in muscle or one of its associated structures (the neuromuscular junction, t-tubules, sarcolemma, sarcoplasmic reticulum, contractile proteins and mitochondria) may form the basis for a possible cause of the PSS.

The neuromuscular junction, sarcolemma and t-tubule function as a trigger mechanism for muscle contraction. The neuromuscular junction of the PSS pig was shown to have a greater mean maximum end plate diameter, more terminal

sprouting and more double end plates in both red and white type muscle (Swatland and Cassens, 1972). Yet the use of 4-aminopyridine which increases acetylcholine (Ach) secretion, which in turn increases muscle contractility, does not cause PSS or MH (Hall et al., 1980a). It also has been shown that there are less neural inhibitors in SS pigs (Altrogge et al., 1980). Deficits of dopamine, which inhibit excitatory neurons, suggest that the overstimulation of the neuromuscular junctions during stress may be the trigger which begins the cascade in muscle creating the final effects seen in the PSS. The t-tubules, which have not been studied in great detail, are not considered to be a major initiator of the PSS (Okumura et al., 1980).

The sarcoplasmic reticulum is involved in the release of calcium during muscle contraction. Calcium release, if very rapid and sustained longer than normal, could cause both muscle contraction and a large generation of lactate through the normal chain of events in muscle contraction (Ebashi et al., 1967). The rapid onset of rigidity evidenced after a large calcium release is different from rigor mortis, which is caused by a depletion of ATP and a fall in muscle pH (Bate-Smith and Bendall, 1947). The theorized cause of the rapid rigidity may be a sustained high level of myoplasmic calcium. Since the majority (80%) of the muscle calcium is bound in the sarcoplasmic reticulum, this seems to implicate the sarcoplasmic reticulum as another possible site of a primary lesion

(Britt, 1979; Britt and Kalow, 1970b). Decreasing pH further enhances uncoupling of the sarcoplasmic ATPase (McIntosh et al., 1977; McIntosh and Berman, 1974). It was assumed that the decrease in pH caused sarcoplasmic reticular protein to denature which increased calcium efflux. The decrease in pH also stimulates glycolysis which results in cyclic and uncontrolled calcium release (Inesi et al., 1973).

The discussion in the previous paragraphs seem to indicate that the neuromuscular junction, t-tubule and sarcoplasmic reticulum are probably not the primary initiators of the PSS. This leads to a suggestion of possible involvement of the contractile protein in the etiology of the PSS. Fuchs (1975) and Fuchs et al. (1975) have shown that, at temperatures slightly greater than those occurring physiologically, there is a loss of calcium dependence for the occurrence of superprecipitation of natural actinomyosin. Since ATP levels of the cell will fall during MH and magnesium enters the plasma, it appears possible that muscle contraction during MH or the PSS can become independent of calcium as temperatures increase and as ATP and magnesium leave the muscle cells (Mitchell et al., 1980; Berman et al., 1970; Heffron and Mitchell, 1976; Nelson et al., 1974; Hall et al., 1975). Yet these changes involving hyperthermia, a fall of muscle ATP and magnesium leakage to the plasma will also occur later in the PSS-MH due to ATP usage and membrane damage due to hyperthermia and acidosis. This leaves the contractile proteins

secondary to some initiating factor.

The last cellular structures to examine are the mitochondria. Previous research has not indicated a specific organelle or structure as primarily associated with the onset of the PSS-MH. In the mitochondria of the rat, oxidative phosphorylation was uncoupled at all oxidative sites using a very high non-clinical concentration of halothane (Snodgrass and Piras, 1966). Other researchers have shown that the mitochondria contain 40% lipid and since anesthetics are highly lipid soluble, halothane is very effective in disrupting the mitochondrial membrane. The disruption of the membrane also inhibits the entry of pyruvate into the mitochondria which would effectively remove the oxidative phosphorylation of ATP (Fink and Kenny, 1968). This reduction of oxidative ATP cannot be compensated for by the production of glycolytic ATP. This reduction in oxidative ATP will also stimulate increased anaerobic glycolysis in an attempt to produce ATP. Campion et al. (1974) found no differences in the respiration rate of the mitochondria between SS and control pigs. The uncoupling of mitochondrial function occurs but the abnormalities are not a primary problem (Campion and Topel, 1975; Britt et al., 1975). The membrane defect shown affecting pyruvate movement has also been shown to decrease calcium uptake by the mitochondria (Heffron and Gronert, 1977; Gronert and Heffron, 1979; Cheah and Cheah, 1976, 1978). Cheah and Cheah (1979) have shown that reduced calcium binding is a result of rapid

calcium efflux. This deficit in calcium accumulation by the mitochondria may contribute to a rise in myoplasmic calcium but the effect is not enough to be the primary cause for both MH and PSS.

The examination of the mitochondrion, sarcoplasmic reticulum, and neuromuscular junction has not revealed a key genetic defect (Sulakhe et al., 1973). It has also been shown that halothane will produce conformational changes in the protein component of the sarcoplasmic reticulum, which is reversible in normal animals. This reversibility is not evident in affected animals (Augustin and Hasselbach, 1973). An SS animal under the influence of halothane accumulates 60% less calcium in the sarcoplasmic reticulum (Heffron and Mitchell, 1976), while in another group of SS pigs, the sarcoplasmic reticulum has been shown to bind 50% less calcium (Britt et al., 1975). On the other hand, other researchers have found that the sarcoplasmic reticulum of the SS pigs accumulates normal amounts of calcium in the absence of halothane (Berman and Kench, 1973; Nelson et al., 1972).

The most likely causes of impaired sarcoplasmic reticular function are hyperthermia and acidosis. The increase in temperature causes a change in the sarcoplasmic reticular proteins as well as uncoupling ATPase. Both of these events will cause leakage of calcium (Inesi et al., 1973). A weakness in this theory is that the temperature increases needed to cause these changes (hyperthermia and acidosis) occur

relatively late in the syndrome and after the effect of sarcoplasmic reticular damage and calcium release have already become evident with the onset of the PSS. The effect of temperature may serve only to exacerbate the problem of the sarcoplasmic reticulum's ability to bind calcium.

The acidosis seen in the SS pigs also will affect the function of the sarcoplasmic reticulum. It has been shown that the sarcoplasmic reticulum of the SS pigs have decreased calcium binding activity despite high ATPase activity and that an examination of sarcoplasmic reticulum, sarcolemma, t-tubules, and the neuromuscular junction for a primary lesion has not been conclusive.

The research into more complex hormonal systems is next to be examined for a primary lesion. These would include the neuro-transmitters of the sympathetic nervous system especially the catecholamines, as well as thyroid hormone and corticosteroids. The catecholamines, epinephrine and norepinephrine are integral parts of the sympathetic nervous system (SNS). The pig undergoing natural stress as in MH has been shown to have elevated levels of plasma catecholamines (Gronert et al., 1977, 1978; Hall et al., 1976; Lucke et al., 1976). The injection of catecholamines into the SS type pigs has been shown to cause PSS, whereas the use of alpha adrenergic blockers, epidural anesthesia, and adrenalectomy will prevent or attenuate suxamethonium-induced PSS (Kerr et al., 1975; Lister et al., 1974; Hall et al., 1977b; Lucke et al.,

1978). The release of the catecholamines from the SNS after halothane or physical stress will cause vasoconstriction (alpha receptor), stimulate muscle glycogenolysis, and stimulate rapid onset of anaerobic glycolysis. Other changes in cardiac function, hyperglycemia, skin blotchiness, cyanosis, and lactic acidosis can also be explained by the effect of the catecholamines (Gronert et al., 1978; Lucke et al., 1976; Harrison et al., 1968). The release of catecholamines is followed by a magnification of the initial release resulting in a continuation or worsening of effects. All of these aspects of catecholamine effects on MH or the PSS are dampened by the failure of catecholamines injected into normal pigs to produce MH or the PSS (Hall et al., 1977a). Altrogge et al. (1980) has shown that the SS and SR pigs had no significant differences in urinary norepinephrine and epinephrine. In these same SS pigs, urinary dopamine was shown to be significantly less. Hallberg et al. (1983) also showed that the SS pigs had significantly reduced concentrations of central nervous system dopamine, norepinephrine and epinephrine in the caudate nucleus and substantia nigra. The lack of dopamine could be the basis for uncontrolled stimulation of the rest of the body after stress. A similar lack of dopamine is seen in human Parkinson's Disease (Hornykiewicz, 1973, 1975).

The effect of the other two hormone systems (thyroid hormone and corticosteroids) seem to be secondary. The thyroid hormone level has been shown to be elevated in the SS

pig (Judge et al., 1966; Marple et al., 1975). Thyroidectomy in the SS pig has been shown to retard lactate accumulation in muscle and injection of large doses of triiodothryonine will cause the PSS (Lister, 1973; Marple et al., 1975). High levels of thyroid hormone during growth and development may have a permissive effect on the action of adrenergic receptors making them more sensitive to normal sympathetic stimulation (Melander et al., 1974). The SS pig also shows a reduced production of plasma cortisol in response to the administration of ACTH. This may indicate some type of adrenal cortical insufficiency with a disturbance in the feedback control of ACTH. More exactly, dexamethazone which will normally inhibit ACTH release does not inhibit ACTH production in the SS pig (Sebranek et al., 1973; Mitchell and Heffron, 1981). This will also reduce any stress response due to lack of response to elevated ACTH. So, the SS pig also seems to have a reduced adrenal response to stress thereby making it susceptible to any type of environmental stress.

In examination of possible hormonal, structural and developmental aspects of the PSS, a single definitive initiating factor for the PSS did not become obvious. All of these areas seem to be secondary to a single initiating problem which causes changes in adrenal response, sarcoplasmic reticular and mitochondrial membrane function as well as an increased anaerobic glycolysis. A deficiency in central nervous system dopamine which will decrease CNS control over

even the simplest muscle contraction is the leading contender. This lack of CNS dopamine such as in Parkinson's Disease may provide insight into a possible etiology of the PSS.

Pulmonary Function Testing

Because of the clinical signs of the PSS, including blotchy cyanosis, labored respiration, elevated blood pCO_2 and decreased blood pH, some definite pulmonary problems may be an integral part of the PSS (Topel et al., 1968; Forrest et al., 1968).

The use of tests for pulmonary function began as early as 1849 with initial measurements of vital capacity (Milic-Emili, 1974; Forster, 1974). Many procedural modifications have been made to allow adaptation to the clinical setting. Unlike the tests for function of other organs (kidney, heart, liver), little preliminary work on pulmonary function has been done in laboratory animals because there are some basic functional differences in the respiratory systems of different species (Drorbaugh, 1960; Stahl, 1967). Studies have been completed on the pulmonary functions in several species of animals (Guyton, 1947a, 1947b; Cook et al., 1959; Mead and Collier, 1959; Attinger, 1960; Attinger and Cahill, 1960; Drorbaugh, 1960; Crosfill and Widdicome, 1961; Piiper et al., 1961; Stahl, 1967; Dubin and Westcott, 1969; Dubin, 1970; Dubin et al., 1971; Pickrell et al., 1971; Feigl and D'Alecy, 1972; Gillespie and Hyatt, 1974; Mauderly, 1974; Liu and

Delanter, 1977; Ulrich et al., 1977; Kiorpes et al., 1978; Aguggini et al., 1979; Intraraksa et al., in press). Yet with all the species previously involved in pulmonary function testing, the pig has been largely ignored. Attinger and Cahill (1960) reported on the only major pulmonary function study done on the pig.

Lung function may be easily divided into several aspects. These include lung volumes, pulmonary mechanics, pulmonary blood flow, blood gas analysis, and pulmonary ventilation.

Lung Volume

Lung volume can be considered as four different volumes and four capacities (Comroe et al., 1962; Forster, 1974). Tidal volume is the volume of gas inspired or expired during a respiratory cycle. The inspiratory reserve volume is the maximum amount of air that can be inspired from a resting position. Expiratory reserve volume is the volume of air that can be forceably exhaled after a maximal inhalation. Finally, residual volume is the volume of gas remaining in the lung at the end of a maximal expiration (West, 1979).

Lung capacities are a combination of two or more lung volumes. Total lung capacity is the amount of air contained in the lung at the end of maximal inspiration. Vital capacity is the maximal amount of air that can be forceably expelled from the lung following a maximal inspiration. Inspiratory capacity is the maximal amount of gas that can be

inspired from a resting level or after normal expiration. Finally, functional residual capacity (FRC) is the volume of air left in the lung at the resting expiratory level. The measurement of these values in people is accomplished by respiration into a spirometer and may vary by as much as 20% between individuals (Comroe, 1974; Comroe et al., 1962; Forster, 1974; Ruppel, 1975). These measurements are the basic initial screening method in humans. They are valuable in the detection of such disorders as pulmonary edema, emphysema, pneumonia, bronchiogenic carcinoma, congestion or atelectasis. The use of these tests on a conscious animal can be very difficult because there is a distinct need for a voluntary breathing pattern. These tests must be conducted with anesthetized animals.

One of the measurements which can easily be conducted on an anesthetized animal is FRC. The method of choice is the multiple-breath, nitrogen-washout method (Dubin and Westcott, 1969; Gillespie and Hyatt, 1974; Pickrell et al., 1971; Stafford and Boecker, 1966). With a stable respiratory pattern, the animal is allowed to breath only 100% oxygen. The tidal volume and nitrogen content are continuously monitored. The expired air is collected until the nitrogen content in expired air falls below 10%. The values of nitrogen content in alveoli before and at the end of the washout, the concentration in expired and inspired air, tidal volume and the dead space of the apparatus allow the calculation of the FRC.

Pulmonary Mechanics

Pulmonary mechanics provide an assessment of the forces and elasticity governing the lung during the respiratory cycle. The most important measures include compliance and respiratory resistance.

Compliance is defined as the volume change per unit pressure change. It is basically a measurement of the ability of the lung and chest wall to expand or contract with a definite change in lung volume (Slonin and Hamilton, 1971; West, 1979). Compliance can also be divided into distinct components. Total compliance of the lung is made up of the compliance of the lung (Cl) in combination with the compliance of the thoracic wall (Ct). The compliance of the lung itself can be used clinically to note any drastic changes in lung elasticity in disease states (Forster, 1974; Gillespie and Robinson, 1974; Robinson and Gillespie, 1975). The determination of compliance needs a constant measurement of tidal volume with a concurrent value of intrapleural pressure. Intraesophageal pressure provides the best non-invasive estimate of intrapleural pressure available (Dubin, 1970; Gillespie and Hyatt, 1974; Milic-Emili et al., 1964). Other researchers contend that there is a great variability of intraesophageal pressure because of the position of the catheter in the esophagus (Dubin, 1970; Gillespie et al., 1973). It would seem that the use of a true intrapleural measurement would be difficult as well as risky in a clinical setting.

Compliance is the slope of the line when lung volume is plotted against intrapleural pressure. Compliance also can be divided into different functional components. These include dynamic and specific compliance. Dynamic compliance is determined during actual uninterrupted respiration. It is defined as the ratio of tidal volume to the difference in intrapleural pressure at the instant of zero airflow (Dubin, 1970). This is the best method to use in animals because of difficulties in having animals hold their breath. In humans, static compliance is used by getting specific volumes of inhalation and measuring the pressure required. Specific compliance is defined as the ratio of compliance to FRC (Dubin, 1970). This is calculated because compliance can vary with different amounts of FRC and volume remaining in the lung at the end expiration (Comroe, 1974; Ruppel, 1975). Changes, especially decreases in compliance, can be caused by interstitial and pleural fibrosis, edema, atelectasis, pneumonia, congestion and reduction in FRC (Forster, 1974; Ruppel, 1975).

Airway resistance is defined as the amount of pressure needed for a unit change in airflow. The total pulmonary resistance is composed of parts from the airways and the pulmonary tissue with the airway component being the most important. Any reduction in the number of available airway numbers such as in a disease state will increase the pressure required to move air from the mouth to the alveoli. The flow of air through the airways is governed under Poiseuilles Law.

This law indicates that decreases in air resistance are directly related to the fourth power of the effective airway radius (Comroe, 1974). This means that the major airways, the bronchi, and trachea, and not the smaller terminal airways are responsible for the major portion of airway resistance (Grimby et al., 1968; Hogg et al., 1972; Lapp, 1973; Macklem and Mead, 1967). Resistance can be increased by conditions such as asthma, emphysema or any type of bronchial disease (Robinson and Gillespie, 1975). A decrease in resistance is caused by any dilation of the respiratory system under sympathetic nervous system stimulation.

Blood gas determination of pCO_2 and HCO_3 values allows assessment of the efficiency of cardiopulmonary function. Alteration in blood gas coefficients especially pCO_2 and pO_2 can be used to show hypoventilation, ventilation perfusion inequality, or pulmonary disease (West, 1979; Ruppel, 1975).

The movement of oxygen from the atmosphere to the lung, to the blood and finally to the tissue is a very fine-tuned mechanism. Any impairment of function will cause a decrease in arterial pO_2 with a subsequent increase in pCO_2. Several things can cause such problems. These include hypoventilation, shunting or a ventilation perfusion inequality.

Hypoventilation will occur with any decrease in the alveolar supply of oxygen. Ideally, the system is well balanced so any increase in blood pCO_2 is countered by an increase in respiratory drive to increase the amount of oxygen

available to the lungs. There are several possible etiologies to hypoventilation. Drugs including morphine or barbiturates depress central nervous system ventilatory drive. Chest wall damage or respiratory muscle paralysis will physically prevent proper ventilation. Finally, any cause of unusually high respiratory resistance will also lead to an increase in pCO_2 and a decrease in pO_2. Hypoventilation will always result in a decrease in alveolar ventilation thus resulting in an increased arterial pCO_2. A one-half reduction in ventilation will result in a doubling of arterial pCO_2 (West, 1979).

Shunting occurs when blood passes through the lung field but does not come in contact with oxygen. In the perfect lung, the pO_2 of arterial blood should approach the pO_2 of alveolar air. Even under an optimal situation, some of the pulmonary blood does not go through the alveoli. A prime example is the output of the bronchial artery which supplies the lung parenchyma. In certain situations, there are problems such as hypoxic vasoconstriction where contraction of arterial smooth muscle is seen in regions where there is little ventilation, such as in diseased lung tissue. Finally, any right to left side of the heart shunting of blood will also be a possible site of pulmonary shunting. The determination of the presence of a shunt encompasses two facts. First the presence of hypoxia cannot be abolished by the use of 100% O_2, because shunted blood is never in contact with a

ventilated region of the lung. Secondly, a shunt will not produce any increase in pCO_2 because central nervous system chemoreceptors will respond to the increased pCO_2 with an increase in ventilation which will reduce pCO_2 (West, 1979).

Finally, the ventilation perfusion ratio (V/Q) must be considered. This is a comparison of pulmonary ventilation to pulmonary perfusion. Two alternatives are possible. These are a decrease in ventilation without any change in blood flow. Secondly, any decrease in perfusion such as caused by any cardiac insufficiency is important. Lungs with a $\dot{V}/\dot{Q}$ inequality, therefore, cannot maintain as high a pO_2 or as low a pCO_2. The only way patients of these disorders can maintain pCO_2 in normal limits is through an increase in ventilation rate due to central nervous system stimulation.

Along with $\dot{V}/\dot{Q}$ is the evaluation of the ratio (Vd/Vt) of the volume of physiologic dead space (Vd) to tidal volume (Vt). The $\dot{V}/\dot{Q}$ and Vd are measured in an attempt to determine the exact location of any cause of altered blood gas values (West, 1979).

The ratio of Vd/Vt is calculated through the use of the Bohr equation which states: $Vd/Vt - \frac{PaCO_2 - Pe\ CO_2}{PaCO_2}$. This measurement is valid because of the assumption that all of the CO_2 that is expired is derived from the alveolar region of the lung. So in effect, Bohr's equation measures that portion of the lung anatomy which does not eliminate CO_2. In

patients with lung disease, this volume can be greatly increased. An abnormal physiologic dead space volume indicates large areas of the lung which cannot excrete CO_2. Consequently, the use of measurements of Vd/Vt, hypoventilation, shunting and $\dot{V}/\dot{Q}$ can be used in combination to help pinpoint possible areas of abnormality.

Possible Neural Aspects of the Porcine Stress Syndrome

Previous research into the etiology of the PSS has shown a deficiency of dopamine in the caudate nucleus of the susceptible pigs (Altrogge et al., 1980). The caudate nucleus is a portion of a larger body called the basal ganglia. The basal ganglia are a large group of nuclei in the upper forebrain and midbrain. It is composed of the caudate nucleus (CN), putamen, globus pallidus, substantia nigra (SN), and subthalamic nucleus (STN) (Carpenter, 1976; Dray, 1980). The CN and putamen together are described as the striatum. They are separated from one another by the internal capsule. They function as a single entity and together constitute the largest component of the basal ganglia (Carpenter, 1976).

The afferent and efferent fibers to and from the basal ganglia connect with many different regions of the brain. The main afferent fibers to the striatum come from the cortex, thalamus and SN. The efferent projections from the striatum include those to the SN and globus pallidus. These structures then project to the cortex, thalamus, and mesencephalic

and pontine nuclei (Cheramy et al., 1981). The striatonigral pathway arises from the striatum and terminates in the pars compacta and pars reticulata of the SN (Schywyn and Fox, 1974). A pathway from the globus pallidus to the SN has also been shown (Kanazawa et al., 1976). The apparent function of these neurons is to synapse on neurons within the SN and inhibit them postsynaptically. The inhibition may be mediated through gamma aminobutyric acid (GABA) which has been shown to be present in the axon terminals of these fibers (Precht and Yosida, 1971; McGeer et al., 1974; Brownstein et al., 1977; Gale et al., 1977; Ribak et al., 1980). The GABA terminals to the SN may terminate on SN dopaminergic neurons and will also form connections on SN interneurons, terminal afferents to the SN and nigral efferent projections (Cheramy et al., 1981). This pathway is a feedback mechanism for adjusting the movement of information through the striatum, which consists of both excitatory and inhibitory components (Cheramy et al., 1981; Walters et al., 1975; Costa et al., 1978).

The presence of the neurotransmitter, dopamine (DA), also has been shown in the striatum. DA may regulate the activity of adjacent dopaminergic neurons in the SN through its release and local feedback mechanisms. The release of DA from the dendrites of the nigrostriatal neurons may be involved in the self-regulation and the control of neural transmitters from the nigral efferents (Cheramy et al., 1981).

In the striatum, these DA terminals synapse on striatal neurons. These may be important in control of projections to the cerebral cortex, globus pallidus, and SN (Dray, 1979; Bartholini, 1980; Gale, 1980).

These nigrostriatal neurons arise from the pars compacta of the SN and consist largely of dopaminergic neurons (Bjorklund and Lindvall, 1975). There is evidence that a major portion of the DA present in the striatum originates from axons of the nigrostriatal pathway. These axon terminals can store and release DA, which is thought to function in local feedback pathways (Bjorklund and Lindvall, 1975; Geffen et al., 1976; Shepherd, 1978; Pickel et al., 1976). These pathways are used in self-control of dopaminergic neurons, which control the release of other non-dopaminergic cells (Gale et al., 1977; Spano et al., 1972; Cheramy et al., 1981). The terminal of the nigrostriatal neurons will synapse on interneurons of the striatum as well as projections from the cerebral cortex to the striatum. There are also connections onto efferents to the SN and globus pallidus (GP). The projection to the GP is of importance because it forms the major route of efferents from basal ganglia to the thalamus, SN, and subthalamic nuclei (STN). This connection may be very important as a modulator in striatal output (Bjorklund and Lindvall, 1975).

The interconnections of the basal ganglia are very complex. The presence of dopamine is important in the modula-

tion and regulation of activity of the striatum, SN, STN, and the extrapyramidal motor pathways. Because of the complexity of the basal ganglia, their function is best explained by a discussion of the symptoms of basal ganglia deficiencies. Primary examples of diseases produced by basal ganglia deficiency would be Parkinson's disease (PD) and Huntington's Chorea (HC). Possible problems encountered with basal ganglia deficiency include akinesia, chorea, athetosis, dystonia, ballism, rigidity, and tremor (Marsden and Parkes, 1973; Marks, 1977).

Akinesia is the absence or marked reduction of muscle movements. Chorea is described as a ceaseless occurrence of a wide variety of rapid, highly complex jerky movements. These movements appear well-coordinated but are performed involuntarily mostly at distal joints. When these movements are limited to only one side of the body, they are referred to as hemiballism. Athetosis is a derangement marked by the ceaseless occurrence of slow sinuous writhing movements especially in the hands which are performed involuntarily. There is also a noted instability of posture. Dystonia is a disordered tonicity of muscles. This is characterized by a persistent maintenance of posture. Rigidity such as plastic rigidity is a marked resistance to stretching of the muscles and may be accompanied by a tremor. The tremor seen in these diseases is a rhythmic alternating contraction of opposing muscle groups. The tremors can also be associated with

rigidity especially in PD.

With the lack of central nervous system modulation of movement, a distinct group of clinical signs of a PD patient are present. Facial features include deep palpebral fissures, frequent blinking, a staring appearance and immobile facial muscles. Posture-wise, a stooped posture, difficulty in movement, and slowness in any performed movement (akinesia, bradykinesia) are noted. Thoracic expansion during inspiration is reduced with a subsequent increase in diaphragmatic contraction. Slow shuffling movements with tremor and rigidity are noted. The tremor is most noted in the hands and upper limbs. The reflexes appear to be unimpaired but are in reality difficult for the person to perform. There seems to be some autonomic dysfunction, including flushing of the skin, tendency to prefer cold temperatures, low resting blood pressure and urine retention. Finally disorders of personality and mood have also been noted (Walton, 1977).

The presence of any of these symptoms can vary greatly between people with the same disease. The symptoms tend to merge with one another and form a combination of effects which usually progress and worsen with time (Walton, 1977).

There also seems to be distinct relationships between lesion location and the clinical expression of the disease. Athetosis has been linked specifically to lesions of the outer segment of the globus pallidus. Chorea results from a lesion in the caudate nucleus. Dystonia is due to lesions similar

to those of athetosis as well as others in the thalamus and cerebral cortex. Parkinsonian tremor and rigidity are due to lesions in the globus pallidus and later in the SN. The nigral lesion is associated with damage to the nigropallidal and nigrostriatal pathways. Lesions in the caudate nucleus are associated with increased movement, neuron excitement and a reduction in the tonic stretch mechanism. Thus, the function of the basal ganglia may be directly involved in the regulation of cortical control of voluntary movement by a process of graded inhibition which would normally result in smoothness of movement. The globus pallidus is the final efferent station in the basal ganglia and its activity may be regulated by input from the cortex, CN, putamen, SN and STN (Walton, 1977).

It has been accepted that the loss of dopaminergic nigrostriatal neurons and dopamine deficiency in the striatum is the main problem in the etiology of PD (Hornykiewicz, 1966; Bernheimer et al., 1973). There also may be some involvement of non-dopaminergic transmitters such as acetylcholine (Ach) and GABA (Lloyd and Hornykiewicz, 1973; Lloyd et al., 1975; McGeer and McGeer, 1976). In contrast, Huntington's Chorea is associated with the loss of striatal GABA function, while concentrations of dopamine in the striatum are normal or slightly decreased (McGeer and McGeer, 1976; Spokes, 1980).

Despite all of the previous research, the exact function of the basal ganglia and its individual components is still confusing at best. Many theories have been advanced dealing with exact function of the basal ganglia. All of these may be correct at least in part. It has been shown that the basal ganglia may play a cooperative role with other systems but have a separate autonomy from the rest of the brain (Dray, 1980). Conde et al. (1981) suggested two possible ideas. Firstly, the basal ganglia act as a ramp generator for the command of "voluntary" goal controlled movement. Secondly, the basal ganglia provide a "Cognitive" control aspect to the function of the brain. This in essence means that the brain with basal ganglia function has the ability to compare stimuli from previous experiences. This aspect is supported by the findings that PD patients will show cognitive defects, memory loss and impairment of perception and psychomotor speed (Reitan and Boll, 1971; Loranger et al., 1972; Portin and Rinne, 1980).

It seems that the basal ganglia affect the ability to handle and respond to environmental challenges. Consequently, lesions in any region of the basal ganglia will affect many functions and produce a wide array of clinical signs and different syndromes including HC, PD, the rest of the extrapyramidal syndromes. This includes possibly the Porcine Stress Syndrome.

NEURAL CATECHOLAMINE DEFICIENCIES IN THE PORCINE STRESS SYNDROME

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SECTION I: NEURAL CATECHOLAMINE DEFICIENCIES IN THE PORCINE STRESS SYNDROME

Summary

A study was conducted to compare catecholamine concentrations in nervous tissues of stress-susceptible (SS) and stress-resistant (SR) pigs that were physically stressed. Ten pigs were included in each group on the basis of halothane screening tests, blood typing analysis, and serum creatine phosphokinase activities at 6 weeks of age. The nervous tissue analyzed included the substantia nigra (SN) and the caudate nucleus (CN). These tissues were taken from pigs as soon as possible after death, frozen in liquid nitrogen, and later radioenzymatically assayed for dopamine, norepinephrine, and epinephrine concentrations.

The SS pigs exhibited significantly greater ($P < .001$) creatine phosphokinase (CPK) concentrations than did SR pigs before and after physical stress. Concentrations of dopamine, norepinephrine, and epinephrine in the CN of SS pigs were significantly lower ($P < .05$) than those in the CN of SR pigs. Similarly, the SN of SS pigs had lower dopamine, norepinephrine, and epinephrine concentrations than did the SN of SR pigs. The catecholamine deficiencies observed in the porcine stress syndrome (PSS) seem to have similarities with certain human extrapyramidal diseases.

Introduction

Research on the etiology of the porcine stress syndrome (PSS) has followed many pathways. Investigations into possible abnormalities in muscle structure, function, and metabolism have received major attention (Allen et al., 1970b; Watson et al., 1980; Hallberg et al., 1979; Christian, 1974; Ahern et al., 1980; Gallant et al., 1979; Steiss et al., 1981; Gallant, 1980; Cheah and Cheah, 1981; Kerr et al., 1975; Lucke et al., 1976). The SS pig has been used as a research model for studying the etiology of a similar syndrome--malignant hyperthermia (MH) in humans. Research with SS pigs has demonstrated elevated activities of creatine phosphokinase (CPK) in the serum after physical or anesthetic-induced stress (Allen et al., 1970b; Watson et al., 1980; Hallberg et al., 1979; Christian, 1974).

The role of the central nervous system in the PSS is unclear, although a possible involvement was suggested by early workers who used epidural blocking agents to prevent malignant hyperthermia (Kerr et al., 1975). Others, however, found that the catecholamine response to stress and the sympathetic involvement were secondary to the main syndrome (Lucke et al., 1976; Weiss et al., 1974; Gronert et al., 1977). Additionally, the metabolic responses of skeletal muscle from SS pigs to cholinergic agonists and to increased body temperature are greater than the responses in muscles of SR pigs. The muscle response seems to be one of a normal

nerve stimulation of abnormal muscle rather than a somatic or sympathetic nervous system disorder (Gronert et al., 1980). Recently, however, our research group has shown that SS pigs have abnormally low concentrations of dopamine in both their urine and the caudate nucleus (CN) as compared with SR pigs (Altrogge et al., 1980). This suggests some neural involvement in the PSS. The dopamine in the CN is thought to be present in axon terminals of the nigrostriatal tract. This tract arises from the substantia nigra (SN), which is one of the extrapyramidal nuclei of the midbrain (Dray, 1979). Because of the close structural and functional relationship between the SN and CN and the fact that SS pigs exhibit lower dopamine concentrations in the CN, a study was conducted to determine the concentrations of dopamine, norepinephrine, and epinephrine in the SN of SS and SR pigs. An additional purpose of the study was to determine the effects of physical stress on catecholamine concentrations in the CN and SN of SS and SR pigs.

Materials and Methods

Animals

Ten SS pigs and ten SR pigs, maintained at the Iowa State University Swine Breeding Farm, were classified as either SS or SR by halothane screening, H blood typing, and serum CPK levels at six weeks of age (Christian, 1974; Rasmussen and Christian, 1976; Rosalki, 1965; Sigma Chemical

Company, 1973). The halothane response times, specific blood types, and serum CPK levels for each pig are shown in Table 1. When the pigs were 4.5 months old, they were transported to the Iowa State University Meat Laboratory for physical stress tests and slaughter. The pigs weighed between 60 and 90 kg at this time. Four days prior to slaughter, the cranial vena cava of all pigs was catheterized to facilitate blood collection for determination of serum CPK activity before and after the stress test. The catheters consisted of 50-68 cm of intramedic nonradiopaque polyethylene tubing (.86 mm inside diameter). A 20-gauge needle with an injection cap attached was inserted into the end of the catheter and was used for flushing with heparinized saline. The catheter was secured with tape over the shoulder of the pig. Three days of post-implantation recovery was allowed before any further work was done or collections made. The pigs were fed ad libitum a 16% protein corn-soy nonmedicated feed from weaning until death.

Stress test

Three days after catheterization, all pigs were stressed physically by rapid running for 5 minutes. Blood samples were taken just before stress (0 hr.), 2 hours after stress (2 hr. post), and 4 hours after stress (4 hr. post). These blood samples were allowed to clot and serum was assayed for CPK activities, which, in turn, were used as an indicator that the desired level of stress had been achieved (Rosalki,

1965; Sigma Chemical Company, 1973).

Catecholamine analysis

After the 4-hour post-stress blood sample was collected, all pigs were exsanguinated. A craniotomy was performed, and the brain removed within an average of 3 minutes after death. The corpus callosum was cut longitudinally and the cerebral hemispheres were reflected laterally thus exposing the CN that extends into the lateral ventricle. A glass dissecting rod was used to peel the head of the CN from the laterally positioned internal capsule. The SN was obtained by making two transverse cuts through the brainstem immediately in front of the pons and immediately caudal to the mammillary bodies, thus removing most of the mesencephalon. The mesencephalon subsequently was sectioned obliquely from the dorsal edge of the cerebral peduncle, located laterally, to the midline of the interpeduncular fossa. Because the SN is attached intimately to the cerebral peduncles, no attempt was made to separate them. The CN and SN were placed in liquid nitrogen as soon as possible after isolation. Concentrations of dopamine, norepinephrine, and epinephrine in tissues were assayed radioenzymatically (Passon and Peuler, 1973; Upjohn Diagnostics, 1978).

The data were analyzed statistically by least-squares analysis of variance (Snedecor and Cochran, 1967).

Results and Discussion

Concentrations of dopamine, norepinephrine, and epinephrine in the CN and SN are shown in Tables 2 and 3, respectively. Mean dopamine concentrations in the CN for the SS pigs were significantly less ($P<.05$) than those for SR pigs. Norepinephrine and epinephrine concentrations in the CN of SS pigs also were significantly less ($P<.05$) than those in SR pigs.

Concentrations of dopamine, norepinephrine, and epinephrine in the SN followed trends similar to those observed in the CN. Mean dopamine concentrations for SS pigs were less ($P < 0.1$) than those for SR pigs. Norepinephrine levels for SS pigs also were less ($P < .06$) than the concentrations in SR pigs. Mean epinephrine concentrations for the SS pigs were less ($P < .09$) than those of SR pigs. The activities of CPK in the serum from SS and SR pigs are shown in Table 4. At rest, (0 hr.), SS pigs had significantly greater CPK activities in serum than did SR pigs. This trend continued for both the 2-hour and 4-hour post-stress samples.

The possibility of neural involvement in the PSS is supported by the observation of lower catecholamine concentrations in the CN and SN of SS pigs than in CN and SN of SR pigs. In the CN of SS pigs, dopamine concentrations were nearly half as much as the concentrations observed in SR pigs. This finding is in agreement with earlier work from our laboratory (Altrogge et al., 1980). In addition, the dopamine

concentrations observed in the SR pigs were similar to the concentrations of dopamine reported previously (Altrogge et al., 1980; Bertler and Rosengren, 1959). Dopamine concentrations in the SN of SS pigs were substantially below those of SR pigs and were statistically significantly different at the 10% level. Abnormally low dopamine levels were expected in the SN of SS pigs because the SN contains the dopaminergic neurons that project to the CN (Dray, 1979), and because the dendrites of the nigral dopaminergic neurons release dopamine locally (Cheramy et al., 1981). A technical problem that may have biased dopamine concentrations is that the SN is very difficult to isolate as an individual structure because it is located between the cerebral peduncles and ventral tegmentum of the midbrain. Therefore, the samples may have been diluted by inclusions of these adjacent neural tissues, which may have lower concentrations of dopamine than does the SN. The considerable genetic variation of SS pigs also may account for some of the variation in dopamine concentrations.

The abnormally low concentrations of dopamine seen in the CN, SN, and urine of SS pigs seem similar to deficiencies observed in certain human extrapyramidal diseases. Specifically, low dopamine levels in the striatum (CN and putamen) and SN are characteristic of Parkinson's disease (Barbeau, 1960; Barbeau et al., 1961; Ehringer and Hornykiewicz, 1960; Carlsson, 1972; Hornykiewicz, 1973).

The low dopamine concentrations in Parkinson's patients is thought to be because of a degeneration of either the dopaminergic neurons in the SN or the nigrostriatal pathway from the SN (Birkmayer et al., 1975; Bernheimer et al., 1973; Hornykiewicz, 1975). The death of nigral dopaminergic neurons and consequential loss of striatal dopamine have been related to the tremors and rigidity seen in Parkinson's disease (Marsden et al., 1975). Similar events may take place in SS pigs during growth. Likewise, lower dopamine concentration in the CN could be because of either a loss of nigral dopaminergic neurons and their processes or to disturbances of dopamine metabolism.

Significantly lower striatal norepinephrine concentrations were observed in SS pigs. This finding is in contrast to previous results from our laboratory in which we found no difference between the norepinephrine concentrations in either the CN or urine of SS and SR pigs. We believe this discrepancy is because of the differences in handling the pigs immediately before slaughter. In the present study, the animals experienced surgery (catheter implants), physical stress (running), and several blood sample collections. The effects of stress on central norepinephrine concentrations is unknown in the pig; in the rat, however, there is a rapid depletion of central norepinephrine accompanying both physical and psychological stress in most brain regions (Bliss and Zwanziger, 1966; Corrodi et al., 1968; Nakagawa et al., 1981;

Iimori et al., 1982). In our experiment, the SS pigs seemingly were unable to adapt as rapidly to the physical stress of running and, therefore, exhibited lower norepinephrine concentrations than did the SR pigs. Additional investigations are necessary to clarify the effect of stress on central catecholamine concentrations in the pig. There is also a need to determine the role of central noradrenergic neurons in the PSS. There may be a loss of noradrenergic neurons in the SS pig. Noradrenergic neurons in the locus ceruleus of the pons are known to project to the CN where they release norepinephrine. Patients with Parkinson's disease exhibit a norepinephrine deficiency which is thought to be because of fewer noradrenergic neurons in locus ceruleus (Farley and Hornykiewicz, 1976). A tendency towards lower norepinephrine concentrations also was noted in the SN. A more precise method of isolating the SN would aid in substantiating or refuting the effect seen in the present study.

Epinephrine concentrations were also significantly lower in the CN of SS pigs than in SR pigs. A similar pattern was seen in the SN of SS pigs. The reason for the lower epinephrine is most likely because of the physical stress that the pigs experienced. Indeed, rats that have experienced many types of stress have substantially lower epinephrine levels in all areas measured except the hypothalamus (Saavedra, 1980). The source of central epinephrine in the pig is unknown. However, in other species, moderate amounts

are present in the locus ceruleus, SN, raphe nuclei, reticular formation, and certain hypothalamic nuclei (Van Der Guten et al., 1976; Palkovits et al., 1980). It is likely that neurons in some of these structures project to the CN and release epinephrine.

SS pigs had higher serum CPK values than did SR pigs when chemically (halothane anesthesia) or physically (running) stressed. Anesthetic stress consistently yielded higher CPK values than did physical stress. The CPK levels measured under both types of stress were similar to those obtained in previous studies in our laboratory and to those values reported by others (Allen et al., 1970b; Hallberg et al., 1979; Ahern et al., 1980; Altrogge et al., 1980).

The change in CPK activities in SS pigs in response to physical stress is similar to CPK changes seen in patients with Parkinson's disease (Tanner and Goetz, 1981). Despite the elevated CPK values in SS pigs, there is little evidence for any typical myopathy (Steiss et al., 1981).

The demonstration that neural catecholamine deficiencies are associated with the PSS adds a new dimension to our understanding of the PSS and provides some indication that the PSS may be similar in some neuropharmacologic aspects to Parkinson's disease.

Table 1. Classification of experimental animals

Pig No.	Type	Halothane Exposure Time[a]	CPK[b]	H-Blood Type
		min:sec	(mIU/ml)	
554-3	Stress-susceptible	1:25	1666	- a/a
130-2	Stress-susceptible	:35	2333	- a/a
556-2	Stress-susceptible	:42	2833	0 a/-
755-2	Stress-susceptible	:45	4748	0 a/-
757-2	Stress-susceptible	:26	3199	0 -/-
551-3	Stress-susceptible	:55	1333	0 a/-
230-3	Stress-susceptible	1:45	1100	- a/a
1261-2	Stress-susceptible	:24	1583	- a/a
542-3	Stress-susceptible	:30	1333	0 a/-
421-3	Stress-resistant	3:00	183	0 a/c
428-2	Stress-resistant	3:00	100	0 a/c
420-2	Stress-resistant	3:00	217	0 a/c
425-3	Stress-resistant	3:00	67	0 a/-
1276-3	Stress-resistant	3:00	450	0 a/a
756-2	Stress-resistant	3:00	217	0 a/c
1270-3	Stress-resistant	3:00	183	0 a/-
1275-3	Stress-resistant	3:00	67	0 a/-
1271-3	Stress-resistant	3:00	150	0 a/a
515-2	Stress-resistant	3:00	425	0 c/-

[a]Halothane exposure time was measured up to a maximum of 3 minutes or until muscle rigidity occurred.

[b]Creatine phosphokinase.

Table 2. Catecholamine concentrations in the caudate nucleus[a]

Item	Dopamine	Norepinephrine	Epinephrine
Stress-susceptible	5128	110	260
Stress-resistant	8093	262	404
Std. error	1005	37	48
Significance	$P < 0.05$	$P < 0.01$	$P < 0.05$

[a]Data are expressed (in ng/g tissue) as the mean of 10 animals of each type.

Table 3. Catecholamine concentrations in the substantia nigra[a]

Item	Dopamine	Norepinephrine	Epinephrine
Stress-susceptible	198	273	50
Stress-resistant	317	309	108
Std. error	48	42	23
Significance	$P < 0.10$	$P < 0.06$	$P < 0.09$

[a]Data are expressed (in ng/g tissue) as the mean of 10 animals of each type.

Table 4. CPK activities in serum following physical stress[a]

Item	Before Stress (0 hr)	2 hr Post Stress	4 hr Post Stress
Stress-susceptible	637	1090	1245
Stress-resistant	124	192	161
Std. error	80	157	185
Significance	$P < 0.0003$	$P < 0.0008$	$P < 0.0006$

[a]Data are expressed (in mIU/ml) as the mean of 10 animals of each type.

PULMONARY AND HEMATOLOGIC FUNCTIONS IN STRESS-SUSCEPTIBLE AND STRESS-RESISTANT PIGS

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SECTION II: PULMONARY AND HEMATOLOGIC FUNCTIONS IN STRESS-SUSCEPTIBLE AND STRESS-RESISTANT PIGS

Summary

A study was conducted to compare hematologic and pulmonary functions of pigs of stress-resistant (SR) and stress-susceptible (SS) genotypes. Several significant differences in hematologic values were found between the two genotypes of pigs. All SS pigs had significantly less hemoglobin than the SR pigs did. In addition, the SS pigs had significantly greater values for arterial pCO_2, base excess (BE), HCO_3^-, and total CO_2 than did SR pigs. The SS pigs also had significantly less venous BE but greater HCO_3^- and total CO_2 than did the SR pigs.

Genotypic differences in pulmonary function values also were observed. The SS pigs had significantly less pulmonary resistance than did the SR pigs. Moreover, the SS pigs had significantly greater physiologic dead space and a significantly lower ventilation/perfusion ratio than did the SR pigs. The pulmonary and hematologic differences between SS and SR pigs provide some explanation for some of the clinical signs seen in the porcine stress syndrome (PSS) and suggest that the pathophysiologic mechanisms of this disease include abnormalities of the respiratory systems as well as those of the muscular and nervous systems.

Introduction

The PSS has been researched intensively for some time, but the cause remains unknown. Pigs of the SS genotype have abnormalities in muscle function, serum creatine phosphokinase isoenzymes, and central nervous system catecholamines (Watson et al., 1980; Hallberg et al., 1979; Altrogge et al., 1980; Hallberg et al., 1983). The development of the syndrome follows a very definite sequence. After an initial stress (running, sorting, castration, or fighting), muscle tremors and blotchy cyanosis develop. The SS pigs, when stressed, show dyspnea and open-mouthed shallow respiration. Within 20-60 minutes after onset of clinical signs, the SS pig becomes reluctant to move and collapses into lateral recumbency with all four legs in extensor rigidity (Topel et al., 1968). Physiologic changes seen in the SS pig include increased heart and respiration rates, marked increase in body temperature, increased blood CO_2, and a drop in blood pH (7.57 to 6.97) (Forrest et al., 1968). Additionally, muscle pH drops dramatically to levels of 5.33-5.97 at 1 hour post-mortem (Topel et al., 1968).

Because of the clinical signs associated with the PSS (particularly respiratory difficulty), it was anticipated that the SS pig might have some abnormalities in pulmonary functions. The purposes of this study were to investigate and compare pulmonary and hematologic functions in pigs of

the SS and SR genotypes and to provide additional normal pulmonary function values for the pig.

Materials and Methods

Animals

Six SS pigs (two males and four females) and eight SR pigs (four males and four females) were obtained from the Iowa State University (ISU) Swine Breeding Farm and delivered to an animal holding room at the ISU College of Veterinary Medicine. The pigs were allowed 3 days to acclimate to their new surroundings. They were fed a 16% protein corn-soybean meal diet with ad libitum water. The pigs were classified as either SR or SS based on a combination of halothane screening, H blood typing, and serum CPK levels (Christian, 1974; Rasmussen and Christian, 1976; Rosalki, 1965; Sigma Chemical Company, 1973).

Pulmonary function procedures

The pigs were not allowed food or water the night before pulmonary function tests. Each pig was dosed with 4% Thiamyl sodium (Surital, Parke Davis, 11 mg/kg) intraperitoneally to facilitate anesthesia. When the pig was recumbent, a catheter was inserted in the lateral auricular vein to maintain anesthesia. The anesthetized pig then was moved to the pulmonary function laboratory and placed in dorsal recumbency. A ventral midline incision was made on the neck to expose the right and left carotid arteries and the trachea. A right

paramedian incision was made also to allow access to the right jugular vein. Care was taken in all surgical procedures to prevent any damage to either the sympathetic trunk or the vagus nerve.

A heparinized catheter was introduced into the right or left carotid artery and sutured into place. The carotid catheter then was connected to a Statham P23Db differential pressure transducer, connected electrically to a Beckman 611 recorder. Arterial blood samples and pressure recordings were obtained from this catheter.

A heparinized Swan-Ganz catheter was introduced into the right jugular vein and directed toward the right ventricle. The catheter was attached to a Statham transducer, which allowed the placement of the catheter to be determined by the right ventricular pressure wave forms. Mixed venous blood samples and right ventricular pressures were obtained from this catheter.

A third catheter was inserted in the esophagus. The esophageal pressure was recorded on the Beckman recorder and provided an estimate of intrapleural pressure changes.

An incision was made between the first two tracheal cartilages, an endotracheal tube introduced, and the cuff of the tube inflated. A Statham differential pressure transducer with a Fleisch #0 pneumotach was placed on the endotracheal tube to measure airflow. Airflow measurements were electrically integrated to give tidal volume (V_t). Both airflow and

tidal volume were recorded on individual channels of the Beckman recorder. Lead II electrocardiograms were recorded to allow measurements of heart rate.

Each pig was allowed to stabilize for 10 minutes while attached to the recording system. After stabilization, two testing periods of 1-minute duration were made 15 minutes apart. During each test, a meteorological balloon was attached to the expiratory part of the system to collect expired air. This sample was used to determine end tidal oxygen (O_2) values. Two arterial and venous blood samples were collected before and after each testing period. All blood samples were collected anaerobically into 3-ml plastic syringes wetted with heparin solution (1000 IU/ml). The blood samples were refrigerated immediately at $4^{o}C$ and analyzed on an Instrument Laboratories 513 Blood Gas Analyzer.

Blood parameters measured directly included pH, partial pressure of carbon dioxide (pCO_2), and partial pressure of oxygen (pO_2). Base excess (BE), serum bicarbonate (HCO_3^-), and total serum carbon dioxide (CO_2C^+) were calculated by the blood gas analyzer. An extra venous sample was obtained for measurement of hemoglobin (g/100 ml), via the cyanomethemoglobin method, and packed cell volume (PCV).

The multiple-breath, nitrogen-washout method was used to measure functional residual capacity (FRC) (Stafford and Boecker, 1966; Engwall, 1980). Pigs were attached via endotracheal tube to a combination of a pneumotach and a nitrogen

analyzer. The instrument presented digital and analog outputs. The analog outputs of the pneumotach (tidal volume) and nitrogen analyzer (nitrogen content) were recorded on channels 1 and 2 of a Brush recorder. When a stable respiratory pattern was established, the pig was switched to breathing 100% oxygen. An evacuated meteorological balloon was attached simultaneously to the expiratory part of the system to allow collection of an expired air sample. When the level of nitrogen in expired gas dropped below 10%, the pig was removed from the pneumotach-nitrogen analyzer system. The contents of the balloon were forced through the nitrogen analyzer for a measurement of nitrogen gas concentration in the expired air sample.

The total amount of air flowing through the system during the experimental period for each pig was measured on a Singer Dry Test Air meter. Total inspired air flow, duration of the experimental period, and anaerobic arterial and venous blood gas values allowed for the calculation of cardiac output via the Fick principle (Engwall, 1980).

Calculations and data analysis

The output of the Beckman 611 recorder, blood gas analyzer, and Brush recorder produced 24 different measurements whose values were used in other calculations of pulmonary and cardiac function.

Temperature and pO_2 measurements were used to calculate

arterial and venous hemoglobin saturation values (Rossing and Cain, 1966). From these saturation values, arterial and venous oxygen concentrations were calculated (Engwall, 1980).

Lung compliance, lung resistance, cardiac output, functional residual capacity, volume of alveolar dead space/tidal volume (physiological dead space VD/VT), and the ventilation perfusion ratio ($\dot{V}/\dot{Q}$) were calculated by using published formulas verified in our laboratory (Engwall, 1980; Dubin, 1970; Gillespie and Robinson, 1974; Forster, 1974; Robinson and Gillespie, 1975; Slonim and Hamilton, 1971; Macklem, 1975; Ganong, 1975; Ruppel, 1975; West, 1979).

All data were analyzed by analysis of variance under the Statistical Analysis System. The effects of genotype and sex, and the interaction of genotype by sex on various physiological, blood gas, and pulmonary function values, were included in the model.

Results and Discussion

Hematologic and Blood Gas Analyses

The SS pigs (44.6 kg) in this study were lighter ($P<0.08$) than the SR pigs (52.7 kg), even though their ages were identical. A significant interaction between sex and genotype was noted for hemoglobin values. The SR males (12.91 g/100 ml) had significantly greater ($P< 0.05$) hemoglobin values than did SR (11.16 g/100 ml) and SS females (11.12 g/100 ml). In addition, the SR males (12.91 g/100 ml)

had significantly greater ($P < 0.02$) hemoglobin values than did SS males (10.00 g/100 ml). As a group, the pigs of SS genotype (10.56 g/100 ml) had significantly less ($P < 0.05$) hemoglobin than did pigs of the SR genotype (12.04 g/100 ml). No significant genotype differences were found for packed cell volume, diastolic pressure, systolic pressure, right heart pressure, heart rate, or cardiac output. The mean values for these parameters of all pigs were within normal ranges.

Arterial and venous blood gas values are presented in Table 1. Several significant genotypic differences were found for blood gas parameters. The SS pigs had significantly greater values for arterial pCO_2 ($P < 0.01$), BE ($P < 0.04$), HCO_3^- ($P < 0.07$), and total arterial CO_2 ($P < 0.07$). For arterial pCO_2, there was a significant sex difference, with males having greater values ($P < 0.01$) than females did. In addition, the SS pigs had less BE ($P < 0.07$), but greater HCO_3^- ($P < 0.03$) and total CO_2 ($P < 0.01$) in venous blood than did SR pigs. There was also a trend for SS pigs to have higher venous pCO_2 levels than did the SR pigs.

The increase in both arterial and venous CO_2 levels in SS pigs as compared with SR pigs is likely related to hypoventilation or decreased ventilatory drive. Clinically, the SS pigs in a stressed state show labored, shallow respiration. In addition, other workers have demonstrated that barbiturate anesthesia causes a definite depression of ventilatory

drive as well as a decrease in compliance because of barbiturate-induced atelectasis (Dubin, 1970; Goodman and Gilman, 1975). Even with the common use of an ultra-short-acting barbiturate (Surital) in both genotypes of pigs, the SS pigs still showed statistically significant differences in arterial pCO_2, HCO_3^-, BE, and total CO_2 and in venous BE, HCO_3^-, and total CO_2 as compared with SR pigs. Collectively, the blood gas differences observed in this study point to some type of hypoventilation, ventilation/perfusion inequality, hypoperfusion, or shunting in the SS pig.

Pulmonary function analysis

Pulmonary function values from several species, including those of the pigs in the present study, are presented in Table 2. In general, the pulmonary function values of the pig seem to fall between those of dog and man. When the pulmonary values of those species listed in Table 2 were compared, a relationship was noted between weight and pulmonary function parameters. As the weight of the animal increased, so did FRC, tidal volume, minute volume, and compliance. In contrast, respiratory resistance and rate decreased with increasing weight of the different animal species. The pulmonary function values of the pigs in this study were similar to those reported by others (Attinger and Cahill, 1960) for the pig except that respiratory resistance values were greater in our pigs. The respiratory resistance values were probably greater because of the inclusion of SR pigs in our study.

Genotypic differences were found in several pulmonary function values (Table 3). The SS pigs had significantly less ($P < 0.01$) pulmonary resistance than did the SR pigs. Additionally, the SS pigs had a significantly greater ($P < 0.05$) ratio of physiologic dead space to tidal volume (VD/VT) than did the SR pigs. The SS pigs also had lower (P .0076) ventilation/perfusion ratios ($\mathring{V}/\mathring{Q}$) than did SR pigs. No significant differences were observed between genotypes of pigs for respiratory rate, compliance, tidal volume, or FRC.

A precise explanation for the preceding results of pulmonary function tests is not yet possible. Any stimulation of the sympathetic nervous system leading to a release of norepinephrine or indirectly of epinephrine could elicit bronchodilation, increased heart rate, and blood pressure. If this response was more exaggerated in the SS pig, some of the preceding results could be explained. An exaggerated response to sympathetic nervous system stimulation could result in excess bronchodilation, which could be a reason for the significant decrease in respiratory resistance. The decrease in resistance, along with ventilatory depression due to barbiturate anesthesia, could result in the significant increase in VD/VT as well as the significant decrease in $\mathring{V}/\mathring{Q}$ (Dubin, 1970; Goodman and Gilman, 1975). The SS pigs showed significantly decreased respiratory resistance and a significantly increased VD/VT without differences in tidal volume. There may have been some increase in physiologic dead space

in the SS pig that was not shown statistically in our data. The decrease in $\dot{V}/\dot{Q}$ and the increase in VD/VT reinforce the idea that some type of hypoperfusion (hypoxic vasoconstriction), hypoventilation, or shunting may have occurred in the SS pigs (West, 1979).

As for hypoperfusion, any release of serotonin, histamine, or norepinephrine can cause contraction of arteriolar smooth muscle and constrict blood flow by increased pulmonary vascular resistance. Hypoxic vasoconstriction would work similarly. If a region of the lung was being poorly ventilated, release of local factors would cause contraction of arterioles leading to that area, thus not allowing adequate oxygenation of blood. Hypoventilation, on the other hand, will cause an increase in pCO_2 to the point at which a 50% decrease in ventilation will lead to a twofold increase in pCO_2 (West, 1979). Shunting, however, would not show an increase in pCO_2 because any increase in pCO_2 should increase ventilatory drive and lower arterial pCO_2. Barbiturate depression of ventilatory drive or a true $\dot{V}/\dot{Q}$ inequality are both explanations for the inability to transfer as much O_2 and CO_2 in the SS pigs. If the same amounts of gas are being transferred (because these amounts are set by metabolic demands of the body), the lung with a $\dot{V}/\dot{Q}$ inequality cannot maintain as high an arterial pO_2 or as low an arterial pCO_2 (West, 1979).

It is possible that SS pigs have a twofold problem. First, upon experiencing any minimal stress, they respond very quickly with severe sympathetic nervous system stimulation, which may be magnified as compared with SR pigs by a deficiency of central nervous system dopamine (Altrogge et al., 1980; Hallberg et al., 1983). After stress, there is a fast onset of muscle anaerobic glycolysis as well as an early onset of muscle rigidity. The severe muscle contractions with accompanying anaerobic glycolysis result in large quantities of lactic acid being released into the system. This significantly lowers the post stress blood pH (Topel et al., 1968).

Second, some of the major pulmonary function changes seen in this experiment may also greatly exaggerate the SS pig's ability to handle stress. The shallow, rapid open-mouth respiration seen in the SS pigs, along with elevated VD/VT and a possibly increased physiologic dead space, could result in a greatly reduced alveolar ventilation. A release of serotonin, histamine, and norepinephrine after severe sympathetic nervous system stimulation will cause terminal bronchiolar constriction. This then may be the cause of the elevated arterial and venous pCO_2 levels and the rapid shallow breathing seen in the resting SS pigs in this experiment. The inability to ventilate properly would greatly magnify any metabolic changes by effectively removing the pig's ability to compensate through its respiratory system. Thus, the SS

pig under stress may not have the ability to handle excess lactic acid except through the renal excretion route. Additional pulmonary function studies of SS pigs experiencing stress would clarify these possibilities and provide some explanation of the clinical signs seen in the PSS.

In summary, we have demonstrated significant differences in several hematologic and pulmonary function parameters between pigs of SS and SR genotypes. Our data suggest that pigs prone to PSS have abnormalities of the respiratory system in addition to malfunctions of the muscular and nervous systems.

Table 1. Arterial and venous blood gas values for stress-susceptible and stress-resistant pigs[a]

Blood Gas Variable	Stress-Susceptible (6)	Stress-Resistant (8)
Arterial pCO_2 (mm Hg)	53.96 ± 1.91^A	46.67 ± 1.56^A
Arterial pO_2 (mm Hg)	74.73 ± 5.99	74.43 ± 4.89
Arterial Base Excess (meq/l)	10.72 ± 1.02^B	7.61 ± 0.83^B
Arterial HCO_3 (meq/l)	34.69 ± 1.16^C	31.69 ± 0.95^C
Total Arterial CO_2 (meq/l)	36.00 ± 1.14^D	33.08 ± 0.93^D
Venous pCO_2 (mm Hg)	58.25 ± 2.47	54.86 ± 2.01
Venous pO_2 (mm Hg)	34.79 ± 2.53	33.23 ± 2.07
Venous Base Excess (meq/l)	3.26 ± 1.35^E	6.79 ± 1.09^E
Venous HCO_3 (meq/l)	36.81 ± 1.02^F	33.52 ± 0.84^F
Total Venous CO_2 (meq/l)	38.65 ± 1.01^G	34.28 ± 0.83^G

[a]Data are expressed as the mean ± SEM. Numbers in parentheses indicate the number of pigs per group. Means with the same superscript within a row are significantly different (A: P 0.01; B: P 0.04; C: P 0.07; D: P 0.07; E: P 0.07; F: P 0.03; G: P 0.01).

Table 2. Pulmonary function values for several species of animals

Animal	Body Weight (Kg)	Functional Residual Capacity (l)	Tidal Volume (l)	Minute Volume (l/min)
Mouse (Crosfill and Widdicome, 1961)	.032	.00029	.00018	.21
Mouse (Drorbaugh, 1960)	.024	---	.00015	---
Rat (Crosfill and Widdicome, 1961)	.25	.0015	.0015	.16
Rat (Drorbaugh, 1960)	.203	---	.0013	---
Guinea Pig (Crosfill and Widdicome, 1961)	.69	.00475	.0037	.13
Rabbit (Crosfill and Widdicome, 1961)	2.4	.0113	.0158	.62
Rabbit (Drorbaugh, 1960)	2.6	---	.016	---
Squirrel Monkey (Ulrich et al., 1977)	---	---	.0089	.494
Rhesus Monkey (Liu and Delanter, 1977)	---	.113	.038	1.26
Cat (Crosfill and Widdicome, 1961)	3.7	.066	.034	.96
Dog (Crosfill and Widdicome, 1961)	12.6	.252	.144	3.1
Dog (Drorbaugh, 1960)	17.0	---	.107	---
Dog (Dubin, 1970)	---	---	---	---

Lung Compliance (l/cm H_2O)	Respiratory Resistance (cm H_2O*sec/l)	Respiratory Rate (breath/min)
.00005	480	109
.00029	---	154
.0004	90	97
.000148	---	80
.00126	59	42
.006	25	39
.0024	---	38
.0017	69	57
.0083	31.4	33
.0134	11.5	30
.040	1.3	21
.030	---	22
.046	---	---

Table 2. Continued

Animal	Body Weight (Kg)	Functional Residual Capacity (l)	Tidal Volume (l)	Minute Volume (l/min)
Dog (Dubin and Westcott, 1969)	---	.348[a]	---	---
Dog (Pickrell et al., 1971)	---	.367	.220	---
Pig (Aguggini et al., 1979)	---	---	.170	4.7
Pig (Attinger and Cahill, 1960)	28	.738	.286	6.7
Pig (Intraraksa et al., in press)	---	---	.178	3.26
Calf (Kiorpes et al., 1978)	59	3.4	.500	---
Pony (Mauderly, 1974)	100	5.2	---	17.70
Man (Crosfill and Widdicome, 1961)	70	2.0	.400	6.4
Man (Drorbaugh, 1960)	70	---	.500	---
Pig[b]	48.67	1.07	.233	6.9

[a]Reported as 3.48 l/kg (Dubin and Westcott, 1969).

[b]Values from current study.

Lung Compliance (l/cm H_2O)	Respiratory Resistance (cm H_2)*sec/l)	Respiratory Rate (breath/min)
---	---	---
.048	10.44	24
---	---	30
.057	4.7	24.5
.024	21.02	18.0
.15	3.1	38.8
---	---	---
.200	.90	16
.085	---	15
.035	8.675	29.7

Table 3. Pulmonary function values for stress-susceptible and stress-resistant pigs[a]

Pulmonary Function Parameter	Stress-Susceptible (6)	Stress-Resistant (8)
Respiration Rate (Breath/min)	26.75 ± 4.13	32.66 ± 3.37
Tidal Volume (l)	0.229 ± 0.033	0.326 ± 0.027
Compliance (l/cm H_2O)	0.033 ± 0.008	0.037 ± 0.006
Respiratory Resistance (cm H_2O*sec/l)	6.81 ± 1.03[A]	10.54 ± 0.84[A]
Functional Residual Capacity (l)	1.07 ± 0.06	1.07 ± 0.05
Ratio of Physiological Dead Space to Tidal Volume (VD/VT)	0.460 ± 0.027[B]	0.379 ± 0.022[B]
Dead Space Volume (l)	0.105 ± 0.014	0.092 ± 0.014
Ventilation Perfusion ($\dot{V}/\dot{Q}$)	.378 ± 0.025[C]	.637 ± 0.075[C]

[a]Data are expressed as the mean ± SEM. Numbers in parentheses indicate the number of animals per group. Means with the same superscript within a row are significantly different (A: P 0.01; B: P 0.04; C: P 0.0076).

CONCLUSION

The results of these two projects have been helpful but have generated more questions in the search for a cause for the PSS.

The deficiencies of dopamine seen in the CN, SN and urine of the SS pigs are quite similar to that of man suffering from extrapyramidal disease, especially Parkinson's disease (Barbeau, 1960; Ehringer and Hornykiewicz, 1960; Barbeau et al., 1961; Carlsson, 1972; Hornykiewicz, 1973; Altrogge et al., 1980). The deficiency of dopamine in these pigs may be a result of degeneration of the dopaminergic neurons in the SN. The loss of these neurons and the resulting loss of striatal dopamine, which is related to the tremor and rigidity seen in Parkinson's disease (Bernheimer et al., 1973; Birkmayer et al., 1975; Hornykiewicz, 1975), may be related to the tail tremors before stress and the severe rigidity seen in the SS pigs after stress. Concurrent deficiencies in norepinephrine and epinephrine were also shown in this study. In rats, a rapid depletion of both norepinephrine and epinephrine was shown to occur accompanying any type of physical or psychological stress (Bliss and Zwanziger, 1966; Corrodi et al., 1968; Nakagawa et al., 1981; Iimori et al., 1982). These reduced levels can be easily explained by the very nervous disposition of the SS pig who

seldom adapts to new environments or any type of handling such as intravenous catheterization, stressing or blood sample collection.

Concurrent deficiencies in the respiratory system of the unstressed SS pig are also present. These changes revolve around decreases in pulmonary resistance, a decrease in the ventilation perfusion ratios, increases in Vd/Vt and possible significant increases in the physiologic dead space (Vd). The decreased ability to ventilate is easily demonstrated by the labored respiration seen in the stressed SS pigs. These SS pigs with labored, shallow open mouth respiration are only exchanging gases within physiologic dead space and have little ventilation of the alveolar regions of the lung.

So with all of these changes, the exact etiology of the PSS is still uncertain. The deficiency of dopamine in the basal ganglia would result in a definite lack of central nervous system (CNS) modulation of descending motor pathways. The other connections of the basal ganglia to the cortex, thalamus, and many other regions of the brain encompass very important areas of possible malfunction. So, in the end, the PSS susceptible pig may have a major deficiency in modulatory control over motor systems.

The deficiencies in pulmonary function are also difficult to explain. The CNS modulatory control problem may greatly exaggerate any sympathetic stimulation to the lung

thereby changing normal pulmonary function. Also, any anesthesia with barbiturates will affect the lung function because of the respiratory depression effects of the drug. Additional research involving lung function as a pig initially experiences and reacts to stress may also shed some light onto what other changes may be present.

All of these changes seem secondary to some unknown problem which is stimulating uncontrolled anaerobic glycolysis which in turn cannot be accommodated through increased respiratory ventilation. Further research into neuron number as well as GABA function in these brain regions may shed some light on the etiology of the PSS.

It seems very likely that the basic lesion lies in the basal ganglia, particularly since the clinical signs of the Parkinson's patient are suspiciously similar to that of the SS pig. Determining the appropriate stressors as well as isolating the exact regions of the brain will make this research a very challenging hypothesis to explore. Finally, all of this work makes the PSS susceptible pig a very likely animal model for the research into the extrapyramidal syndromes, especially Parkinson's Disease.

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