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BEHAVIOR AND THE BALANCE BETWEEN NOREPINEPHRINE AND SEROTONIN

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Abstract. The functions of the central monoamines Norepinephrine (NE) and Serotonin (5HT) can be clarified by the study of behaviors of rats administered selective monoamine toxins. In his home environment the low NE rat has drive deficits and is lethargic, tending to remain in his burrow, but in novel envronments this animal acts less frightened than Controls. The low 5HT rat is conversely active and exploratory in familiar environments but frightened in novel environments. These two animals model aspects of depression and anxiety, respectively. 5HT can be thought of as placing the brain into a state of consciousness appropriate for an animal in his nest (i.e., 5HT neurons act as relaxers), and as involved in a type of positive affect related to security, whereas NE neurons are dominant when an animal is vigilant, foraging out in the environment and are involved in a type of positive affect related to goal-directed approach arousal. Monoamine toxins may be produced when the behaviors elicited by these central neuronal systems are negatively reinforced (extinguished).

I worked closely with Professor Jerzy Konorski during my Postdoctoral Fellowship at the Nencki Institute. Together we did several experiments, including one demonstrating that the classically conditioned salivary response and an instrumental lever-pressing response could be separated in dogs trained on a task especially designed to do this (Ellison and Konorski 1964). But it was only when the instrumental response was

highly overtrained and became virtually automatic in these animals that the separation could be demonstrated. In the initial stages of learning in our dogs these two responses had been closely interrelated, as originally discovered by Konorski and Miller (1933). During this period Professor Konorski talked with me at length about some of the developing ideas which culminated in his book *The integrative activity of the brain.* One of these involved the relationship between drives, on the one hand, and antidrives and satiety mechanisms, on the other (Konorski 1967). We discussed how this related to research on reciprocal relationships between lateral hypothalamic drive mechanisms and medial satiety centers (Stellar 1954, Hoebel and Teitelbaum 1962). When I later studied aggressive and feeding behavior after neural isolation of the hypothalamus (Ellison and Flynn 1968) reciprocal balances between medial and lateral areas was implied. For example, a rat with lesions of the lateral hypothalamic "hunger" area actively rejected food placed in his mouth not so much because his hunger drive was decreased but because of the now unbalanced medial satiety signals (Ellison et al. 1970).

Anatomical and biochemical evidence implying brainstem control of emotion

My subsequent research has continued the study of similar issues but at a midbrain level. My interest in this area was stimulated by classical studies of the brainstem reticular system (Lindsley 1961, Magoun 1963, Moruzzi 1972) which showed that the neuronal circuitry within the brainstem core regions in and around the reticular formation were important controllers of consciousness, attention, and arousal, and that this control circuitry had projections both caudally and rostrally. Inhibitory and facilitatory pathways were described where lesions or electrical stimulation would facilitate or inhibit lower spinal motor reflexes, spinal and brainstem sympathetic and parasympathetic reflexes, cardiovascular and respiratory centers, and produce unresponsiveness ("unconsciousness") or enhanced responsivity ("arousal") in higher sensory, motor, and integrative centers. Massively branching cells from this region were found to radiate out to innervate wide portions of the brain simultaneously and to show long cycles of activity and inactivity, presumably reflecting the primitive brain's control over arousal (Scheibel and Scheibel 1967).

Biochemistry and neuroanatomy then intersected with the demonstration of Norepinephrine (NE) neurons with cell bodies in the lateral reticular system and Serotonin (5-hydroxytryptamine, or 5HT) neurons more medially in the raphe system (Dahlstrom and Fuxe 1964, Ungerstedt 1971). Compelling lines of evidence implicated these two monoami-

nes in the control of sleep, aggression, feeding, sexual behavior, spinal reflexes, pain sensitivity, hormonal release, stress reactions, and brain arousal (see Fuxe et al. 1971). Serotonin appeared to be necessary for slow-wave sleep norepinephrine for arousal and REM sleep (Jouvet 1972). It seemed clear that these monoaminergic circuits were involved in the control of many diverse brain functions in an extremely general, all pervasive manner. With cell bodies lying principally in the brainstem sending highly branched axons to many other parts of the brain, the cells containing the monoamines NE and 5HT appeared poorly designed to carry discrete pieces of information (they branched too diffusely) but rather well designed to place the entire brain into different states of arousal, emotion, or consciousness as demanded by the survival needs of the organism (see Kety 1967).

Studies from the psychiatric clinic implied that alterations in NE and 5HT, as well as the third monoamine, Dopamine (DA), were present in emotional disorders in humans. Drugs such as reserpine and tetrabenezine, which decreased the levels of the monoamines (by preventing their storage), induced a psychological depression in some humans (Bunney and Davis 1965); in monkeys and lower animals they produced a lethargic, withdrawn state characterized by irritability, weight loss, social withdrawal, decreased activity, and other behaviors which seemed to mimic those of human depressives (McKinney et al. 1971). A common characteristic of a variety of pharmacological agents which had been found efficacious in the treatment of depression was that they all raised the levels of the monoamines at their synaptic targets (Schildkraut and Kety 1967, Davis 1970) — monoamine oxidase inhibitors doing so by inhibiting the breakdown of the monoamines and tricyclic antidepressants doing so by blocking the reuptake of NE and 5HT. There was also some evidence of lowered levels of these two amines (or, more precisely, of their metabolites) in depressed humans and suicide victims (Coppen et al. 1972, Maas et al. 1972).

Attempts to construct animal models of emotional disorders

My investigations into this area began when 6-hydroxydopamine (6-OHDA), a neurotoxin which lesioned NE terminals, was introduced to me by a graduate student of mine, Al Sorenson. We began an attempt to model depression by studying the behaviors of rats after 6-OHDA lesions made with small, multiple injections of 6-OHDA directly into the brain. Intraventricular injections of 6-OHDA had been found to lead to a persisting biochemical depletion of central catecholamines (Uretsky and Iversen 1970) which was the result of actual terminal destruction (Bloom et al. 1969). Although when administered in large doses 6-OHDA

also produced widespread, non-selective neural damage (Hedreen and Chalmers 1972), when multiple small doses were given the central lesions were more selectively confirmed to NE terminals (Simmonds and Uretsky 1970).

In his Ph. D. thesis Sorenson studied animals with two levels of NE lesions. One group was given three daily 25 μg intraventricular injections of 6-OHDA and allowed to recover ("6-OHDA × 3"). A second group was initially lesioned in the same manner, allowed to recover, and relesioned 2 weeks later ("6-OHDA × 6"). This was done in an attempt to contrast the behavior of rats with partially lesioned, partially recovered NE circuitry ("6-OHDA × 3") with that of animals with more extensive, more nearly maximal (asymptotic) selective lesioning ("6-OHDA × 6").

When the behavior of these two groups were compared to controls, it was found that both lesioned groups showed altered emotional reactivity. The "6-OHDA × 6" animals did show low arousal behaviors suggesting depression but the partially lesioned group was paradoxically hyperactive in running wheels, hyperresponsive to handling, showed heightened shock-elicited aggression, and had a potentiated amphetamine activation effect. These exaggerated arousual behaviors in the partially lesioned, partially recovered "6-OHDA × 3" rat correlated with the increased NE turnover in the brainstem which had been observed to gradually develop following 6-OHDA lesions (Nakamura and Thoenen 1972) and the sprouting observed in lesioned NE axons (Katzman et al. 1971). In the discussion section of this paper we pointed out that if the "6-OHDA × 6" rat is used as an animal model of retarded depression (Bunney and Davis 1965, Schildkraut and Kety 1967), the exaggerated ("supersensitive") NE behaviors shown by the partially lesioned, partially recovered 6-OHDA rat would seem to model heightened arousal, activity, and irritibility seen in chronic but incomplete depression and in childhood hyperkinesis (Sorenson and Ellison 1973).

The results of this experiment indicated that the best way to produce an animal with a basic low NE depression was to lesion him, let him recover, relesion him, and then behaviorally test him. Armed with this knowledge, a second graduate student of mine, David Bresler, conducted as part of his thesis a second experiment (Ellison and Bresler 1974) which permitted a comparison of the behavioral syndromes of animals with extensive NE lesions ("6-OHDA × 6") to that of animals with extensive depletion of 5HT (chronic administration of para-chlorophenylalanine, PCPA), and to that of animals depleted of both (6-OHDA and PCPA). Depletion of both NE and 5HT was of special interest because reserpine, which depleted all monoamines, maximally induced dysphoria in humans.

This experiment represented an attempt to mimic the reserpine model of dysphoria, and so a battery of tests were constructed to compare the effects of relatively natural positive and negative reinforcers in the drug-treated rats. This was done because the core symptom of dysphoria is a shift in affect towards negativity, and it was reasoned that an animal with a shift in emotional or affectual control towards negativity would be less responsive to positive reinforcers but more reactive to aversive stimuli.

The results of this experiment were clear. Only the animals with depletion of both NE and 5HT (i.e., the "6-OHDA + PCPA" group) were less responsive to all positive reinforcers used but more reactive to all negative reinforcers used, and only these animals with double monoamine depletion were helpless in open field (showed a suppression of all behaviors). The behavioral syndromes of animals treated with only 6-OHDA were then compared with those of animals treated with only PCPA in an attempt to better understand these two drug manipulations which summated to produce maximal behavioral disruptions. These two groups ("6-OHDA alone" and "PCPA alone") behaved conversely on most tests, validating the hypothesis that NE and 5HT exert partially opposed, balanced actions on the nervous system (Brodie and Shore 1957). "PCPA" rats showed freezing postures and decreased locomotion in open field, became "agitated" when given visual stimulation, overconsumed sucrose, and showed increased shock-elicited aggression. They were anxious and frightened animals with low pain thresholds. "6-OHDA" rats behaved conversely. They fearlessly ambulated more in novel environments than Controls, decreased their activity levels when stimulated, had hunger drive deficits, and showed an initially decreased rate of rearing (observing) responses in open field. Other evidence relating lowered levels of NE to the symptomatology of depression (retardation) and lowered levels of 5HT to the symptomatology of anxiety (Buneo and Himwich 1967, Carlsson et al. 1969) was compatible with these results. For example, the low 5HT (PCPA) rat predominantly reacted in open field by assuming fear postures and becoming agitated when stimulated whereas the low NE (6-OHDA) rats showed hunger drive deficits and a dull, retarded kind of slow onset but slowly habituating rearing in open field and became progressively more lethargic with continued stimulation.

We decided to further pursue these results using another way of depleting 5HT: making central 5HT lesions with 5,6 dihydroxytryptamine (5,6 DHT), a compound which had been reported to destroy central 5HT terminals and axons (Baumgarten et al. 1971). As in the initial 6-OHDA study we used small, multiple injections and lesioned two

groups, one in which small biochemical lesions were made and a recovery period allowed ("5,6 DHT × 3") and a second group which was treated similarly but again relesioned after recovery ("5,6 DHT × 6"). The results of this experiment were that the more extensively 5HT depleted group ("5,6 DHT × 6") again were frightened, anxious animals: freezing but rearing near the walls in open field, being hypersensitive to stimulation, and consuming small, frequent meals. They also had decreased responsivity to the analgesic properties of morphine. Again, a converse, "supersensitive" syndrome was observed in the animals in which partial lesions were made and a recovery period allowed ("5,6 DHT × 3"); these animals showed increased locomotion but decreased rearing in open field (more like a 6-OHDA animal), consumed large, infrequent meals, and had exaggerated morphine analgesia. This "supersensitive 5HT" result was consonant with the exaggerated recovery of 5HT levels in the brainstem and the sprouting observed to gradually develop following 5HT lesions (Baumgarten 1973). In the discussion section of this paper we pointed out that the withdrawn, inattentive behavior based on exaggerated recovery from a fundamental anxiety in the partially lesioned, partially recovered "5,6 DHT × 3" rat might model some aspects of childhood autism and schizophrenia (Diaz, Ellison, and Masouoka 1974).

Ne-5HT balance and the ergotropic-trophotropic dichotomy

These results suggest that the functions of NE-5HT balance in the nervous system are similar to the ergotrophic–trophotropic systems described by Hess (1957). Hess, in studying the behavior of unanesthetized cats during stimulation of the brain, found a system running through the anterior hypothalamus, supra- and preoptic areas, septum, and inferior lateral hypothalamus where stimulation elicited rest-like, parasympathetic, or digestive behaviors such as decreased blood pressure and respiration, micturition, defecation, pupilloconstriction, and sleep. This system seemed part of a trophotropic system underlying rest, sleep, and digestion. Stimulation of a converse system (running from the anterior midbrain to the more posterior and medial hypothalamus) produced arousal (dilation of pupils, increased blood pressure, activation of respiration) and increased motor excitability, culminating in fight or flight. This system he named the ergotropic system. The two systems became intermixed in the midbrain.

Others have noted the similarity of the balanced functional systems Hess proposed to account for his results (1966) to noradrenergic–serotonergic balance (Brodie and Shore 1957, Weil-Malherve and Szara 1971, Jouvet 1972). NE tends to be distributed more laterally and 5HT more

in ventricle-near regions of the brain (Vogt and Wilson 1972). As with the antagonistic ergotropic–trophotropic dimension, noradrenergic and serotonergic circuitry appear to be mutually antagonistic systems. This implies that these two neurotransmitters vie for control, reciprocally inhibiting each other. They exert opposed effects on a variety of functions, including temperature regulation (Feldberg, and Myers 1964), autonomic reflexes (Hare et al. 1972) and arousal (Jouvet 1972). Likewise, many of the functions performed by the parasympathetic nervous system are concerned with the conservation and storage of energy, while the sympathetic nervous systems rules during the fight or flight situation (Cannon 1939). Brodie and Shore (1957) first pointed out the parallel between parasympathetic-sympathetic balance and serotonergic-noradrenergic dominance: drugs which cause a release of serotonin are correlated with parasympathetic activity, while those which are heavily noradrenergic are usually sympathetic stimulants (Goodman and Gilman 1970).

Simple models often serve to clarify one's thinking, and it may be of benefit to consider this extremely basic functional dichotomy between behaviors which expend energy (such as flight or fight) and those which conserve energy (such as rest) at a primitive stage of evolution — perhaps that of the primitive aquatic vertebrate. The monoamines NE and 5HT, with cell bodies deep in the brainstem, probably evolved at such a primitive stage in evolution. The basic mechanisms for meeting the needs and regulations appropriate for survival in the life of a primitive fish or terrestrial vertebrate are considerably less complicated by higher circuitry than in higher mammals, and a consideration of their actions at this simple level may clarify their role in affect. Glickman and Schiff (1967) trace the most fundamental mechanisms of reinforcement to such a primitive aquatic vertebrate, pointing out that at its heart reinforcement involves the selective facilitation of motor patterns organized within the brainstem. As the higher brain continued to evolve, learning came to play an increasingly more pervasive role, but at this primal level reinforcement consisted of the facilitation of activity in neural systems which mediated species-specific response patterns — i.e., consummatory acts such as feeding, aggression, sex, and escape from danger. Others have pointed out that even the most simple organism must regulate a fundamental balance: that between energy expenditure and energy conservation. For example, in order to replenish food reserves, the animal must venture from a place of rest or hiding into the environment, but this burns up energy. Energies expended during moments of stress must be replenished, and in fact energies must be stored away to stand ready for an emergency:

"There must be proper homeostatic balance between the activity of the parasympathetic, the accumulator of reserves, and that of the sympathetic, the spender of energies" (Pick 1954).

"It is, therefore, the natural opposition between these two processes in the body — between saving and expenditure, between preparation and use, between anabolism and catabolism — and the correlated opposition of central innervations, that underlie the antipathy between the emotional states which normally accompany the processes". (Cannon 1939, page 336).

Two distinctively different and partially opposed types of control of brain states of operation are suggested by this dichotomy, including fundamentally different types of reinforcement or affectual control. An aid to thinking about how these concepts relate to affect is a consideration of the different physical locations in which these two states occur. In most primitive animals there is some place or ecological niche where energy conservation occurs (rest, digestion, regeneration). This might be the school for a fish (Morrow 1948), the bird's nest, or the rat's hole. Conversely, energy is expended out in the environment, but it is principally out in the environment that the consummatory responses biologically necessary for survival are made (such as predation and food seeking, exploration, and territorial defense). When the primitive fish or terrestrial vertebrate was resting securely in the middle of the school, or in a safe hiding place such as his hole or nest, one type of brain and body state was appropriate: there are a huge number of physiological functions which would have adaptively been turned on, energized, or allowed to operate — all of the trophotropic functions. As the organism leaves the nest this state of brain operation must be shut off and, when out meeting the environment, another, almost converse set of physiological and behavioral circuits are appropriate and should be energized (sympathetic dominance, arousal and vigilence high, approach and withdrawal systems activated and ready, etc.), corresponding to the ergotropic functions described by Hess (1964).

Furthermore, two antagonistic (or at least very different) types of positive affect are suggested: one which pulled the primitive animal out of hiding and into the environment by positively rewarding him when he engaged in appetitive consummatory responses, but another which pulled him back into the security of the nest by satisfying a reciprocal set of needs. This emphasis on affects is implied by the words ergotropic (toward work or energy expenditure) and trophotropic (towards nourishment).

These two types of positive affect remind me strongly of a debate which I encountered during my Ph. D. training at Yale University bet-

ween two learning theorists, F. D. Sheffield and N. E. Miller. Sheffield (1966), in his drive induction theory of reinforcement, described an approach reward system whereby the sight of an appropriate goal object (i.e., food, sex, novelty) elicited a state of arousal which fed into motor responses and goaded the animal toward the consummatory response. Miller (1959) espoused a drive reduction theory and held that the primary reinforcer was the reduction of strong stimulation, such as in fear learning (shock avoidance) and feeding behavior (satiation). 5HT can be thought of as placing the brain into a state of consciousness appropriate for an animal in his nest (i.e., 5HT neurons act as relaxers), and as involved in a type of positive affect related to security, whereas norepinephrine (NE) neurons are dominant when the animal is vigilant, foraging out in the environment and is involved in a type of positive affect related to goal-directed approach arousal. But if two fundamental positive affects can be discerned, two converse, negative affectual poles must also be recognized. For example, as the primitive animal left his nest and came under the control of goal directed approach circuitry, which goaded him forward and fixated his attention on goal objects, he had to simultaneously maintain a balanced watch for danger. The greater was the animal's drive, the farther out into hostile territory he had to venture. This was correlated biochemically with increases in NE but the lowering of 5HT. This can be schematically represented as in Table I: the converse of a high NE arousal is a low NE depression while the converse of high 5HT relaxation is a low 5HT anxiety.

TABLE I

Schematic representation of NE–5HT balance as it relates to territoriality and affect

Physical location	Periphery of animal's territory	Center of animal's territory
State of monoamine balance	NE High 5HT Low	5HT High NE LOW
Positive affect	Excitement, approach toward goal objects	Security and relaxation
Negative affect	Anxiety	Lack of arousal, depression

Effects of monoamine poisons in a more natural environment

But this scheme is highly oversimplified. Complex effects on behavior of the monoamine poisons 6-OHDA and 5,6 DHT can be especially well seen in a rat colony which my students and I have constructed. It has a large ($4 \times 4 \times 6$ m) arena with a straw-covered floor, ramps lead-

ing to a water tower, climbing structures, and numerous high ledges. At one end of this arena are 12 holes leading through tubes to straw-lined burrows. At the other end is a valve leading to a separate feeding area, where food is available for 1 hour per day. We have raised two colonies, each of 24 young male hooded rats, in this environment. We introduce the rats when they are quite young and allow them about 2 months to grow and set up dominance hierarchies. They are then captured, marked with a fur dye, and holes are drilled in their skulls above the lateral ventricles. The rats are then returned to the colony for a recovery period, during which their behavior is observed. We then recapture the rats and, under ether anesthesia, inject into their brains on 3 successive days either 25 μg of 6-OHDA, or 10 μg of 5,6 DHT, or saline. They are then returned to the colony.

During the first week after lesioning there are remarkably different behaviors in the 6-OHDA and 5,6 DHT groups, with the Controls intermediate. The low NE (6-OHDA) animals stay in the burrows more than any other group, but when they come out they engage in more fights than Controls. The low 5HT (5,6 DHT) animals stay out of the burrows, in the arena, more than Controls, and they more frequently than any other group fight and mount. But they also run in activity wheels present on the arena floor, and they approach the human observers, looking and sniffing through the wire screening, more than any other group. They seem curious and exploratory in this familiar environment. While the animals were still in this initial stage, we removed them and tested them in a modified open field test (a novel environment consisting of a round enclosure with a small table under which the rats could hide). In this novel environment the 5,6 DHT animals acted more frightened than controls (they hid under the table more) whereas the 6-OHDA animals hid less than controls. Yet in the familiar colony environment the 5,6 DHT animals stayed in their holes less than controls (acting less frightened) and the 6-OHDA animals behaved conversely (Table II).

This shows that low 5HT is best thought of as correlated with a state of consciousness appropriate for being out in the environment (sensitive to stimulation, etc). In familiar environments (where approach behaviors have been positively reinforced) this means increased activity and approach toward stimulation but in novel, untested environments this leads to fear and paranoia. Low NE is the converse: a state of consciousness of being at the center of one's territory. In the colony environment this means the low NE rats stay in their burrows, but in novel environments it means they are less frightened than the other animals.

The effects of being in a chronic state of NE-5HT imbalance become progressively more disruptive. After about 3 weeks following the lesion-

TABLE II

Effects of familiarity of environment on the behavior of animals in NE–5HT imbalance. When tested in a colony situation which is their home environment, low 5HT animals are out of their holes more than Controls and approach humans. But when in a novel environment these same animals are frightened: they freeze and hide. The low NE animal in the colony situation stays in his hole, but in a novel situation is less frightened than Controls

	Low 5HT (5,6 DHT lesions)	Low NE (6-OHDA lesions)
Familiar (home) environment	"Aroused and exploratory" In burrows less than Controls Running in activity wheels Approach humans	"Driveless and withdrawn" Stay in burrows more than Controls Inactive, last to come to feeding
Novel environment (open field test)	"Frightened and paranoid" Decreased locomotion (freezing) Increased rearing (vigilant) Stay near walls or hide under objects	"Fearless and non-vigilant" Locomote more than Controls Decreased rearing (non-vigilant) Enter center of field, hide less than Controls
Drug model	Amphetamines, LSD	Heroin, barbiturates, tranquilizers

ing in the colony the low 5HT animals have become extremely vicious, and in both colonies the largest 5,6 DHT rat began to terrorize the entire colony during and after feeding, attacking and biting animals in a wild frenzy and driving all of the other rats up into the rafters or back into the burrows. The 6-OHDA rats, during this same time, progressively fell in dominance, as measured by order of entrance into the feeding area and outcome of fights. It is thus some time after lesioning that the best social models of anxiety and depression are observed. After about 45 days the colony appears to recover to a more normal level of social behaviors; presumably this reflects the regrowth of the damaged circuitry. But persisting deficits can still be detected in the lesioned animals.

Possible autoproduction of monoamine toxins

The fact that one can mimic affective disorders and emotional imbalances with biochemical depletors tells little about how these chemical systems become "depleted" in clinically dysphoric humans. It seems likely that the type of "depletion" relevant for an understanding of prolonged affective negativity in humans is rarely a simple lack of available

transmitter material (such as might occur in starvation), but rather represents a more complex reaction related to an inability to cope (or hostile introjects) and the subsequent extinction of monoaminergic innervations. According to psychological theories of depression it is prolonged responding in vain (i.e., excessive non-reinforcement) which leads to apathy and turning inward. Neurally this might correspond to the extinction of NE innervations. Both NE and 5HT axons have a remarkable ability to regenerate and sprout following their experimental destruction (Katzman et al. 1971, Bjorklund et al. 1973). It is possible that these primitive midbrain neurons have a primitive way of learning — that in response to environmental influences they rearrange or switch their output connections through the physical growth of connections when reinforced and the destruction of terminals when extinguished.

This can be restated in a simple neurochemical model (Ellison et al. 1975). Monoamine neurons release their transmitter material into the synaptic cleft when they fire; at some later time, they take it back up and restore it for use again. It can be hypothesized that when the behaviors produced by these neural systems are negatively reinforced or extinguished an erase message is sent through these circuits, converting the neurotransmitter out in the synaptic cleft to a deactivated or autotoxin form. The subsequent reuptake of this modified monoamine would deactivate the negatively reinforced innervation (Stein and Wise 1971). Tricyclic antidepressants block the reuptake process and would therefore block this extinction process. An implication of this is that one factor in the mode of action of tricyclic antidepressants may be that of setting a bias which tends to prevent the extinction of monoaminergic innervations and their erosion by the wear and tear of daily life. This would explain why tricyclics take several weeks to become clinically effective: a similar time span is observed for the life vesicular stores and for monoaminergic sprouting.

Speculations on the third monoamine, Dopamine

The above discussion has focussed on NE and 5HT because these have been the subject of my recent research. But while reading Tinbergen, one is struck with some similarities between the development of behaviors Tinbergen calls "derived" and the development of dopaminergic (DA) systems. Tinbergen (1952) cites a large variety of examples where simple stereotyped motor activities such as grooming, pecking at the ground, wing-flapping, and head-tossing appear out of context with the situation an animal is in. They occur when the animal is in an irresolvable approach–withdrawal conflict. These he calls "displacement activities":

"These observations show that two drives, attack and escape, are activated at the same time. Neither can find an outlet in complete behavior, for they are incompatible, but the alternation of mere intention movements seems to be a sufficient outlet so long as the drives are not too strong... Essentially the same situation, only in a more intense form, leads to displacement activities. Our hypothesis therefore is that the displacement activities are outlets through which the thwarted drives can express themselves in motion". (Tinbergen 1952, p. 12).

Because displacement activities come to have an effect on other members of the same species (signalling intentions, etc.), according to Tinbergen they started a new evolutionary development during which the displacement activities became ritualized, resulting in courtship dances and sexual displays, threat postures, etc., finally breaking free from the original structures. This permitted the evolution of voluntary behavior ("neurophysiological emancipation") for it finally broke behavior free from the immediate control by approach and withdrawal circuitry.

These considerations seem to correlate with dopaminergic systems in several ways. DA systems to the caudate represent a phylogenetically more recent development than NE and 5HT and clearly are heavily involved in the control of voluntary behavior (Hornykiewicz 1966); DA stimulation has been implicated in stereotyped behaviors, elicited by a hyperaroused nervous system. A variety of experiments have shown that amphetamines at high doses or DA receptor stimulators lead to simple stereotyped behaviors (chewing, gnawing, and grooming in rats; fingering of objects, etc. in humans); because these disappear with lesions of the caudate or DA receptor blockers they are thought to reflect the appearance of DA circuits (Randrup and Munkvad 1970, Snyder 1972).

Dopaminergic behaviors are especially apparent in neuroses and compulsions. The stereotyped behavior and thought patterns of schizophrenics have been widely related to hyperaroused DA circuitry, and those drugs used to treat schizophrenic symptoms are generally DA receptor blockers (Anden et al. 1970). After watching Liddell's sheep in training conditions designed to produce experimental neurosis, Tinbergen observed that:

"This work seems to show that neurosis may be the result of long-continued thwarting of the escape drive. The fact that displacement activities appear before a neurotic stage is reached, or rather that neurosis follows a long period of thwarting of a drive and consequent displacement activity, indicates that outlet through displacement behavior is

a form of defence against neurotic disorded of the central nervous system, enabling it to 'get rid' of the surplus of impulses which would otherwise damage it". (Tinbergen 1952, p. 23).

But I believe that the most important contribution to the schizophrenic crisis is the dissolution of 5HT control of the nervous system. Eventually it is the animal with no place to hide or rest which functionally disintegrates.

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