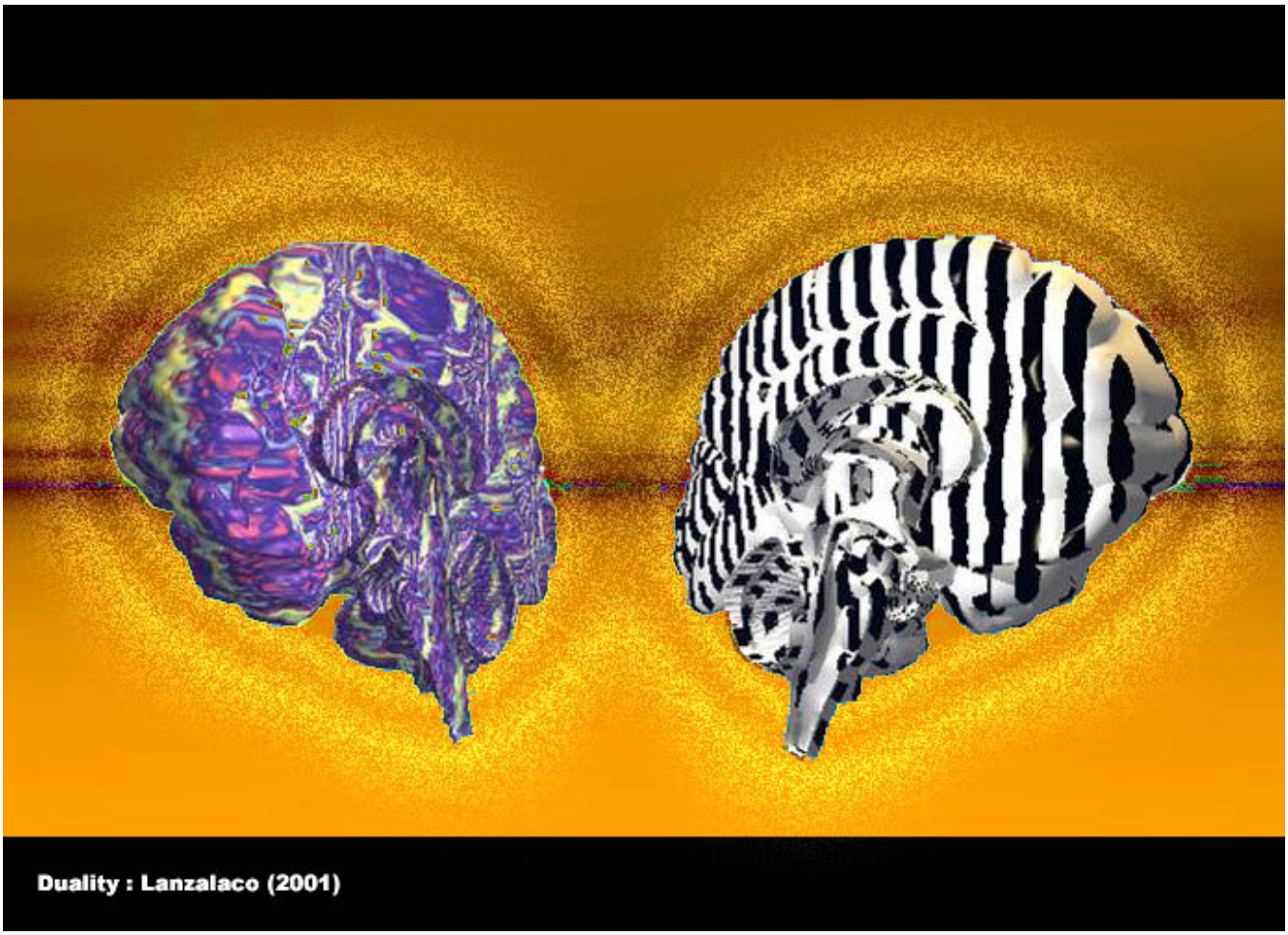
NEUROCHEMICAL MODULATORS

(3rd paper of supporting evidence for a Brain Dipole model)

Supported by Wajidz Zia, Edinburgh University Dept of Psychology.



ABSTRACT

While the Glutamate / Gaba system dominates the 100 billion neurons in the brain. The more well known transmitters such as dopamine and serotonin are co-transmitters which work in conjuction with glutamate to modulate brain systems. The numbers of these co-transmitters is much smaller about 100,000, (estimate) yet they profoundly model our behaviour.

A case will be made that these chemicals with their receptor groups, are the basis of brain modulation which fits the lines of convergent, digital / divergent, analouge axis within the LCH/RCH (left cerebral / right cerebral hemispheres) respectively, and that this is due to the acid / base chemistry of Tyrosine / Tryptophan from which these co-modulators are derived.

SECTION 4

NEUROCHEMICAL MODULATORS

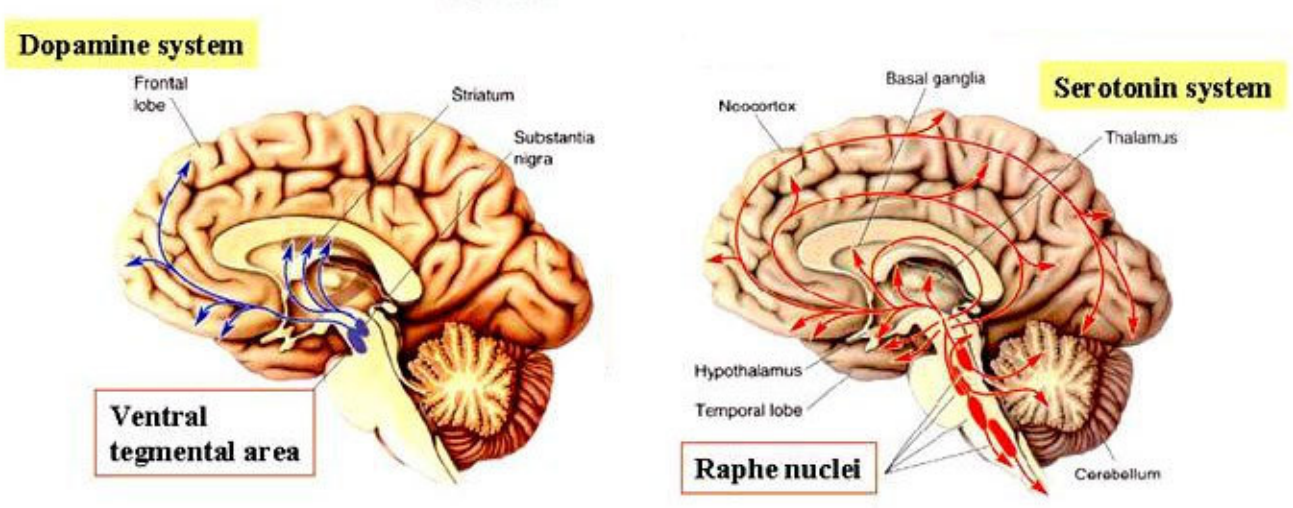
INTRODUCTION

Glutamate is the neurotransmitter for cortical processing and memory, with Gaba acting as it's inhibitory mechanism. The remaining transmitters such as serotonin and dopamine account for only a very small number of neurons. These are located in direct pathways from the limbic regions to the executive areas which allows them profound effects on our behaviour and perceptions. These are said to be "Co-modulators" because they innervate and entwine coming to rest within the larger glutamate / gaba neurons and interneurons.

The main focus of this paper, is to prove inverse neurochemical symmetry between cerebral hemispheres. The co-modulators Dopamine and serotonin are derived from the two amino acids with the most re-active aromatic rings, Tyrosine and Tryptophan respectively.

Also apart from unravelling a rich legacy of redundant medical research for a brain Dipole theory, which follow from a series of previous sections (01,02,03) It is also sought to propose that the inverse behaviours which arise from these co-modulators are due to the properties of inverse chemistry. The evolution of systems to alter a chemical group to reverse the electrogenic properties of a molecule into a similar but oppositely behaved partner seems to be consistent throughout organic chemistry.

The focus here is the amino acids from which the co-modulators are derived, along with their receptor families and how they affect the primary brain network. If it is agreed after reading this that these modulators are not arbitrary keys, but that the chemical and physical properties of the keys, reflect their role. Then hopefully this will encourage more predictions taken from systematic methods like this used here, *(application of Tensegrity)* to be applied elsewhere.



Opposite differences between innervation of serotonin and dopamine. Dopamine operates within key areas of regulation. Serotonin proliferates everywhere. In spite of this they are still lateralized. In the left and right hemispheres respectively.

1.1 BEHAVIOURAL MANIFESTATIONS OF DOPAMINE AND SEROTONIN.

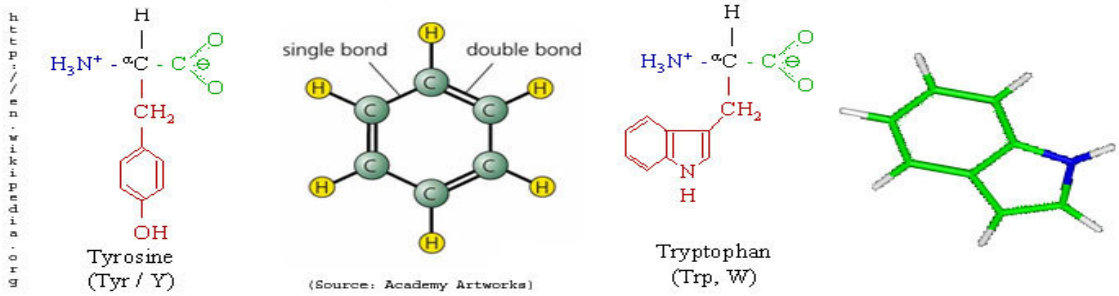
A good place to begin, before getting into details, is to observe these chemicals modulating human behaviour.

Dopamine effects on behaviour are centred round risk and rewards. (62, 63) Within a social group context higher dopamine levels are correlated with dominant behaviour. (66) The inverse is true of serotonin.. Within a group, the pattern reflecting the dynamics of a mammals serotonin level becomes reflected within their social status, primarily reducing the dominance hierarchies, (70, 72)

These effects on personal and group behaviour could not be more opposite. Perhaps reflecting a push / pull axis of social behaviour. The depressive energy dip associated with lowered serotonin implies that serotonin appears to be directly linked to the dynamics of energy expenditure. During this period, the increased aggression and impulsive risk taking could be the manifestation of the remaining dopamine levels driving a system which is higher than normal in cognitive executive deficits from depression.

Conversely primates lacking dopamine receptors seem to be unable to maintain any kind of behaviours involved in reducing energy expenditure for maximum risk and reward. Instead the primates maintained continuous energy levels. (62) These kinds of unrewarded energy levels are usually associated with creative or social behaviours. Generalized evidence exists that the mixture of right brain hemisphere and the chemical groups from which serotonin is derived are implicated in creativity, family bonding and spirituality. (74,76,78)

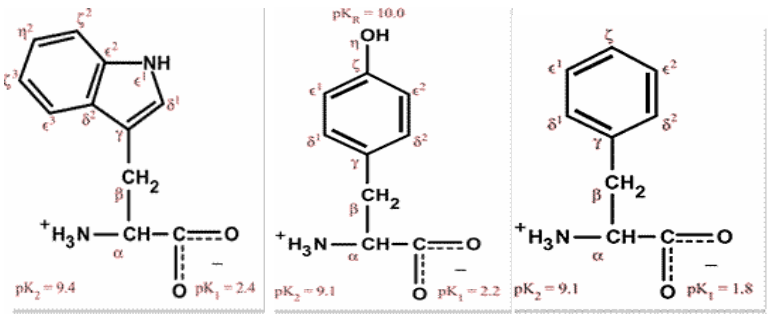
2 CHEMISTRY OF CO-MODULATORS.



Tyrosine and Tryptophan with their aromatic rings have the greatest mass and volume of all the amino acids. (82) Tyrosine from which dopamine is derived is said to belong to Hyperpolarizing chemical groups (84) while Tryptophan from which serotonin is derived is said to belong to depolarizing groups (84) Of these two amino acids, tryptophan is the bigger and due to the addition of a pyrrole ring, found in indole alkaloids. (86) The electrophilic susceptibility (attractor of electron loving reagents) at the Amide (NH) position makes it ideal electron rich source for donation of electrons in Cation – Pi reactions.

	pKa	Solubility	Side Chain	Residue accessibility	Van der Waals	
Tyrosine	9 - 12 (88)	0.0453 (90)	Hydrophilic (82)	0.13 (88)	141	
Tryptophan	- (90)	1.136 (90)	Hydrophobic (82)	0.07 (88)	163	

Tyrosine has a phenolic ring. The hydroxyl, can give up it's proton for Tyrosine to become negatively charged Anion. Tryptophan and Tyrosine could have many possible interactions, they could become neutral, positive or even Zwitterionic. This is also true of the neurotransmitters derived from them. (92, 94) The nature of the previously mentioned observed human behaviours and chemical reactions, from the derived families of each of these aromatics, such as dopamine and serotonin, would predict that they are likely to react dominantly as inhibitory and excitatory respectively. The studies of receptors, agonists and transporters which follows, argues that the respective receptor groups for dopamine and serotonin, have both inhibitory and excitatory representations, which mirror each other in a reverse but not similiar manner. Each group is still adhering to the dominant Convergent / Divergent properties for Dopamine / Serotonin respectively. This is the kind of reverse layering that has been predicted for brain systems from the original Dipole Neurology proposal. (01)



Three of the four aromatic amino acids above. Tryptophan, tyrosine and phenylalanine. Of these Phenylalanine most resembles the previous of the neutral aromatic benzene. The Carboxyl-amine groups attached to it have a disassociation constant (Ph of break up into acid or base) which lies on either side of side the physiological Ph of 7.4 (see values in example above). This means it has no functional attachments by which it can interact with it's environment or be an electron donor or acceptor.

2.1 AIM OF FOLLOWING SECTIONS

This section looks at existing evidence which suggests that the neurotransmitters derived from Tyrosine / Tryptophan operate with respective acid / base properties and are lateralized as LCH / RCH (Left cerebral hemisphere / Right cerebral hemisphere). It will be shown that Dopamine is LCH and Serotonin is RCH.

For these Neurotransmitters, existing research was found to propose that dopamine interacts through the D1 receptor by lowering local PH through it's hydroxyl. For Serotonin through the 5HT1 receptors by electron donation through the pyrrole ring. As mentioned previously, simple answers like this do not appear in the receptors for dopamine and serotonin. *(The dopamine / serotonin receptor groups proposed as being reverse patterns of each other with an overall property of convergent (negative energy) for dopamine and Divergent (positive energy) for Serotonin.)* It is not proposed that these are the docking properties for the neurotransmitters in every receptor, but that they would be the dominant ones.

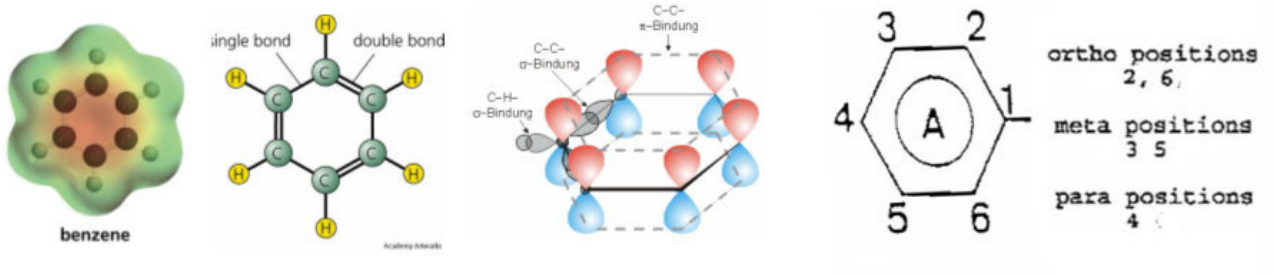
To begin this will require *(for those unfamiliar with aromatic-pi systems)* looking in detail at the principles of organic chemistry which are relevant to getting a feel for how reverse properties can rise from aromatic molecules.

2.2 CATION / ANION Pi INTERACTIONS

To begin discussion about neurotransmitters derived from aromatic amino acids (Tyrosine and Tryptophan) having acid base properties. Involves discussion of the aromatic Acid / Bases properties first.

The definition of acid / base used for aromatics is the Lewis system. The acids are defined as chemical species which can form a new covalent bond by accepting a pair of electrons and the Bases are defined ass a species that can from a new covalent bond by donating a pair of electrons. (98)

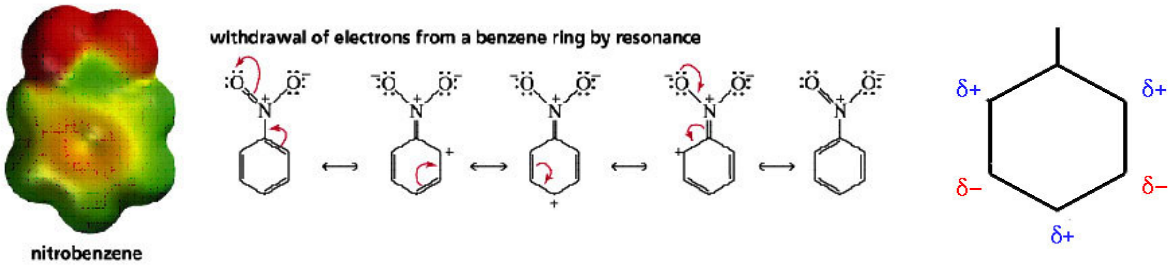
For aromatic molecules these Acid / Base properties are known as Cation / Anion pi interactions, due to the electron resonance occurring within aromatic rings, *(see figure below)* which can be donated or accepted *(each being a reverse process of the other)* through groups attached to the ring.



The two types of electron orbitals in benzene. Benzene is the basic standard core of most regular aromatics. The sigma bonds occur as regular chemical bonds. Pi electron orbitals occur as figure of 8 loops creating a north / south ring sandwich for the aromatic ring. Final image.

Benzene is neutral for cation / anion pi interactions. (98) Benzene forms the basis for the main families of aromatic molecules. As mentioned previously a wide range of molecular attachments altering it towards cation or anion pi behaviours. The following two sections reveal the details behind these properties, as a bridge to the next stage where these anion / cation properties will be proposed for tyrosine, tryptophan and the derived and lateralized neurotransmitters from each respectively.

2.3 ANION PI MOLECULES AROMATIC ELECTRON ACCEPTORS (Lewis Acid)



1. Withdrawal of electrons from a benzene ring 2. Result is ring is electron deficient. (electrons are negative)

Classification of Aromatic anion Pi molecules is relatively recent in organic chemistry. (100) They have been found to be deficient of electrons within their aromatic ring. (102) The example *(see figure above)* from a Textbook (104) describes the process of how this withdrawal of electrons occurs from a benzene ring *(Nitrobenzene).* Red indicates greatest electron activity. The positive charge due to electron withdrawal becomes concentrated at the ortho-para positions**.** *(see figure 3 for ortho para positions)* This activates the aromatic ring for nucleophilic substitution towards the oxygen atom.

" In chemistry, a nucleophile (literally nucleus lover) is a reagent ***(Nitrogen in the case above)*** *which is attracted to centres of positive charge. A nucleophile participates in a chemical reaction by donating electrons to a species known as an electrophile* ***(Oxygen in the example above.)*** *All molecules or ions with a free pair of electrons can act as nucleophiles, although negative ions (anions) are more potent than neutral reagents.* ***Wikipedia***

In the case above Nitrogen is attracted towards the greater concentration of positive charge within the oxygen molecule which is larger than the carbon it is attached to at the aromatic end. It withdraws electrons from the ortho para positions leaving them positive. While leaving the meta positions electronegative. NO2 is a meta-director, meaning that interactions will be directed towards the meta positions of the aromatic ring. These positions are deactivated towards nucleophilic aromatic substitution.

NO2 added to neutral charge benzene creates nitrobenzene which has two carbocations at the meta positions.
(A carbocation is an ion with a positively-charged carbon atom. The carbon atom has only six electrons in its outer valence shell instead of the eight valence electrons that ensures maximum stability. Therefore the carbon cation is unstable and very reactive, seeking to fill its octet of valence electrons as well as regain its neutral charge. Wikipedia)

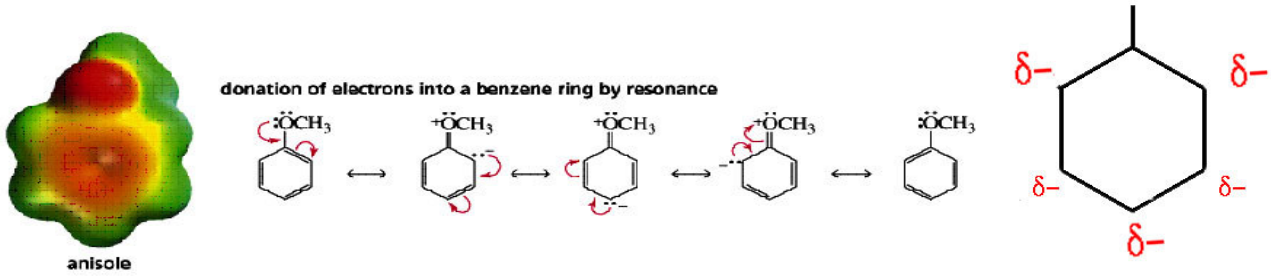
Nitrobenzene is a lewis acid *(A Lewis acid is a species with accepts an electron pair in it's lowest unoccupied molecular orbit LUMO (98))* The pi electrons from the ring are delocalized onto the substituent oxygen which has the highest occupied molecular orbit HOMO. The electron ring is now electron deficient, and becomes an electrophilic reagent at the meta positions.

Previously it was stated that the Nitrogen within the ring was a nucleophile, however this does not mean that nitrobenzene is an nucleophile. Rather the process of benzene being attached to by a nucleophile, activates the whole aromatic ring to become an electrophile..

In chemistry, an electrophile (literally electron-lover) is a reagent which is attracted to electrons that participates in a chemical reaction by accepting an electron pair in order to bond to a substance. Most electrophiles are positively charged. ***wikipedia***

Because electrophiles accepts electrons, they are Lewis acids.

2.4 CATION PI MOLECULES. AROMATIC ELECTRON DONORS (Lewis Base)



1. Donation of electrons into a benzene ring. 2. Result is Ring is electron rich (larger icons indicate more electrons)

Classification of Aromatic Cation Pi has already been established in organic chemistry. (106, 108) The aromatic rings are found to electron rich donors (110, 112)
The example (see figure above) from a Textbook (104) describes the process of how this donation of electrons into a benzene ring (anisole) occurs. Red indicates greatest electron activity. *(Notice how the density is darker within the ring than the previous example nitrobenzene)*

The negative charge due to electron donation becomes concentrated at the ortho-para positions**.** (see figure for ortho para positions) This activates the aromatic ring for electrophilic substitution towards the oxygen atom.

In chemistry, an electrophile (literally electron-lover) is a reagent ***(Oxygen in the example above)*** *which is attracted to electrons that participates in a chemical reaction by accepting an electron pair in order to bond to a substance. Most electrophiles are positively charged. wikipedia*

In the case above oxygen gives electrons towards the greater concentration of resonant carbon within the aromatic ring. It donates electrons to the ortho para positions leaving them more negative than previously. OCH3 is an ortho / para director, meaning interactions will be directed towards the ortho / para positions of the aromatic ring. These positions are activated towards electrophilic aromatic substitution.

OCH3 added to neutral charge benzene creates anisole which has three carbanions at the ortho / para positions. *"A carbanion is an anion in which carbon has an unshared pair of electrons and bears a negative charge. Wikipdedia "*

Anisole is a lewis base base *(A Lewis base is a species which donates an electron pair from it's highest occupied molecular orbit HOMO (98))* The electrons from the oxygen are delocalized into the benzene ring. The aromatic ring is now electron rich, and becomes a nucleophilic reagent at the ortho / para positions.

Previously it was stated that the Oxygen within the ring was an electrophile, however this does not mean that anisole is an electrophile. Rather the process of benzene being attached to by an electrophile, activates the whole aromatic ring to become a nucleophile.

" In chemistry, a nucleophile (literally nucleus lover) is a reagent which is attracted to centres of positive charge. A nucleophile participates in a chemical reaction by donating electrons to a species known as an electrophile. All molecules or ions with a free pair of electrons can act as nucleophiles, although negative ions (anions) are more potent than neutral reagents. ***Wikipedia***

Because nucleophiles donate electrons, they are Lewis bases.

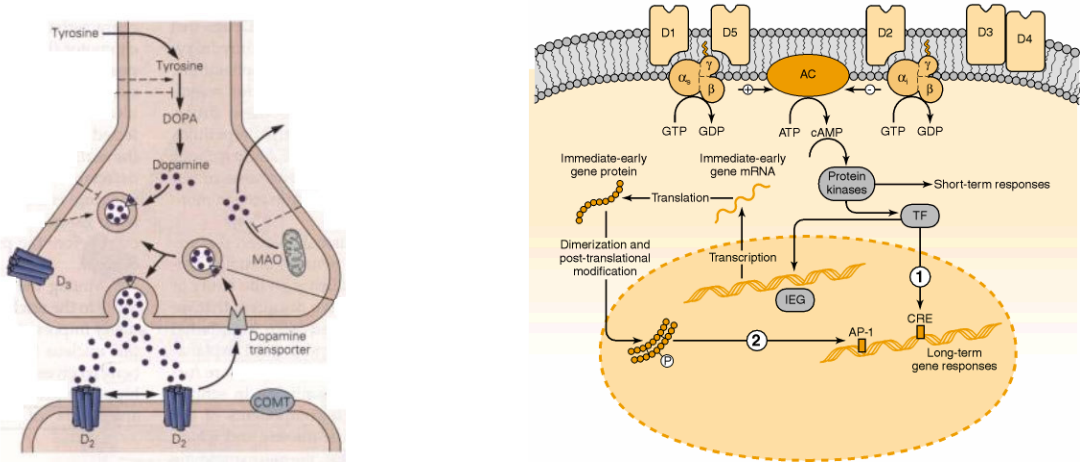
3 ION PREFERENCES OF DOPAMINE RECEPTORS AND TRANSPORTERS

3.1 DOPAMINE TRANSPORTERS

The Dopamine Receptors (DA) and transporters (DAT) appear to have a clear preference for particular ions to assist with Reuptake and transmission When more Na(+) is made available intracellularly to the presynaptic transporter, this reversed the The DAT-mediated uptake of DA. (114)

Examination of the allosteric sites within the transporter found that Zinc potentiates an uncoupled Chlorine anion conductance associated with the dopamine transporter.

"potentiation of the uncoupled Cl- conductance is critical for Zn2+-induced inhibition of DA-uptake and Zn2+-induced enhancement of carrier-mediated substrate efflux. Zn2+ is the first example of an allosteric modulator that can regulate transporter function by potentiating a specific uncoupled ion conductance." (120)



LEFT : Diagram of dopamine transmission. Note position of dopamine transporter.
RIGHT : Post synaptic Action is not ionic but triggers G-protein cascade.

*"Research into addiction reveals **Dopamine excitability result from the DAT chloride current**. .....mediated inward chloride currents were uncoupled from the uptake of dopamine and did not result simply from ionic movements associated with dopamine transport..... Neurons contain tightly regulated concentrations of chloride ions and the chloride equilibrium potential is generally close to the resting potential. This means that small changes in membrane potential that result from the DAT chloride current could have important effects on neuronal excitability and dopamine release.... they analysed the kinetics of the DAT-mediated currents, the authors found that the dopamine affinity of the currents was tenfold higher than the affinity for dopamine uptake by DAT. In other words, the DAT currents were uncoupled from the uptake of dopamine and did not result simply from ionic movements associated with dopamine.... Dopamine released during bursts feeds back onto (presynaptic) D(2) autoreceptors that depress neuronal activity. New findings from Ingram and colleagues suggest that, by contrast, tonic activity excites these neurons by activating an uncoupled Cl- conductance that is mediated by the dopamine uptake transporter."* (122)

The chloride current affects neuronal function itself.

"DA transporters not only transport DA but also exhibit a channel mode of conduction that directly modulates membrane potential and neuronal function" (116)

Another reason that co-modulators are a subsystem could be due to the less powerful re-uptake transport system. Glutamate molecules are transported by three sodium ions, Gaba two, and two of the co-modulators examined Serotonin and Norepinephrine, one. (57) The re-uptake transport system of dopamine is three times slower than the transmitter firing rate.

3.2 DOPAMINE RECEPTORS

Table 1. *Properties of dopamine receptors*

Type	Amino acids	Chromosome (human)	Highest tissue sites	Selective agonists	Selective antagonists	Effectors
D_1 like receptors						
D_1	446 (h) 446 (r)	5	Basal ganglia Nucleus accumbens Cerebral cortex	Hydroxybenzazepines A-68930 CY-208-245 Dihyrexidines	Halobenzazepines (SCH- 23390) Thioxanthenes	AC(+) PLC(+)
D_5	477 (h) 475 (r)	4	Hippocampus Thalamus	Hydroxybenzazepines	Halobenzazepines	AC(+)
D_2 like receptors						
D_2	443 (h)	11	Anterior pituitary, Basal ganglia	Ergolines Hyroxyaporphines Aminotetralins	Benzamides Butyrophenones Phenothiazines	AC(−) PLC(−); AA(+) K^+channels(+) Ca^{2+} channels (−)
D_3	400 (h) 444 (r)	3	Islands of Calleja, Olfactory Tubercle Cerebellum	(+)7-OH-DPAT (+)PD-128,907	Nafadotride S-14297	AC(−) (?)
D_4	387 (h) (& variants) 368(r)	11	Frontal cortex, Hippocampus, Amagdyla	CP-226,269 PD-106,077	L-745,870 U-101,387 RBI-257 NGD-94-1	AC(−) AA(+)

Peptide length varies with species (h=human, r=rat); chromosome number are for human.
AA=arachidonic acid; AC=adenylyl cyclase; PI=phosphatidyl inositol cycle; PLC=phospholipase C; K+ channels = potassium channels; Ca^{2+} channels = calcium channels;
(+) = activation; (−) = inhibition.
(?) indicates a tentatively proposed, or weak, association.

Table of dopamine receptors.

Answers for this could come from looking at calculated physical properties of dopamine and it's receptors. Cl- is proposed to interact with a neutral base dopmine to alter the the rotamer *(molecular twist)* type of the dopamine molecule towards a "trans" conformer, which has a higher electronic energy than the other two dopamine rotamer conformations Gauche- and gauche + *(see figure below)* (118)

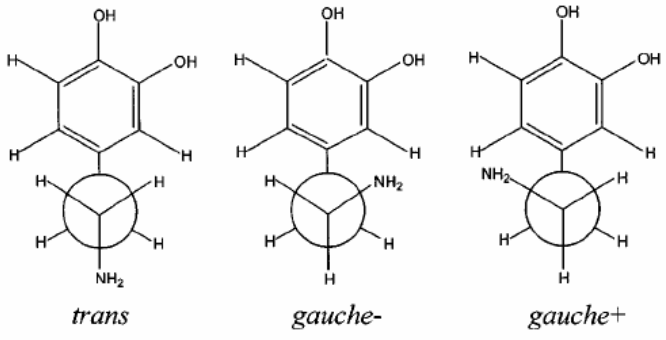
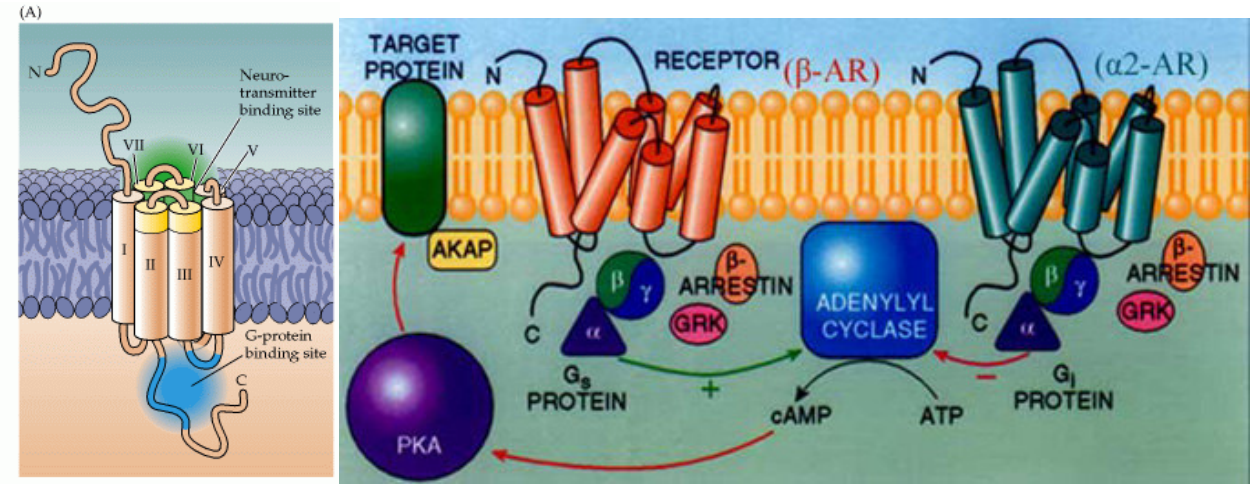


Figure 2. Three staggered conformations (*trans*, *gauche-*, and *gauche+*) of dopamine neutral base.

Structure analysis of dopamine by the same researchers, reveals dopamine could be a cationic species, or lose one or two protons at two hydroxyl groups of the catechol ring moiety to be a monoanionic, dianionic, or zwitterions. (92, 118) Recent analysis of Dopamine within it's receptor by Nishihira and Tachikawa (126) takes this further and finds a proposal which could explain why dopamine has always been considered the brains "clock" molecule.



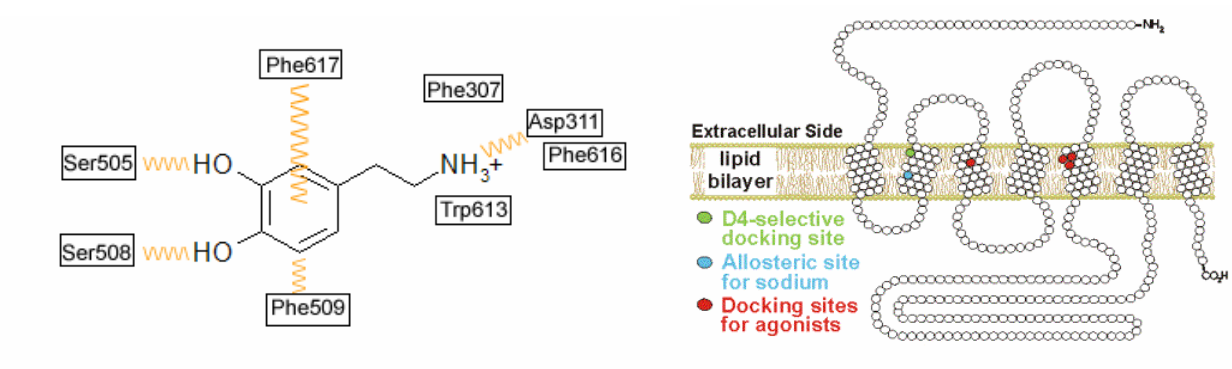
LEFT : Stucture of a G-protein receptor. RIGHT : Example of the pathways from the G-protein receptors. These vary for each receptor.

Below the Dopamine receptors there are no ionic triggers, like the glutamate / Gabs system. (3) There are G-proteins systems, which trigger a series of intracellular signals.

"Considering these theoretical results together, we hereby propose a model of the dopamine-receptor interaction:

(1) ***a protonation-deprotonation at the meta-position hydroxy group takes place****,*
(2) the protonated side-chain amino group of dopamine binds to a negatively charged receptor site by an ionic bond, and
(3) the para-position hydroxy group not only contributes to stabilization for dopamine binding but may also enhance the protonation-deprotonation at the meta-position through bond interaction along the pi-bond between OH and the benzene ring.

It was considered that proton flopping, which occurred within the receptor site via the meta-position hydroxy group, appeared to be essential for exerting the biological action of dopamine". (126)



LEFT : Example of how dopamine is held in a receptor RIGHT : Modulation sites of the receptor itself.

3.2.1 OPTIMUM PH OF DOPAMINE

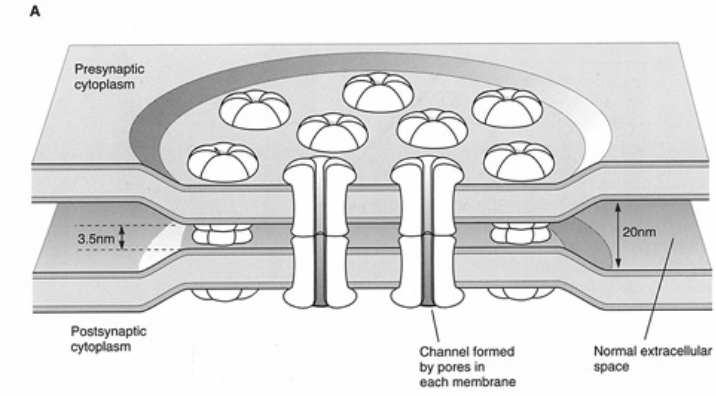
While the amine groups is held in the receptor in this scenario, (receptor example above first image) dopamine is proposed to protonate periodically. (122) The meta Hydroxyl modulates receptor held dopamine as an electron deficient anion Pi species, which would increase the acidity of it's environment. Dopamine operates in lower local Ph environments. (98)

"***Optimal pH for dopamine production is 6.1 and when experiments were performed at pH 7.4 the rate of dopamine formation decreased to about 25% of that at pH 6.1."*** (128)

Dopamine receptor activation appears to be anionic. Dopamine reduces voltage gated sodium current in goldfish retinal ganglion cells. (130) Dopamine receptors were found to be insensitive to sodium in a more detailed study of their distinct sites of allosteric modulation *(fine tuning areas within receptors)* (132).

3.3 DOPAMINE GAP JUNCTIONS

Electrical synapse "gap junctions", are two way ionotropic connections through neighbouring cells, as opposed to regular "Metabotropic" synapses, which transmit neurotransmitters in one direction.



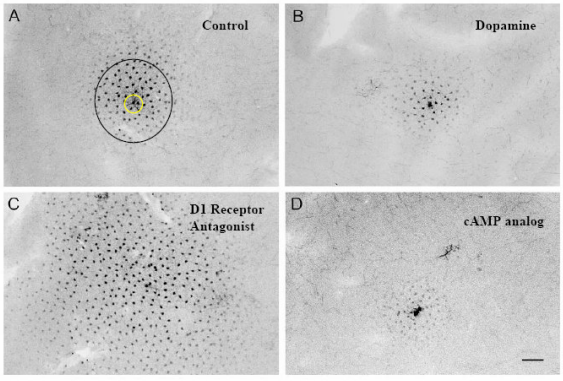
RECEPTORS

TRANSMITTER	LIGAND-GATED	G-PROTEIN
ACh	NICOTINIC	MUSCARINIC 1-5
DA		D 1-5
NE		α 1,2; β 1,2,3, 4(?)
5HT	$5HT_3$	$5HT_1$ A-D $5HT_2$, $5HT_4$
GLU	AMPA, NMDA	ACPD
GABA	$GABA_A$	$GABA_B$

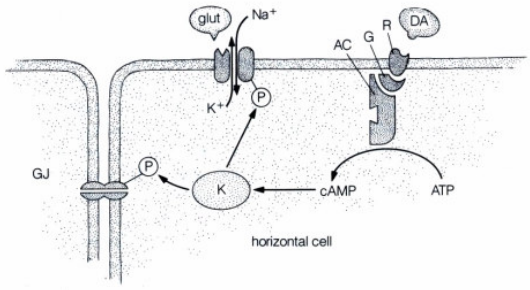
LEFT : Diagram of gap junction showing channels between cell walls. RIGHT : Differences between dopamine and serotonin receptors.

None of the tyrosine derived catecholamines neurotransmitters have electrical junctions within their receptors. (See figure above right) Is this related to acidity ? Intracellular acidification reduces gap junction coupling. (134)

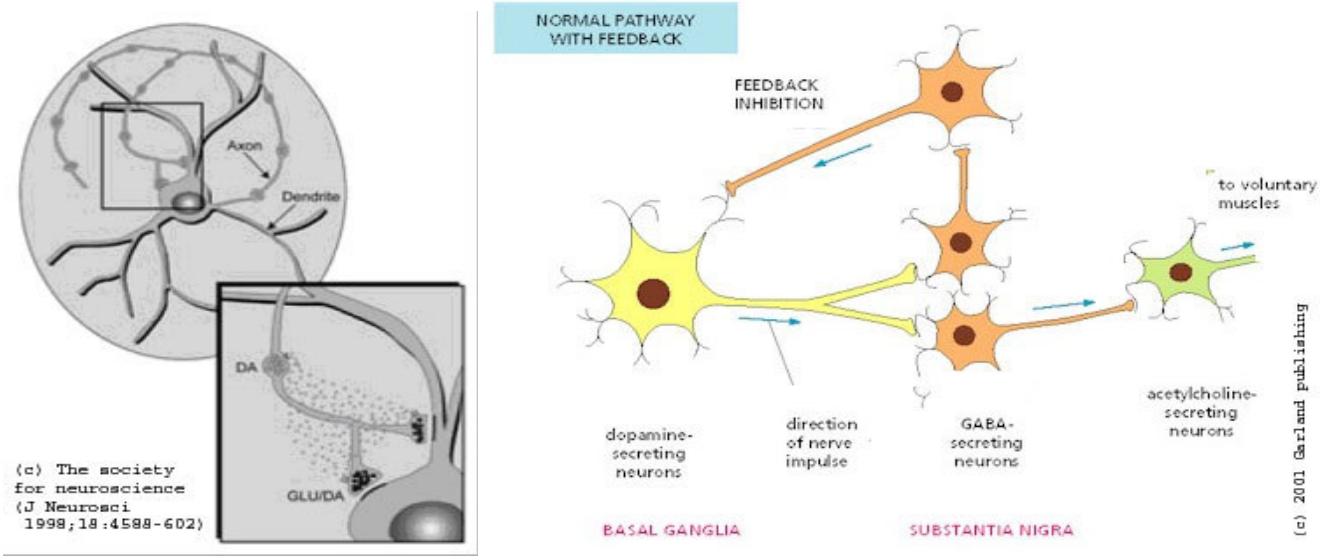
Dopamine Regulation of Gap Junctional Coupling



Intracellular Pathway for Dopamine Modulation



Dopamine D1 receptors decrease inhibition in fast spiking inhibitory Gaba neurons (electrical transmission), while enhancing inhibition in non fast spiking Gaba neurons. (chemical transmission) (136) Dopamine D1 receptors increase resistance between gap junction axons, (138) and reduces coupling between developing pyramidal neurons by it's G-protein triggered Protein Kinase A activation. (140) Dopamine reduces coupling between retinal cells by G-protein triggered cAMP production (142) (see figure above)



LEFT : A dopamine synapse DA operates in conjunction with a glutamate synapse GLU/DA. RIGHT : The majority of dopamine modulations are negative re-enforcements.

4 ION PREFERENCES OF SEROTONIN RECEPTORS AND TRANSPORTERS

4.1 SEROTONIN TRANSPORTERS

The previous section reviewing dopamine transporters found Dopamine uptake operated by uncoupled Chlorine conductance. The reverse appears to be true for serotonin. Researchers evaluating hSERT (Serotonin transporter) Propose :

"I5HT represents the transport mode of hSERT, ***in which 5HT and Na couple in a shared pore,*** *(see figure above) gated by external 5HT and modulated by K and Cl". (144)*

"The present results strengthen the conclusion that cationic serotonin is the true substrate for the platelet plasma membrane serotonin transporter. (146)

4.2 SEROTONIN RECEPTORS

Serotonin receptors proliferate divergently. Hence the number of descriptions within this part will proliferate also

"There are four broad 'superfamilies' of receptor: (1) the channel-linked (ionotropic) receptors; (2) the G-protein coupled (metabotropic) receptors; (3) the kinase-linked receptors; and (4) receptors that regulate gene transcription. The 5-HT1, 2, 4, 5, 6 and 7 receptors belong to the G-protein coupled superfamily. They are membrane receptors that have 7 transmembrane spanning a-helices. 5-HT binding to the 'binding groove' on the extracellular portion of the receptor activates the G-proteins, which initiate secondary messenger signalling pathways. The downstream effect is either inhibitory or stimulatory, depending on the type of G-protein linked to the receptor – 5-HT1 receptors are linked to inhibitory G-proteins, whereas 5-HT2, 4, 6 and 7 are linked to stimulatory G-protein" (148)

4.2.1 TABLE OF RECEPTORS

RECEPTOR	LOCATION (refs for table 148 (Serotonin) 150 (Dopamine)	EFFECTOR
5-HT1A	Hippocampus, amygdala, septum, entorhinal cortex, hypothalamus, raphe nuclei	Inhibition of adenylyl cyclase, opening of K+ channels
5-HT1B	?	Inhibition of adenylyl cyclase
5-HT1Da	?	Inhibition of adenylyl cyclase
5-HT1Db	Substantia nigra, basal ganglia, superior colliculus	Inhibition of adenylyl cyclase
5-ht1E		Inhibition of adenylyl cyclase
5-ht1F	Cerebral cortex, striatum, hippocampus, olfactory bulb	Inhibition of adenylyl cyclase
5-HT2A	Claustrum, cerebral cortex, olfactory tubercle, striatum, nucleus accumbens	Stimulation of phosphoinositide-specific phospholipase C, closing of K+ channels
5-HT2B	?	Stimulation of phosphoinositide-specific phospholipase C
5-HT2C	Choroid plexus, globus pallidus, cerebral cortex, hypothalamus, septum, substantia nigra,	Stimulation of phosphoinositide-specific phospholipase C
5-HT3	Hippocampus, entorhinal cortex, amygdala, nucleus accumbens, solitary tract nerve, trigeminal nerve, motor nucleus of the dorsal vagal nerve, area postrema, spinal cord	Ligand-gated cation channel
5-HT4	Hippocampus, striatum, olfactory tubercle, substantia nigr	Stimulation of adenylyl cyclase
5-ht5A	?	Inhibition of adenylyl cyclase
5-HT5B	?	?
5-HT6	?	Stimulation of adenylyl cyclase
5-HT7	Cerebral cortex, septum, thalamus, hypothalamus, amygdala, superior colliculus	Stimulation of adenylyl cyclase,
D1	Basal Ganglia, Nucleus Accumbens, Cerebral cortex	Stimulation of adenylyl cyclase, Stimulation of phosphoinositide-specific phospholipase C
D2	Basal Ganglia, Anterior Pituitary	Inhibition of adenylyl cyclase Inhibition of phosphoinositide-specific phospholipase C Stimulation of Arachidonic acid Opening of K+ channels Closing of Ca2+ channels
D3	Islands of Calleja, Olfactory Tubercle, Cerebellum	Inhibition of adenylyl cyclase
D4	Frontal Cortex, Hippocampus, Amagdyla	Inhibition of adenylyl cyclase
D5	Hippocampus, thalamus	Stimulation of adenylyl cyclase Stimulation of Arachidonic acid

Looking at the table above serotonin receptors profilerate in variety of types, while they trigger very basic g-proteins signals. Conversely there are few dopamine receptors which trigger many g-protein signals.

Also the reversal is apparent within their g-protein mechanisms.

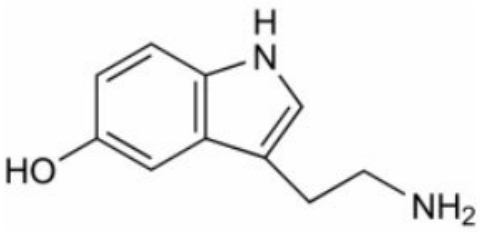
D1 receptors : **Stimulation of adenylyl cyclase,**

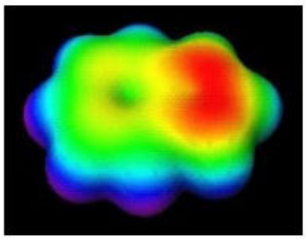
5HT1 receptors : **Inhibition of adenylyl cyclase**

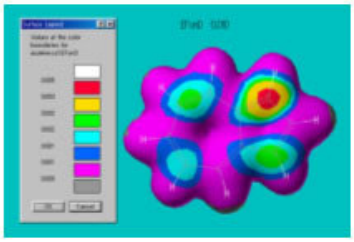
D2 receptors : **Inhibition of phosphoinositide-specific phospholipase C**

5HT2 receptors : **Stimulation of phosphoinositide-specific phospholipase C**

4.2.2 SEROTONIN AROMATIC PROPERTIES







1. The Serotonin molecule 2. Electrostatic distribution of Azulene. (towards red is –ve (electrons) Towards blue +ve.) Azulene illustrates where density lies between 5 and 6 carbon aromatics combined. 3. Electrophilic susceptibility highlighting (red) the most electrophilic point of azulene is where substitution takes place with Indoles NH.

Why is Serotonin so involved in excitability ? Tryptophan *(from which serotonin is derived)* appears to be a molecule of electron donation. Indoles react with electrophiles better than other aromatics because their rings have higher electron densities, and high Electrophilic susceptibility *(Attractor of electron takers)* at the indole side. (130) These properties are already well known in structural biology. 25% of tryptophans (aromatic amino acids) in known proteins posses a cation-p interaction.

"Cation-pi interactions are found to be common among structures in the Protein Data Bank, and it is clearly demonstrated that, when a cationic sidechain (Lys or Arg) is near an aromatic sidechain (Phe, Tyr, or Trp), the geometry is biased toward one that would experience a favorable cation-pi interaction. The sidechain of Arg is more likely than that of Lys to be in a cation-pi interaction. ***Among the aromatics, a strong bias toward Trp (Tryptophan) is clear, such that over one-fourth of all tryptophans in the data bank experience an energetically significant cation-pi interaction." 106***

Within nerve transmission, Studies of some of the receptors for trytophan derived neurotransmitters nicotine and Serotonin find they have cationic binding properties, named Cation-p interactions. (108, 154, 160,162)

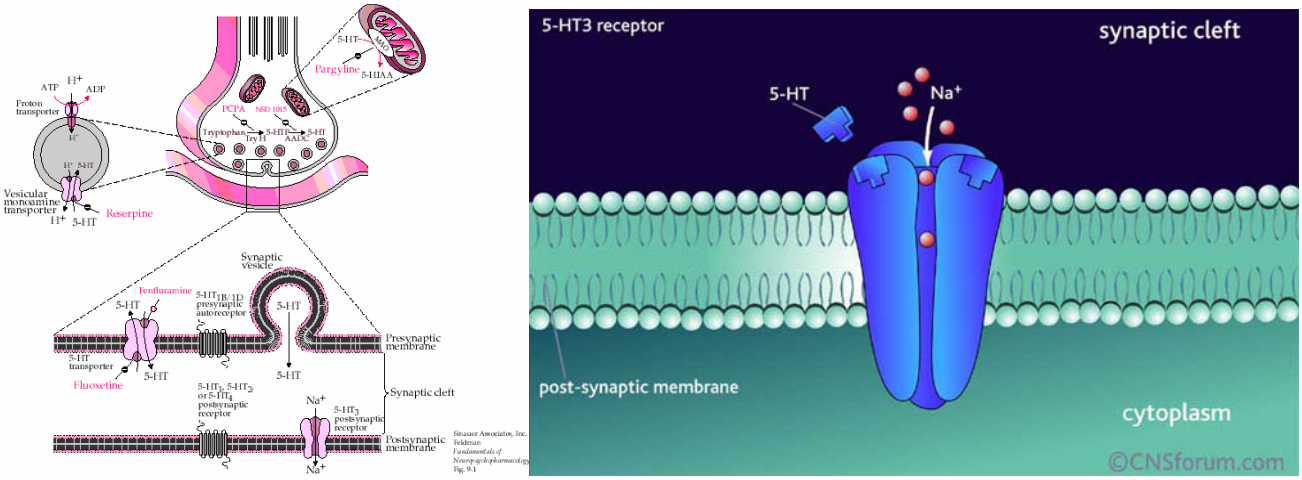
"The nicotinic ***(nicotine is derived from tryptophan)*** *acetylcholine receptor is the prototype ligand-gated ion channel. A number of aromatic amino acids have been identified as contributing to the agonist binding site,* ***suggesting that cation-pi interactions may be involved in binding the quaternary ammonium group of the agonist, acetylcholine. …..on binding, the cationic, quaternary ammonium group of acetylcholine makes van der Waals contact with the indole side chain of alpha tryptophan-149*** *" (108)*

4.2.3 OPTIMUM PH OF SEROTONIN

"It is noteworthy that the KM for serotonin transport by plasma membrane vesicles is the same at pH 6.7 and 9. From this result, it would seem that the mole fraction of substrate species does not change with pH, and that the likely substrate form is the cation "

"The rate of dopamine or serotonin synthesis in rat brain striatal synaptosomes was determined as a function of pH. Optimal pH for serotonin synthesis was about 7.2 and as the pH of the suspension medium decreased below 7 the rate of serotonin formation declined" (134)

4.2.4 IONOTROPIC 5-HT3 SEROTONIN RECEPTORS



LEFT: Ionotropic serotonin receptor RIGHT : 5-HT3 gates sodium cations,

Cation pi interactions have been found to occur between 5HT and its 5-HT3 receptor (154, 160,162) which is an electrical coupled junction, rather than a G-protein trigger. These are twice as energetic as those observed for the Nicotine receptor (160) The receptor itself is comes from a family of receptors, which include the Chlorine gated Gaba receptors. The electrostatic environment can control it's selectivity for anions or cations (166) The 5HT3 receptors are cation selective ion channels for sodium. (164)

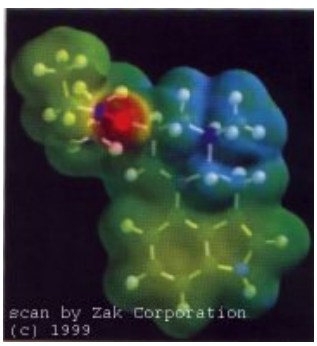
4.2.5 G-PROTEIN – COUPLED 5HT RECEPTORS (1,2,4,5,6,7) – CATION PROPERTIES ?

G-Protein receptors do not appear to possess Cation – pi interactions. Do they still favour processes with Cation properties ?

" assuming that one of these models is correct, it distinguishes the 5-HT binding mechanism of the ligand-gated 5-HT3 receptor from that of the six known metabotropic 5-HT receptors. Here, models suggest that the indole group of 5-HT binds in a hydrophobic pocket formed by tryptophan and tyrosine residues, and that the charged primary amine is compensated by polar or charged residues, not via a cation- interaction. " (168)

4.2.6 USING LSD TO STUDY 5HT RECEPTORS

Study of 5HT receptors with agonists LSD (Lysergic acid diethylamide) or other Tryptophan derived "psychedelics" gives rise to a theory of electron resonance donation or Cation pi interactions.

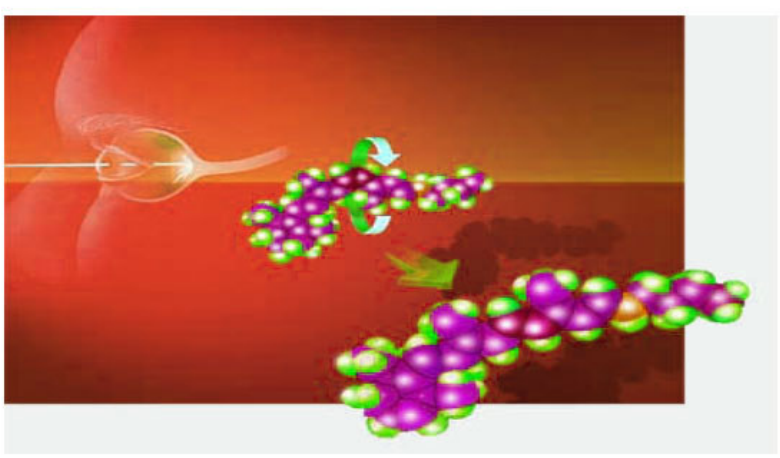


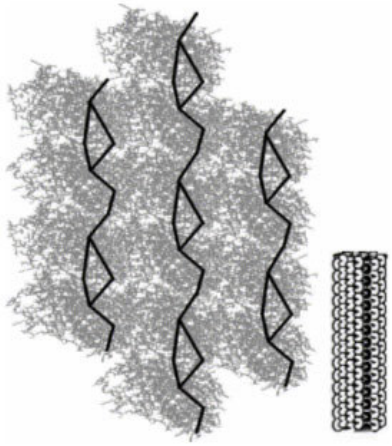
LEFT: LSD electron resonance. RIGHT: LSD molecule.

"Another class of drugs, the hallucinogenic (`psychedelic') tryptamine, ergoline and phenylethylamine derivatives bind and act in hydrophobic pockets within serotonin receptors and elsewhere. For example the hallucinogens LSD (an ergoline) and DMT (a tryptamine) are based on indole rings, exactly like that in tryptophan. Nichols et al. (1977) showed that these psychedelic drugs bind in hydrophobic pockets of less than 0.6 nm (6 Å) length. Kang and Snyder measured the capacity of a series of psychedelic drug molecules to donate electron orbital resonance energy. ***In both studies, the drug's electron resonance donation is correlated with psychedelic potency."*** *(110)*

5-HT2A receptors are found to be the target sites for LSD agonists. (170, 172) 5-HT2A receptors are activated by disruption of a pre-existing ionic brige within the receptor. (176) The bridge consists of a positively charged arginine in transmembrane helice 3 and a negatively charged glutamate in transmembrane helice 6. LSD interacts in this receptor via the amine nitrogen embedded in an electron rich heterocycle or "indole". (174)

"Taken together, these results predict that the disruption of a strong ionic interaction between transmembrane helices 3 and 6 of 5-HT2A receptors is essential for agonist-induced receptor activation and, as recently predicted by ourselves (B. L. Roth and D. A. Shapiro (2001) Expert Opin. Ther. Targets 5, 685-695) and others, that ***this may represent a general mechanism of activation for many, but not all, G-protein-coupled receptors.****" (178)*





1. "salt bridge" receptors are present in light transduction bipolar retinal cells. 2. Tryptophan has been calculated to be capable of conducting pathways just by it's presence within the microtubule framework (110) which stretches through every neuron. (See figure above)

These ion bridges are found also in beta2 G-protein-coupled receptors, which have a similar receptor mechanism operates for cells involved in light transduction process. (182)

"the photoactivation of rhodopsin involves a change in the relative disposition of transmembrane helices 3 and 6, which contain Trp126 and Trp265 respectively, within the -helical bundle of the receptor." (180)

Interestingly these Beta2 G-proteins are also implicated in transport of brain peptides. (192) Activation of beta2- (184, 186) and beta3-adrenergic (186) receptors increases brain tryptophan and lowers tyrosine. (184) A reason for this could be that Cation Pi interactions involve mainly tryptophan. Because it has well known electron sharing and Fluorescence (light transducing) properties. (112)

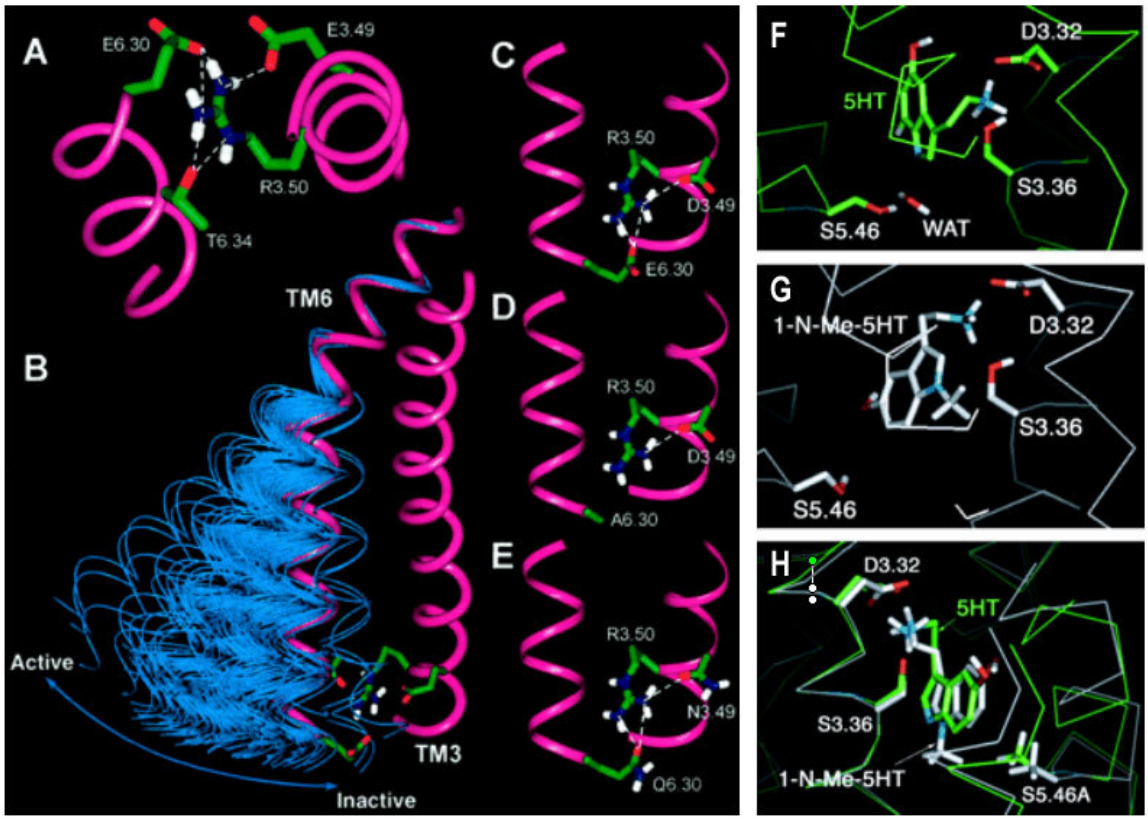
". Adding a hydroxyl group, as in tyrosine, causes a 20 fold increase in fluorescence. If an indole ring is added as in tryptophan, the relative fluorescence increases to 200 times that of phenylalanine." 83

"The amino ***acids tryptophan and tyrosine are convenient depots for electron hopping or tunneling because of the high polarizability of their ring structure****. The `aromatic' amino acids such as tyrosine, tryptophan, phenylalanine and histidine*

have residues with resonant ring structures in which electrons are mobile and delocalizable. ***Tryptophan is the most highly suited amino acid for transiting electrons and exchanging photons****." (110)*

Research differs where the amine end of 5HT binds within the receptor. (188, 176) It appears to be the position of the indole ring which greatly affects agonist activity. The indole ring interacts with elements of a cluster of aromatic residues in helix 6. This is believed to be the main activation trigger. (176)

*"****the chemical information transfer from the extracellular to the cytosolic domains is mediated by a cluster of aromatic amino acids in helix 6****, following the ligand interaction with selected amino acids in the extracellular half of the receptor" (190)*



A, orientation of 5-HT in the binding pocket of the "salt bridge" receptor. A water molecule (WAT) bridges the indole nitrogen of 5-HT and the Ser5.46 hydroxyl group B In blue electrical acitivity of the "salt bridge". Is this re-directed through the 5HT molecule ? C,D,E Deactivation of bridge. F,G,H Various proposed conformations for 5HT within the receptor.

4.3 SEROTONIN GAP JUNCTIONS

Unlike Dopamine, which has no electrical synapses and appears to stop gap junctions from operating, Serotonin has it's own (5-HT3) electrical synapses. Serotonin also modulated developing cortical gap junctions by inhibiting by means of 5HT2 receptors. (156) This would be expected since 5HT2 receptors appear to be inhibitory. Modulation elsewhere by 5HT alone appears to increases the amount of electrical energy.

"During stimulation with 5-HT), junctional conductance increased (29-75%) in all four cell types of muscular junctions (194) "

Which is consistent with the reviews of serotonin modulation where the role is varied but largely excitatory. (156, 154)

5. LATERALIZATION OF CO-MODULATORS

5.1 TYROSINE DERIVED NEUROTRANSMITTERS

The Tyrosine derived Catecholamines are LCH lateralized : Dopamine The most studied (242,198,240,238, 200), Norepinephrine, (198) Noradenaline (234,74,236) and Morphine (234,74,236)

5.1.1 MORPHINE

Morphine is an opioid derived from paired tyrosine, and is produced in the brain (202) Tricyclic anti-depressants which amplify the analgesic effect of morphine (206) were more effective in patients with left brain laterality found under the dichotic listening test (204)

The tyrosine derived opioids are under sodium independent anion transport, adding to the case for LCH actions operating on negative charge. Opioid peptides are transported across the Blood brain barrier by sodium independent organic anion transporting polypeptides (OATP). A transport substrate the opioid peptide deltorphin II enhances extracellular dopamine (Left lateralized) in the nucleus accumbens. (210)

The action of morphine is also bound together with the left hemisphere transmitter GABA. Functional coupling exists among GABA, pentobarbital receptors and chloride channels (214) GABA antagonists (bicuculline and picrotoxin) blocked the effect of GABA, whereas pentobarbital enhanced the action. Morphine significantly potentiates analgesic effects of pentobarbital in control mice. (212)

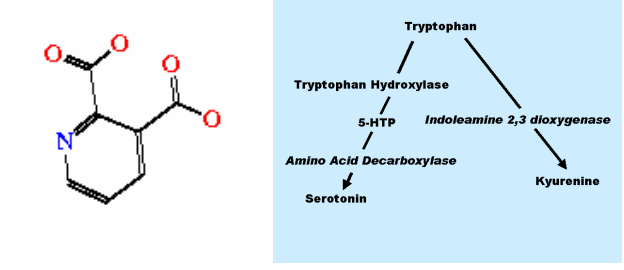
5.2 TRYPTOPHAN DERIVED NEUROTRANSMITTERS

The Tryptophan derived neurotransmitters are RCH lateralized : Serotonin the most recently studied (234,74,236,200) with RCH serotonin asymmetry increasing following brain insult (220, 222) and RCH asymmetry following Serotonin re-uptake antidepressant treatments. (216, 224). The remaining Tryptophan derived neurotransmitters are RCH lateralized : Nicotine (226,228,234,74,236) quinolinic acid (234,74,236).

5.2.1 NICOTINE

The nicotinic acetylcholine receptor is a ligand-gated Cationic ion channel. (106) As just pointed out Nicotine is RCH lateralized. The anxiolytic effects of nicotine are mediated by the right hemisphere (228) Individuals with nicotine dependence experienced greater RCH EEG deactivation following abstinence.(226) Arachadonic acid (AA) which is RCH lateralized (3) cooperatively accelerates desensitization of nicotinic ACh receptor as well as glutamate also RCH (3)

5.2.2 QUINOLINIC ACID



LEFT : Trytophan pathways

The kynurenine metabolic pathway from tryptophan produces quinolininc acid (230) Kynurenine is produced when high levels of tryptophan stimulate the conversion of tryptophan to kynurenine. (218) Quinolinic acid is a Tryptophan derived (230, 234) depolarizing excitotoxic (244) neurotransmitter. (242) Which is RCH lateralized. (234,74,236) This has been found to be more chemically active in cortex and acts primarily at NMDA receptors. (244) NMDA modulation has been found to be RCH lateralized (3)

5.3 TABLE OF LATERALIZED NEUROTRANSMITTERS

MOLECULE	LCH	RCH
Tyrosine		
Derived		
Dopamine	**242,198,240,238, 200**	
Norepinephrine	**198**	
Noradrenaline	**234,74,236**	
Morphine	**234,74,236**	
Tryptophan		
Derived		
Serotonin (tryptamine)		**234,74,236,200,216, 224**
nicotine		**226,228,234,74,236**
quinolinic acid		**234,74,236**

Table above highlights clear lateralization for Tyrosine / Tryptophan derived neurotransmitters (LCH / RCH is Left cerebral hemisphere / Right Cerebral hemisphere)

DISCUSSION

Initial draft of this section, concerned just the neurotransmitters themselves. The receptors systems have provided yet another level of validation. Receptors appear to reflect the proposal for dopamine and serotonin. That is that the transmitters have digital / analogue properties respectively for dopamine and serotonin. Dopamine with a "proton flopping" anionic clock could provide a converging digital signal into an inactive receptor. Serotonin with it's electron transduction and donation properties could provide an energy dynamic through the already active "salt bridge" in it's receptor. Another factor which provides support for reverse anion / cation mechanisms is that dopmine has no electrical junctions, and decouples any local electrical junctions. Is this due to dopamine increasing acidity ? Serotonin has electrical junctions and these release sodium cations.

Looking at an overview, of either receptor group is that the dopamine receptors have a couple of bare on/off mechanisms, (D1,D2) and within the "on" mechanism (D2) there appears to be convergence of many types of positive g-protein activations. Presumably these operate together in an all or nothing manner, as if the D1 receptors "off" position is the dominant player, as a control which allows the (D2) receptor to trigger a set of positive synchronised signals. Does this increase the switch for activation to wait for a convergence of requirements ? Such a scenario would give a clue as to why dopamine has so much regulation power. Every positive signal appears to be held together under the "off" hammer. In a Reverse manner Serotonin g-protein signals are spread in a profuse variety of receptors, ready to re-arrange themselves in any kind of manner for re-modelling Glutamate dominated excitable or "on" circuits. To look at receptors in this way reflects better the proposed digital / analogue aspects for Dopamine / Serotonin.

Are these a tensegrity, a push / pull system. Evolving as they traded pieces from each other ?

Adding serotonin decreases the formation of dopamine and vice versa. These were Ph dependant with dopamine production at a lower Ph than serotonin. (128) Activation of "salt bridge" beta2- (184, 186) and beta3-adrenergic (186) receptors increases brain tryptophan and lowers tyrosine. (184)

"It is known that the level of free tryptophan in the blood can influence the transport of tyrosine across the blood brain barrier into the brain and vice versa, since both these amino acids share the same transport systems and compete with each other." (246)

That quote and a great deal of supporting data for lateralization in this section is taken from very unusual research from Medical College, Trivandrumn, in india. Their research and treatment operates from a smiliar kind of eastern system approach taken here.

"The concentration of serum tryptophan, quinolinic acid and serotonin was increased in the plasma while that of tyrosine, dopamine and noradrenaline was decreased in the pre-therapy group. Post-therapy the concentration of serum tryptophan, quinolinic acid and serotonin was reduced in the plasma while that of tyrosine, dopamine and noradrenaline was increased"

SUMMARY

The neurotransmitters and receptors do appear to fit the requirements of LCH/RCH convergent / divergent or lateralized digital / analogue brain model, and it's hoped this review provides an investigation which reveals more obviously from a chemical view, the negative / positive aspects of each hemisphere in light of their tyrosine / tryptophan roots. This is unlike the Gaba / glutamate system which did not reveal a lateralization of anion / cation abilities in the transmitters themselves. (3) The modulators appear to use aromatic ring properties to operate slower cellular mechanics. Glutamate / Gaba neurotransmitters are functional keys to a negative left /right positive ionic system which operate the release of sodium and chlorine respectively. (3) They are almost reverse systems, most likely the two systems operate together because they do not access each others resources, or get in each others way. The Glutamate / Gaba system predominates, because it has the speed of electrical processing. While the modulators develop more encoded tuning. Hence the deeper effects on our behaviours.

REFERENCES

01 **Dipole Neurology (Concept paper)**
Felix Lanzalaco, Wajidz Zia, Neil Mackay.
No academic affiliation
© March 2005 (Under review for Laterality: Asymmetries of Body, Brain and Cognition. Taylor & Francis group) Pre – review PDF **Available from** www.DipoleNeurology.com

02 **Dipole Neurology (Exploring Visual evidence)**
Felix Lanzalaco, Wajidz Zia.
No academic affiliation
© March 2005 (Under review for Laterality: Asymmetries of Body, Brain and Cognition. Taylor & Francis group) Pre – review PDF Available from www.DipoleNeurology.com

03 **Dipole Neurology (Tensegrity systems within Neuron chemistry)**
Felix Lanzalaco, Wajidz Zia, Neil Mackay.
No academic affiliation
© March 2005 (Under review for Medical Hypotheses, Elsevier B. ScienceDirect) Pre – review PDF Available from www.DipoleNeurology.com

57 **Listening to Neurotransmitter Transporters**
Neuron. 1996 Nov;17(5):807-10.
Henry A. Lester, Yongwei Cao, and Sela Mager.
Division of Biology, California Institute of Technology, Pasadena, California 91125

62 **Brain's Reward Circuitry Revealed in Procrastinating Primates**
August 10, 2004 http://www.nimh.nih.gov/press/prworkaholicmonkey.cfm
RichmondM.D, Zheng Liu, Ph.D., Edward Ginns, M.D
NIMH Laboratory of Neuropsychology, US dept of health and human services.

66 **Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration**
Nat Neurosci 2002 Jan 22
Morgan D, Grant KA, Gage HD, Mach RH, Kaplan JR, Prioleau O, Nader SH, Buchheimer N, Ehrenkaufer RL, Nader MA.
Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157, USA.

70 **Serotonin, social status and aggression.**
Curr Opin Neurobiol. 1997 Dec;7(6):812-9.
Edwards DH, Kravitz EA.
Department of Biology, Georgia State University, Atlanta 30302-4010, USA.

72 **Serotonin reverses dominant social status.**
Behav Brain Res. 2001 Jun;121(1-2):95-102.
Larson ET, Summers CH.
Department of Biology and Neuroscience Group, University of South Dakota, 414 E. Clark Street, 57069-2390, Vermillion, SD, USA

74 **Hypothalamic digoxin, hemispheric chemical dominance, and creativity.**
J Neurosci. 2003 Apr;113(4):565-77.
Kurup RK, Kurup PA.
Department of Neurology, Medical College Hospital, Metabolic Disorders Research Center, Trivandrum, Kerala, India. kvgnair@satyam.net.in

76 **Hypothalamic digoxin, hemispheric dominance, and family bonding behavior.**
Int J Neurosci. 2003 Jul;113(7):989-98.
Kurup RK, Kurup PA.
Department of Neurology, Medical College Hospital, Trivandrum, Kerala, India.

78 **Hypothalamic digoxin, hemispheric chemical dominance, and spirituality.**
Int J Neurosci. 2003 Mar;113(3):383-93.
Kurup RK, Kurup PA.
Department of Neurology, Medical College, Trivandrum, Kerala, India. kvgnair@satyam.net.in

80 **The Davis Hypothesis & Ion trapping**
Kerry Brandis 2001
http://www.anaesthesiamcq.com/AcidBaseBook/ab1_5.php
Australian and New Zealand College of Anaesthetists ANZCA House 630 St Kilda Road Melbourne Vic 3004

82 **Amino acid**
From Wikipedia, the free encyclopedia.
http://en.wikipedia.org/wiki/Amino_acid

84 **Changes in the isoprenoid pathway with transcendental meditation and Reiki healing practices in seizure disorder.**
Neurol India. 2003 Jun;51(2):211-4.
A RK, Kurup PA.
Department of Neurology, Medical College Hospital, Trivandrum 695-003, Kerala, India.

86 **Tyrosine**
From Wikipedia, the free encyclopedia.
http://en.wikipedia.org/wiki/Tyrosine

88 **Individual properties and images of amino acids**
The Amino Acid Repository
http://www.imb-jena.de/IMAGE_AA.html

90 **Tyrosine Y (Tyr) Chemical Properties:**
The Biology Project
Department of Biochemistry and Molecular Biophysics
The University of Arizona
http://www.biology.arizona.edu

92 **Which Form of Dopamine Is the Substrate for the Human Dopamine Transporter**
J Biol Chem, Vol. 274, Issue 8, 4876-4882, February 19, 1999
Janet L. Berfield, Lijuan C. Wang, and Maarten E. A. Reith
From the Department of Biomedical and Therapeutic Sciences, University of Illinois College of Medicine, Peoria, Illinois 61656

94 **Zwitterionic and anionic forms of a serotonin analog as transport substrates**
J. Biol. Chem., Vol. 264, Issue 25, 14865-14868, 09, 1989
G Rudnick, KL Kirk, H Fishkes and S Schuldiner
Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510.

96 **Intrinsic Fluorescence of Proteins and Peptides**
David Brooks
University of Nebraska-Lincoln, USA
http://dwb.unl.edu/Teacher/NSF/C08/C08Links/pps99.cryst.bbk.ac.uk/projects/gmocz/fluor.htm

98 **Chemogenesis: The Story of How Chemical Reactivity Emerges From The Periodic Table of The Elements**
Mark R. Leach
http://www.meta-synthesis.com/webbook.html**100 An Aromatic Anion Receptor: Anion- Interactions do Exist**
Angewandte Chemie Volume 116, Issue 43 , Pages 5939 – 5941 2 Nov 2004
Paul de Hoog 1, Patrick Gamez, Dr. 1 *, Ilpo Mutikainen, Dr. 2, Urho Turpeinen, Dr. 2, Jan Reedijk, Prof. Dr. 1 *
Leiden Institute of Chemistry, Gorlaeus Laboratories, University of Leiden, , Department of Chemistry, Laboratory of Inorganic Chemistry, University of Helsinki, P.O. Box 55

102 **Anion– interactions: must the aromatic ring be electron deficient?**
New J. Chem., 2003, (2), 211 - 214
Carolina Garau , David Quiñonero , Antonio Frontera , Pablo Ballester , Antonio Costa and Pere M. Deyà

104 **Organic chemistry**
Paula, Yurkanis, Bruice © 1995-2002 by Prentice-Hall, Inc.
http://wps.prenhall.com/wps/media/objects/724/741576/chapter_21.html

106 **Cation-pi interactions in structural biology**.
Proc Natl Acad Sci U S A. 1999 Aug 17;96(17):9459-64.
Gallivan JP, Dougherty DA.
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA.

108 **From ab initio quantum mechanics to molecular neurobiology: a cation-pi binding site in the nicotinic receptor.**
Proc Natl Acad Sci U S A. 1998 Oct 13;95(21):12088-93.
Zhong W, Gallivan JP, Zhang Y, Li L, Lester HA, Dougherty DA.
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA.

110 **Conduction pathways in microtubules, biological quantum computation, and consciousness**
Biosystems Volume 64, Issues 1-3, January 2002, Pages 149-168DOI:
Stuart Hameroff, Alex Nip, Mitchell Porter and Jack Tuszynski
Department of Anesthesiology and Psychology, Center for Consciousness Studies, University of Arizona, Tucson, AZ 85721, USA Received 18 May

112 **Intrinsic Fluorescence of Proteins and Peptides**
http://dwb.unl.edu/Teacher/NSF/C08/C08Links/pps99.cryst.bbk.ac.uk/projects/gmocz/fluor.htm
David Brooks
University of Nebraska-Lincoln, USA

114 **Amphetamine-induced dopamine efflux. A voltage-sensitive and intracellular Na+-dependent mechanism.**
Khoshbouei H, Wang H, Lechleiter JD, Javitch JA, Galli
A. Biol Chem. 2003 Apr 4;278(14):12070-7. Epub 2003 Jan 29.
Department of Molecular Physiology and Biophysics and the Center for Molecular Neuroscience, Vanderbilt University, Tennessee, USA.

116 **Dopamine transporters depolarize neurons by a channel mechanism.**
Proc Natl Acad Sci U S A. 2004 Nov 9;101(45):16046-51. Epub 2004 Nov 01. Carvelli L, McDonald PW, Blakely RD, Defelice LJ.
Department of Pharmacology and Center of Neuroscience, Vanderbilt University School of Medicine, Nashville, TN 37232-8548, USA.
lucia.carvelli@vanderbilt.edu

118 **Vibrational Analysis of Dopamine Neutral Base based on Density Functional Force Field**
Korean Chem. Soc. 2000, Vol. 21, No. 10 959
Sun-Kyung Park, Nam-Soo Lee, and Sang-Ho Lee
Department of Chemistry, Chungbuk National University, Korea: Biophysics Research Division, The University of Michigan, Ann Arbor,

120 **Zinc potentiates an uncoupled anion conductance associated with the dopamine transporter**
J. Biol. Chem, 10.1074/jbc.M407660200 Accepted on September 9, 2004
Anne-Kristine Meinild, Harald H. Sitte, and Ulrik Gether
Department of Pharmacology, University of Copenhagen, Copenhagen DK 2200 N

122 **Dopamine transporter-mediated conductances increase excitability of midbrain dopamine neurons.**
Trends Neurosci. 2003 Apr;26(4):173-6.
Ingram SL, Prasad BM, Amara SG.
Vollum Institute and Howard Hughes Medical Institute, Oregon Health & Science University, Portland, Oregon 97201, USA.

124 **The Dopamine Transporter in Mesencephalic Cultures Is Refractory to Physiological Changes in Membrane Voltage**
The Journal of Neuroscience, October 1, 2001, 21(19):7561-7567
Balakrishna M. Prasad and Susan G. Amara
Howard Hughes Medical Institute and Vollum Institute, Oregon Health Sciences University, Portland, Oregon 97201

126 **Theoretical study on the interaction between dopamine and its receptor by ab initio molecular orbital calculation.**
J Theor Biol. 1997 Mar 21;185(2):157-63.
Nishihira J, Tachikawa H.
Central Research Institute, School of Medicine, Hokkaido University, Sapporo, Japan.

128 **The effects of pH on dopamine and serotonin synthesis by rat brain striatal synaptosomes:**
Indian journal of pharmacology year : 1992 | Volume : 24 | Issue : 1 | Page : 32-35
Manoucher, Messripour

130 **Dopamine Receptor Activation Can Reduce Voltage-Gated Na+ Current by Modulating Both Entry Into and Recovery From Inactivation**
Neurobiology, Physiology, and Behavior, University of California, Davis, California 95616 May 2004;
Yuki Hayashida and Andrew T. Ishida

132 **The binding-site crevice of the D4 dopamine receptor is coupled to three distinct sites of allosteric modulation**
J. Pharm. Exp. Ther. 296:359-363.
by John A. Schetz and David R. Sibleyc (2001)

134 **Intracellular acidification reduced gap junction coupling between immature rat neocortical pyramidal neurones.**
J Physiol. 1996 Jan 1;490 (Pt 1):31-49.
Rorig B, Klausa G, Sutor B.
Institute of Physiology, University of Munich, Germany

136 **Dopamine Modulation of Perisomatic and Peridendritic Inhibition in Prefrontal Cortex**
Journal of Neuroscience, March 1, 2003, 23(5):1622
Wen-Jun Gao, Yun Wang, and Patricia S. Goldman-Rakic e
Department of Neurobiology, Yale University School of Medicine, New Haven, Connecticut 06510

138 **Decrease of gap junction permeability induced by dopamine and cyclic adenosine 3':5'-monophosphate in horizontal cells of turtle retina**
ournal of Neuroscience, Vol 4, 2477-2488, Copyright © 1984 by Society for Neuroscience
M Piccolino, J Neyton and HM Gerschenfeld

140 **Dye coupling between pyramidal neurons in developing rat prefrontal and frontal cortex is reduced by protein kinase A activation and dopamine.**
J Neurosci. 1995 Nov;15(11):7386-400.
Rorig B, Klausa G, Sutor B. Department of Physiology
University of Munich, Germany.

142 **Dopaminergic modulation of gap junction permeability between amacrine cells in mammalian retina**
Journal of Neuroscience, Vol 12, 4911-4922, Copyright © 1992 by Society for Neuroscience
EC Hampson, DI Vaney and R Weiler
Department of Physiology and Pharmacology, University of Queensland, Brisbane, Australia.

144 **Ionic Currents in the Human Serotonin Transporter Reveal Inconsistencies in the Alternating Access Hypothesis**
Biophysical Journal Volume 85 September 2003
Scott V. Adams* and Louis J. DeFelicey
Department of Physics and Astronomy and yDepartment of Pharmacology, Vanderbilt University, Nashville, Tennessee 37232

146 **A single ring of charged amino acids at one end of the pore can control ion selectivity in the 5-HT3 receptor.**
Br J Pharmacol. 2003 Sep;140(2):359-65. Epub 2003 Aug 11.
Thompson AJ, Lummis SC.
Department of Biochemistry, University of Cambridge, Cambridge CB2 IGA, UK.

148 **Basic Neurochemistry**
Agranoff, Albers, fisher, uhler
Seighttp://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=bnchm.table.966el

150 **Neuropharmacology of dopamine receptors: Implications in neuropsychiatric diseases**
QU Journal For Scientific Research: Medical Sciences 2001, vol: 3, no: 2, 87–104
Frank I. Tarazi http://www.squ.edu.om/mj/Oct2001/dopamine/
Department of Psychiatry and Neuroscience Program, Harvard Medical School; Boston, MA; Mailman Research Center, Massachusetts Hospital

152 **Synthesis and Pharmacology of the enantiomers of the potential atypical antipsychotic agents 5-OMe-BPAT and 5-OMe-(2,6-di-OMe)-BPAT.**
Bioorg Med Chem. 1999 Jul;7(7):1263-71
Homan EJ, Copinga S, Unelius L, Jackson DM, Wikstrom HV, Grol CJ.
Department of Medicinal Chemistry, University Centre for Pharmacy, University of Groningen, The Netherlands. ehoman@pharmacop.com

154 **Regulation of Membrane Excitability in the Central Nervous System by Serotonin Receptor Subtypesa**
Annals of the New York Academy of Sciences 861:190-203 (1998) © 1998 New York Academy of Sciences
R. ANDRADEb
Department of Psychiatry and Behavioral Neurosciences and Cellular and Clinical Neurobiology, Wayne State University School, Detroit, Michigan

156 **Serotonin regulates gap junction coupling in the developing rat somatosensory cortex.**
Eur J Neurosci. 1996 Aug;8(8):1685-95.
Rorig B, Sutor B.
Department of Physiology, University of Munich, Germany.

160 **Cation-pi interactions in ligand recognition by serotonergic (5-HT3A) and nicotinic acetylcholine receptors: the anomalous binding properties of nicotine.**
Biochemistry. 2002 Aug 13;41(32):10262-9.
Beene DL, Brandt GS, Zhong W, Zacharias NM, Lester HA, Dougherty DA.
Divisions of Chemistry and Chemical Engineering and Biology, California Institute of Technology, Pasadena, California 91125, USA.

162 **Electrostatic potential surfaces of 5-HT(3)R agonists suggest accessory cation-pi site adjacent to agonist binding domain.**
Bioorg Med Chem Lett. 2002 Oct 7;12(19):2743-7.
Parihar HS, Kirschbaum KS.
Department of Basic Pharmaceutical Sciences, College of Pharmacy, The University of Louisiana at Monroe, Monroe, LA 71209, USA.

164 **The 5-hydroxytryptamine type 3 (5-HT3) receptor reveals a novel determinant of single-channel conductance.**
Biochem Soc Trans. 2004 Jun;32(Pt3):547-52.
Peters JA, Kelley SP, Dunlop JI, Kirkness EF, Hales TG, Lambert JJ.
Division of Pathology and Neuroscience, Neurosciences Institute, Ninewells Hospital and Medical School, The University of Dundee

166 **A single ring of charged amino acids at one end of the pore can control ion selectivity in the 5-HT3 receptor.**
Br J Pharmacol. 2003 Sep;140(2):359-65. Epub 2003 Aug 11.
Thompson AJ, Lummis SC.
Department of Biochemistry, University of Cambridge, Cambridge CB2 IGA, UK.

168 **Prediction of 5-HT3 Receptor Agonist-Binding Residues Using Homology Modeling**
Biophysical Journal 84:2338-2334 (2003)
David C. Reeves, Muhammed F. R. Sayed, Pak-Lee Chau, Kerry L. Price and Sarah C. R. Lummis
Department of Biochemistry, University of Cambridge, Cambridge CB2 1AG, United Kingdom

170 **Behavioral Tolerance to Lysergic Acid Diethylamide is Associated with Reduced Serotonin-2A Receptor Signaling in Rat Cortex.**
Neuropsychopharmacology. 2005 Mar 9; [Epub ahead of print]
Gresch PJ, Smith RL, Barrett RJ, Sanders-Bush E.
Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, USA.

172 **LSD and the phenethylamine hallucinogen DOI are potent partial agonists at 5-HT2A receptors on interneurons in rat piriform cortex.**
J Pharmacol Exp Ther. 1996 Sep;278(3):1373-82.
Marek GJ, Aghajanian GK.
Department of Psychiatry, Yale University School of Medicine, Ribicoff Research Facilities of the Connecticut Mental Health Center, New Haven,

174 **Mapping the binding site pocket of the serotonin 5-Hydroxytryptamine2A receptor. Ser3.36(159) provides a second interaction site for the protonated amine of serotonin but not of lysergic acid diethylamide or bufotenin.**
J Biol Chem. 1996 Jun 21;271(25):14672-5.
Almaula N, Ebersole BJ, Zhang D, Weinstein H, Sealfon SC.
Fishberg Research Center in Neurobiology, Mount Sinai School of Medicine, New York, New York 10029, USA.

176 **Molecular Basis of Partial Agonism: Orientation of Indoleamine Ligands in the Binding Pocket of the Human Serotonin 5-HT2A Receptor Determines Relative Efficacy**
Molecular pharmacology Vol. 63, Issue 1, 36-43, January 2003
Barbara J. Ebersole, Irache Visiers, Harel Weinstein, and Stuart C. Sealfon
Departments of Neurology (B.J.E., S.C.S.), Physiology and Biophysics (I.V., H.W.), Pharmacology and Biological Chemistry (H.W., S.C.S.), and the Fishberg Research Center in Neurobiology (S.C.S.), Mount Sinai School of Medicine, New York, New York

178 **Evidence for a Model of Agonist-induced Activation of 5-Hydroxytryptamine 2A Serotonin Receptors That Involves the Disruption of a Strong Ionic Interaction between Helices 3 and 6*,**
J. Biol. Chem., Vol. 277, Issue 13, 11441-11449, March 29, 2002
David A. Shapiro, Kurt Kristiansen§, David M. Weiner¶, Wesley K. Kroeze, and Bryan L. Roth
Dept of Biochemistry, Case Western University Medical School, Cleveland, Ohio ACADIA Pharmaceuticals, San Diego, Dept Neurosciences and Psychiatry, University California, Department of Pharmacology, Institute of Pharmacy, University of Tromsø, Norway

180 **Specific Tryptophan UV-Absorbance Changes Are Probes of the Transition of Rhodopsin to Its Active State**
Biochemistry, 35 (34), 11149 -11159, 1996.
Steven W. Lin and Thomas P. Sakmar*
Howard Hughes Medical Institute, Laboratory of Molecular Biology and Biochemistry, The Rockefeller University, 1230 York Avenue, New York,

182 **Activation of the beta 2-adrenergic receptor involves disruption of an ionic lock between the cytoplasmic ends of transmembrane segments 3 and 6.**
J Biol Chem. 2001 Aug 3;276(31):29171-7. Epub 2001 May 25.
Ballesteros JA, Jensen AD, Liapakis G, Rasmussen SG, Shi L, Gether U, Javitch JA.
Novasite Pharmaceuticals, Inc., San Diego, California 92121, USA.

184 **Effects of the beta 2-adrenoceptor agonist clenbuterol on tyrosine and tryptophan in plasma and brain of the rat.**
Biochem Pharmacol. 1989 Sep 15;38(18):2957-65.
Edwards DJ, Sorisio DA, Knopf S.
Department of Pharmacology-Physiology, University of Pittsburgh School of Dental Medicine, PA 15261.

186 **Activation of beta2- and beta3-adrenergic receptors increases brain tryptophan.**
Pharmacol Exp Ther. 2003 May;305(2):653-9. Epub 2003 Jan 24.
Lenard NR, Gettys TW, Dunn AJ.
Department of Pharmacology and Therapeutics, LSU Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130-3932, USA.

188 **A highly conserved aspartic acid (Asp-155) anchors the terminal amine moiety of tryptamines and is involved in membrane targeting of the 5-HT(2A) serotonin receptor but does not participate in activation via a "salt-bridge disruption" mechanism.**
J Pharmacol Exp Ther. 2000 Jun;293(3):735-46.
Kristiansen K, Kroeze WK, Willins DL, Gelber EI, Savage JE, Glennon RA, Roth BL.

190 **Molecular dynamics simulations of the ligand-induced chemical information transfer in the 5-HT(1A) receptor**.
J Chem Inf Comput Sci. 2003 Sep-Oct;43(5):1520-31.
Seeber M, De Benedetti PG, Fanelli F.
Department of Chemistry, University of Modena and Reggio Emilia, Modena, Italy.

192 **G-protein-coupled receptors at a glance**
Wesley K. Kroeze, Douglas J. Sheffler and Bryan L. Roth*
Cell Science at a Glance Journal of Cell Science 116, 4867-4869 (2003)
Departments of Biochemistry, Neurosciences and Psychiatry, NIMH Psychoactive Drug Screening Program, Case Western Reserve University, School of Medicine, Cleveland, OH 44106, USA

194 **Gap junction function in vascular smooth muscle: influence of serotonin.**
Am J Physiol. 1995 Oct;269(4 Pt 2):H1481-9.
Moore LK, Burt JM.
Department of Physiology, University of Arizona, Tucson 85724, USA.

196 **Deficit and hemispheric asymmetry of GABA uptake sites in the hippocampus in schizophrenia.**
Biol Psychiatry. 1990 May 1;27(9):1038-44.
Reynolds GP, Czudek C, Andrews HB.
Department of Pathology, University of Nottingham Medical School, Queen's Medical Centre, United Kingdom.

198 **Biochemical and electrophysiological correlations of functional asymmetry of the brain**
Bratisl Lek Listy. 1989 Jun;90(6):458-61.
Cernacek J

200 **Sexual issues in brain research**
http://www.vernonjohns.org/nonracists/dvissues.html
Patrick L. Cooney, Ph.D.;year 2003.
The Vernon Johns Society

202 **Endogenous formation of morphine in human cells**
Proceedings of national sciences
Chotima Poeaknapo *, Jürgen Schmidt , Matthias Brandsch *, Birgit Dräger *, and Meinhart H. Zenk * *Biocenter,
Martin Luther University Halle-Wittenberg, Weinbergweg 22, 06120 Halle, Germany; and Leibniz Institute of Plant Biochemistry, Weinberg

204 **Do tricyclic responders have different brain laterality?**
J Abnorm Psychol. 1999 Nov;108(4):707-10.
Stewart JW, Quitkin FM, McGrath PJ, Bruder GE.
Depression Evaluation Service, New York State Psychiatric Institute, New York 10032

206 **ReN 1869, a novel tricyclic antihistamine, is active against neurogenic pain and inflammation.**
Eur J Pharmacol. 2002 Jan 18;435(1):43-57.Olsen UB,
Eltorp CT, Ingvardsen BK, Jorgensen TK, Lundbaek JA, Thomsen C, Hansen
AJ.Department of General Pharmacology, Novo Nordisk A/S, 2760 Maaloev, Denmark

208 **Organic anion-transporting polypeptides mediate transport of opioid peptides across blood-brain barrier.**
J Pharmacol Exp Ther. 2000 Jul;294(1):73-9. Gao B,
Hagenbuch B, Kullak-Ublick GA, Benke D, Aguzzi A, Meier PJ.
Clinical Pharmacology and Toxicology, Department of Medicine, University Hospital Zurich, Zurich, Switzerland

210 **Deltorphin II enhances extracellular levels of dopamine in the nucleus accumbens via opioid receptor-independent mechanisms.**
Eur J Pharmacol. 2004 Apr 26;491(1):31-6.
Murakawa K, Hirose N, Takada K, Suzuki T, Nagase H, Cools AR,
Koshikawa N.Department of Pharmacology, Nihon University School of Dentistry, 1-8-13 Kanda-Surugadai, Chiyoda, Tokyo,

212 **Effects of morphine on pentobarbital-induced responses in mu-opioid receptor knockout mice.**
Brain Res Bull. 2001 Mar 15;54(5):527-31.
Park Y, Ho IK, Jang CG, Tanaka S, Ma T, Loh HH, Ko KH.
Department of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS

214 **Functional coupling of gamma-aminobutyric acid receptors to chloride channels in brain membranes.**
Science. 1985 May 31;228(4703):1108-10
Harris RA, Allan AM.

216 **Electroencephalographic and perceptual asymmetry differences between responders and nonresponders to an SSRI antidepressant.**
Biol Psychiatry. 2001 Mar 1;49(5):416-25.
Bruder GE, Stewart JW, Tenke CE, McGrath PJ, Leite P, Bhattacharya N, Quitkin FM.
Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, New York

218 **5-Hydroxytryptophan: a clinically-effective serotonin precursor**.
Altern Med Rev. 1998 Aug;3(4):271-80.
Birdsall TC.

220 **Mood disorders following stroke: new findings and future directions**
J Geriatr Psychiatry. 1989;22(1):1-15
Robinson RG, Starkstein SE.
Johns Hopkins University, School of Medicine, Baltimore, Maryland

222 **Remote lateralized changes in cortical [3H]spiperone binding following focal frontal cortex lesions in the rat.**
Brain Res. 1990 May 14;516(1):127-31.
Mayberg HS, Moran TH, Robinson RG.
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205.

224 **Does 3H-imipramine binding asymmetry indicate psychiatric illness?**
Acta Psychiatr Scand. 1988 Jun;77(6):746
Demeter E, Tekes K, Majorossy K, Arato M, Somogyi E.
Department of Forensic Medicine, Semmelweis, Medical University, Budapest, Hungary.

226 **Effects of quitting smoking on EEG activation and attention last for more than 31 days and are more severe with stress, dependence, DRD2 A1 allele, and depressive traits.**
Nicotine Tob Res. 2004 Apr;6(2):249-67.
Gilbert D, McClernon J, Rabinovich N, Sugai C, Plath L, Asgaard G, Zuo Y, Huggenvik J, Botros N.
Department of Psychology, Southern Illinois University at Carbondale, Carbondale, IL 62901-6502, USA.

228 **Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie.**
Psychophysiology. 1989 May;26(3):311-20.
Gilbert DG, Robinson JH, Chamberlin CL, Spielberger

230 **The role of kynurenines in the production of neuronal death, and the neuroprotective** effect of purines.
J Alzheimers Dis. 2001 Aug;3(4):355-366.
Stone TW, Behan WM, Jones PA, Darlington LG, Smith RA.
Institute of Biomedical & Life Sciences, University of Glasgow, Glasgow G12 8QQ, UK.

232 **in vivo hydroxyl radical formation after quinolinic acid infusion into rat corpus striatum.**
Neuroreport. 2001 Aug 28;12(12):2693-6.
Santamaria A, Jimenez-Capdeville ME, Camacho A, Rodriguez-Martinez E, Flores A, Galvan-Arzate S.
Departamento de Neuroquimica, Instituto Nacional de Neurologia y Neurocirugia Manuel Velasco Suarez, Mexico.

234 **The concept of cerebral chemical dominance**
J Neurosci. 2003 Jul;113(7):957-70.
Kurup RK, Kurup PA. Department of Neurology, Medical College Hospital, Trivandrum, Kerala, India.

236 **Hypothalamic digoxin, cerebral dominance, and membrane biochemistry.**
Int J Neurosci. 2002 Dec;112(12):1439-47.
Kurup RK, Kurup PA.
Department of Neurology, Medical College, Trivandrum, Kerala,

238 **MAPPING BRAIN ASYMMETRY**
Nature reviews Neuroscience VOLUME 4 | JANUARY 2003 | 37
Arthur W. Toga and Paul M. Thompson

240 **Lateral asymmetry of neurotransmitters in human brain.**
Brain Res. 1982 Feb 18;234(1):53-63
Glick SD, Ross DA, Hough LB

242 **Changes in the isoprenoid pathway with transcendental meditation and Reiki healing practices in seizure disorder.**
Neurol India. 2003 Jun;51(2):211-4.
A RK, Kurup PA.
Department of Neurology, Medical College Hospital, Trivandrum 695-003, Kerala, India.

244 **Pharmacology and regional variations of quinolinic acid-evoked excitations in the rat central nervous system**
Volume 226, Issue 2, pp. 551-557, 08/01/1983 Copyright © 1983 by American Society for Pharmacology and Experimental Therapeutics
MN Perkins and TW

246 **Tryptophan and tyrosine catabolic pattern in neuropsychiatric disorders.**
Neurology India year : 2000 | Volume : 48 | Issue : 3 | Page : 231-8
Ravikumar A, Deepadevi KV, Arun P, Manojkumar V, Kurup PA
Department of Neurology, Medical College, Trivandrum, and Metabolic Disorders Research Centre, Puliyarakonam, Trivandrum, India.